ISSN 2622-7258 (Online)

Asian Institute of Research

Journal of Health and Medical Sciences

Vol. 7, No.1 March 2024

Asian Institute of Research
Connecting Scholars Worldwide

Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7 No.1 March 2024

Journal of Health and Medical Sciences
ISSN 2622-7258 (Online)

The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 1-13
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.299

Old Fracture of Acetabulum Combined with Osteoarthritis Total Hip Arthroplasty (THA)

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Abstract
This review examined the use of total hip arthroplasty as therapeutic option for management of chronic fracture of acetabulum accompanied by osteoarthritis. The article discussed the epidemiology, risk factors, and potential complications associated with this complex condition, as well as its increasing prevalence among the elderly population. The rationale for combining total hip arthroplasty with fracture fixation was discussed, along with the potential benefits of pain relief, increased stability, enhanced long-term outcomes, and decreased healthcare costs. The article also examined the potential risks and complications associated with this approach, as well as the significance of a multidisciplinary treatment approach that takes each patient's unique requirements and goals into account. Overall, it provided a comprehensive overview of the challenges and considerations involved in managing an old fracture of the acetabulum in conjunction with osteoarthritis and emphasized the potential role of total hip arthroplasty as a treatment option for this complex condition.

Keywords: Acetabulum, Fracture Fixation, Hip Replacement, Post-Traumatic Arthritis, Osteoarthritis, Rehabilitation of Fracture

1. Introduction

The annual incidence of Acetabular fractures (AFs) is 3 per 10,000 individuals (Approximately) worldwide. More than 60% of these are caused by high-energy traumas, specifically car accidents. AFs occur when the hip cavity, also known as the acetabulum, breaks. These injuries were the result of factors, such as mishaps, automobile accidents, and sports injuries. While they can occur at any age, the prevalence of osteoporotic bone in the elderly makes them more common. Osteoarthritis is a degenerative joint disease, characterized by the disintegration and loss of cartilage in joints, which causes pain, rigidity, and constrained range of motion (ROM). Osteoarthritis affects any joint, including the hip, and is also more prevalent among the geriatric. Old acetabulum fractures combined with hip osteoarthritis (OAFHAs) can present orthopedic surgeons with a formidable challenge. These fractures are frequently consequence of high-energy trauma, coupled with substantial morbidity and disability. The onset of osteoarthritis in the afflicted hip joint further complicates the management of these cases (Wang et al., 2020). THA is surgical procedure that can alleviate pain and enhance function in patients with acetabular

fractures and osteoarthritis. However, THA in this context is challenging procedure that necessitates meticulous planning and execution to attain optimal results (Sharma et al., 2019). Young patients typically sustain AFs as a consequence of severe trauma, whereas elderly patients are more susceptible to these traumas for low-energy mechanisms. Open Reduction and Internal Fixation (ORIF) is presently regarded as standard treatment for these fractures, but surgery can be challenging for anatomic location and 3-Dimensional complexity of acetabulum. Even with anatomical reduction, posttraumatic arthritis could still develop (Gautam et al., 2020). Different injury mechanisms and the common occurrence of osteoporotic bone can result in distinct fracture patterns in elderly. Typically, these patterns include anterior column, posterior hemi-transverse, and both column injuries. It is complicated to successfully reduce a fracture, and failure to do so may result in joint degradation in vital areas. Prime treatment objectives for geriatric patients with fractures are to alleviate pain, timely weight bearing, and the return to independent daily activities. Treatment options for AFs in this population may include non-surgical and surgical management, but there is currently no consensus regarding the optimal approach (Panteli et al., 2023). AFs treated with surgical fixation can result in complications such as posttraumatic arthritis (PTA), osteonecrosis of femoral head, chondrolysis, and nerve palsies resulting from the procedure. According to a meta-analysis of AFs treated with ORIF, 13- 44 % of patients exhibited PTA, requiring THA to diminish symptoms. Yet, owing to local tissue changes and infections, conversion to THA can be challenging. In addition, patients with a history of AF who undergo THA run the risk of complications including heterotopic ossification, surgical site infection, and implant loosening, which may necessitate revision surgery. Although it was suggested that THA in AF patients is less effective than THA for non-traumatic primary osteoarthritis (Stibolt et al., 2018).

1.1. Rationale of combining total hip arthroplasty with old fracture of acetabulum and osteoarthritis:

Combining THA with OAFHAs has multiple benefits, including pain relief, increased stability, improved long-term outcomes, and decreased healthcare costs. Although there are potential risks associated with this approach, the benefits may outweigh the risks for patients who are carefully selected (Gautam et al., 2020). The surgical procedure known as total hip arthroplasty (THA) involves replacing the hip joint with a prosthetic device. This procedure has become more prevalent over the past few decades as a treatment for various hip conditions, like osteoarthritis and hip fractures. In cases where patients present with OAFHAs, there are multiple reasons to combine THA with fracture fixation (Tiftikçi et al., 2015).

First, THA can provide significant pain alleviation to patients with both osteoarthritis and old fractures of the acetabulum. This is particularly essential for patients experiencing chronic pain for extended time periods, as it can have a significant impact on their life activities. THA can also restore ROM and mobility, allowing patients to return to activities they were formerly unable to engage in. Second, combining THA with fracture fixation can increase the hip joint's stability, thereby decreasing the likelihood of future fractures and other complications. The prosthetic device used in THA can provide additional support and strength to an acetabulum that has been compromised, thereby preventing future fractures. This is especially essential for elderly patients, who may be more susceptible to falls and other accidents. Thirdly, combining THA and fracture fixation can improve patients' long-term outcomes. According to studies, patients undergoing THA for osteoarthritis or other hip conditions report high levels of satisfaction and an enhanced quality of life. Similarly, patients those undergo fracture fixation for elderly acetabulum fractures have favorable outcomes, with high rates of fracture healing and functional recovery. The comprehensive treatment of osteoarthritis and the old fracture can be enhanced through the combination of these two procedures (Shao et al., 2023).

Lastly, the combination of THA and fracture fixation can result in reduced long-term healthcare costs. By treating both conditions concurrently, patients may require fewer follow-up appointments and be able to avoid future operations or treatments. Infection, dislocation, and implant failure are potential hazards associated with the combination of THA and fracture fixation. However, these risks can be mitigated through cautious patient selection, the use of an appropriate surgical technique, and post-operative care and monitoring (De Franco et al., 2023).

1.2. Epidemiology of old fracture of acetabulum combined with osteoarthritis:

The incidence and prevalence of OAFHAs increase with age and are more prevalent in the elderly population. In some instances, non-surgical treatment options may be appropriate, but surgical intervention may be necessary for successful outcomes. Improving outcomes for patients with this complex condition will necessitate a multidisciplinary approach that considers each patient's unique requirements and goals (Cui et al., 2020).

A study was conducted at Liaquat National Hospital, Pakistan, comprising 50 patients with acetabular fractures from 2012-2014. Their average age was 44.20±11.65 years. Using reconstruction plates, ORIF of fractures were performed. At 24 months, mean HHS was 82.368.55. In 35 (70.0%) cases, clinical prognosis was excellent to good, while in 15 (30%) cases, it was fair or poor. In 39 (78%) cases, radiological upshot was anatomical, while in 5 (10%) cases, it was congruent and in 6 (12%) cases, it was incongruent. Thus, functional and radiological outcomes were significantly affected by the mechanism of injury, duration between injury and surgery, initial degree of displacement, and quality of reduction, according to the study's findings.

Five years of prospective data collection at a Level-I trauma centers were followed by a retrospective analysis. Among the identified 1123 cases of acetabular fractures, 156 involved patients older than 65, with an average age of 78. Falls and automobile collisions were the leading causes of injury. 82% of patients had substantial medical comorbidities, 33% of them died within a year, and 75% of those deaths occurred within 90 days of the fracture. 84% of the deceased patients had received non-operative treatment. The one-year mortality rate for patients treated with traction alone was 79%, and the mortality rate within 90 days was 50%. 70% of the total cohort had an ABC or AC/PHT fracture pattern. 36.5% of the surgically treated patients underwent ORIF with standard reduction techniques and surgical implants through the ilioinguinal (69%) and Kocher-Langenbeck (28%). It was discovered that elderly patients with acetabular fractures were uncommon, accounting for only 14% of all cases. Patients those underwent surgical treatment had reduced rates of mortality. ABC and AC/PHT fracture patterns were most prevalent, and standard fixation constructs and implants were efficacious at treating these challenging fractures. During their recuperation, mostly patients were unable to go back home and required skilled nursing care (Deng et al., 2018).

1.3. Total Hip Arthroplasty

THA is a surgical procedure comprising the replacement of hip joint with prosthetic joint. Patients with severe hip pain or dysfunction due to osteoarthritis, rheumatoid arthritis, avascular necrosis, or a previous hip injury frequently undergo this procedure. During this procedure, spoiled portions of hip joint are replaced with metal, plastic, or ceramic components. The new components are designed to replicate the shape and function of a healthy hip joint, allowing for a greater ROM and reduction in pain (Günther et al., 2021). THA is an extremely effective procedure with a high patient satisfaction rate. According to the American Academy of Orthopaedic Surgeons, over 300,000 THAs are performed yearly, with an approximate 90% success rate in the first 10 to 15 years following surgery (Okafor et al., 2019).

THA provides pain relief, enhanced mobility and quality of life, and a reduced risk of falls and fractures. Patients who undergo THA typically experience a substantial reduction in pain, allowing them to resume to activities they were previously unable to engage in. Additionally, THA can enhance general physical function, which can result in enhanced mental health and social interactions (Tayler et al., 2022).

However, THA is not risk-free. Infection, blood clots, dislocation of the prosthetic joint, and implant failure are the most frequent complications associated with THA. Careful patient selection, an appropriate surgical technique, and post-operative monitoring and care can mitigate these risks. There have been numerous advancements in THA techniques and materials in recent years, which have further improved patient outcomes. These include minimally invasive techniques that reduce the size of the surgical incision, post-operative pain, and recovery time, as well as newer prosthetic designs that seek to improve stability and durability (Fontalis et al., 2021).

1.4. Intent of this review article

This article seeks to provide an overview of management of OAFHAs using THA, including patient selection, preoperative planning, surgical techniques, and postoperative care. Also discussed will be the current evidence on the outcomes and complications of THA for this condition.

2. Anatomy

A comprehensive understanding of acetabular anatomy is indispensable for hip arthroscopy procedures. The intricate morphology of the acetabulum and pelvis is crucial for any procedure involving the hip joint. The articular surface of acetabulum is supported between legs of an inverted "Y," with anterior and posterior columns of acetabulum serving as "Y" legs. The iliopectineal line represents the anterior column on radiographic images, while ilioischial line represents the posterior column. Anterior or posterior column fracture is diagnosed if any of these lines are interrupted. The external and internal iliac arteries are closely related to these vessels and, if necessary, must be properly identified and ligated. Anomalous connections between these two arteries, known as corona mortis, are recognized and treated with caution, as their injury can result in severe complications. The lesser and greater sciatic valleys traverse the lumbar plexus and its numerous nerve roots, which are susceptible to injury during portal placement and other hip procedures.

2.1. Bone landmarks

Acetabulum carries three bones: ilium, ischium, and pubis. Understanding the acetabular bone landmarks is essential for diagnosing and treating the hip injuries, as well as the placement of implants during hip replacement surgery. Acetabulum is the socket-like pelvic structure that creates hip joint with the femoral head. On the surface of the acetabulum are two key bony landmarks: acetabular fossa and acetabular rim. Acetabular fossa is the depression in middle of acetabulum where tip of the femur rests. Acetabular margin surrounds the acetabular fossa and stabilizes the hip joint.

2.2. Ligamentous attachments

Networks of robust ligaments that attach to acetabulum maintain stability of hip joint. During movement, these ligaments are essential for sustaining the position and alignment of femur in acetabulum. There are three major categories of acetabular ligaments: iliofemoral, pubofemoral and ischiofemoral ligament. In addition to these ligaments, the hip joint has a fibrous capsule that connects to the acetabulum and surrounds the joint. The ligaments reinforce the base of the acetabulum, where the capsule is thickest. It serves a crucial role in maintaining the integrity of the hip joint and providing movement stability.

2.3. Vascular supply

The acetabulum's blood supply is essential for maintaining bone health and function. Injuries to the blood vessels that nourish the acetabulum can cause avascular necrosis, a condition in which bone tissue dies from lack of blood supply. This can result in arthritis and joint deterioration, so surgeons must be mindful of the vascular supply when operating on the hip joint.

3. Pathophysiology

The pathophysiology refers to abnormal functioning of hip joint as a result of various diseases or traumas:
The most prevalent acetabular pathophysiology is acetabular fracture. A fracture of the bone that forms up the acetabulum is referred to as an acetabular fracture. This type of injury is typically result of trauma, like road accident or a fall from a considerable height. Simple, non-displaced acetabular fractures can range to more complex, displaced fractures involving multiple bone fragments.

Osteoarthritis is a degenerative joint disease accruing when the cartilage covering the extremities of bones in joints begins to deteriorate. This can result in hip joint pain, rigidity, and function less. Osteoarthritis of acetabulum is most prevalent in older individuals or those with a history of hip injuries or surgical procedures. Avascular necrosis occurs when the bone's blood supply is interrupted, resulting in the death of bone tissue. This can be caused by trauma, protracted steroid use, and excessive alcohol consumption, among others. Avascular necrosis of the acetabulum can cause hip joint discomfort, stiffness, and loss of function. Hip dysplasia is a congenital anomaly caused by improper hip development. This can result in joint instability and abnormal wear and strain, causing pain and functional limitations. Hip dysplasia of acetabulum can augment the probability of developing osteoarthritis of hip joint (Gambling et al., 2019).

3.1. Causes and risk factors of old fracture of acetabulum

The most frequent cause of old acetabulum fractures is a high-energy trauma, such as an automobile accident or a fall from a great height. These types of injuries may result in a fracture of the acetabulum bone. If the fracture is not treated properly or heals improperly, it can result in chronic pain and functional limitations. Certain risk factors can increase the probability of developing an acetabular fracture. Among these risk factors are: age, osteoporosis, injuries and trauma, previous hip surgeries, old fractures, low sun exposure, use of corticosteroids, low milk intake, using tobacco and alcoholic abuse (Al-Algawy et al., 2019).

Individuals with osteoporosis are at a greater risk for developing acetabulum fractures. Old fractures of the acetabulum are more likely to occur in individuals who have previously sustained hip injuries or undergone hip surgery. This is due to the fact that these traumas can weaken the bone, making it more susceptible to fractures. Use of corticosteroid medications, such as prednisone, for an extended period of time can weaken the bones and increase the risk of fractures, including ancient fractures of the acetabulum. Abuse of alcohol: Excessive alcohol consumption can weaken bones and increase the risk of fractures, including ancient acetabulum fractures. Tobacco use can weaken bones and reduce blood flow to bone tissue, thereby increasing risk of fractures.

3.2. Mechanisms leading to osteoarthritis

Osteoarthritis is a common joint disease characterized by cartilage degeneration and underlying bone alterations. A hip fracture caused by an acetabular fracture, a type of pelvic fracture, can result in the development of osteoarthritis. Loss of joint congruity is one of the mechanisms that contribute to development of osteoarthritis in acetabular fracture. Normal contact between femoral head and acetabulum is disrupted when joint surface is displaced as a result of a fracture. This can result in abnormal joint loading, resulting to articular cartilage and underlying bone changes. This can contribute to the development of osteoarthritis over time.

Damage to the articular cartilage is another mechanism that contributes to the development of osteoarthritis in acetabular fractures. A joint's articular cartilage is a smooth, lubricated surface that covers the bone extremities. When a fracture disrupts the joint surface, the articular cartilage can become damaged. This can result in the release of inflammatory molecules, which can further harm the cartilage and bone beneath it. This can contribute to the development of osteoarthritis over time. The mechanisms that contribute to the development of osteoarthritis in acetabular fracture are intricate and multifactorial. Loss of joint congruity, articular cartilage damage, and disruption of the surrounding soft tissues can all contribute to the onset of this prevalent joint disease.

3.3. Interplay between old fracture and osteoarthritis

If AF is not properly treated or is severe, it can result in joint instability, increased joint pressure, and increased risk of developing osteoarthritis. When an old acetabular fracture is present, increased joint pressure and aberrant joint biomechanics can hasten the progression of osteoarthritis. The interaction between ancient acetabular fractures and osteoarthritis can also be influenced by joint instability. When the soft tissues encircling hip joint become damaged, joint may become unstable, resulting in abnormal loading and bone changes. This can eventually contribute to the development of osteoarthritis (Lai et al., 2022).

4. Clinical Manifestations

Fractures of acetabulum have many clinical manifestations. Clinical manifestations of this injury may become more complicated when combined with osteoarthritis. It can cause significant hip discomfort and swelling. The pain can be severe and can intensify with movement, weight-bearing, or any form of pressure to the afflicted area. There may be visible edema around the hip joint, as well as possible bruising or redness. When AFs are accompanied by osteoarthritis, pain and edema can become persistent and chronic. Patients may experience pain at repose, and hip joint ROM may be restricted. Walking, standing, and all other weight-bearing activities may be difficult and lead to increased pain and distress. Joint stiffness is one of the most prevalent clinical manifestations of OAFHAs. Loss of articular cartilage and alterations in the underlying bone can lead to stiffness. Patients may experience a diminution in ROM, particularly in flexion and internal rotation. Development of bone spurs or osteophytes is an additional clinical sign. These are bony growths that can form in the joint space and further restrict the hip's ROM. Inflammation and irritation can also be caused by bone spurs, resulting in increased pain and edema.

In addition to muscle weakness or atrophy, patients with OAFHAs may also experience muscle weakness. Consequence to injury, soft tissues surrounding hip joints, including muscles and tendons, may become weakened or damaged. This reduces muscle mass and power, making walking and other physical activities problematic. Early diagnosis and treatment can reduce likelihood of developing chronic symptoms and complications (Shorter et al., 2019).

4.1. Signs of old fracture of acetabulum

Signs and symptoms of an old fracture of the acetabulum may include: Hip discomfort (a dull or sharp pain in the hip joint that may worsen with activity), reduced ROM in hip joint, making it challenging to move the leg, Walking may be difficult or agonizing as a result of the hip joint injury, a clicking or popping sensation may develop in hip joint as a result of alterations that occur in the joint after a fracture and leg length discrepancy may exist if the fracture caused hip joint mal-alignment (Hidaka et al., 2021).

4.2. Signs of osteoarthritis

Osteoarthritis is widespread and degenerative joint diseases that primarily deteriorate cartilage in the joints. Consequently, individuals with osteoarthritis frequently experience joint pain, rigidity, and limited ROM (Horecka et al., 2022). The joint may be difficult to move due to rigidity, and it may feel "locked" or "stuck" in one position. The stiffness typically improves as the joint is moved and loosened, but it may recur after periods of rest or inactivity. Limited ROM is an additional indicator of osteoarthritis. As cartilage in a joint deteriorates, the joint may become less malleable, making it difficult to utilize the joint's full range of motion (Primorac et al., 2020).

5. Diagnosis

The symptoms of OAFHAs can overlap with those of other conditions, making diagnosis difficult. However, comprehensive patient history and physical exam is the first step in diagnosing OAFHAs.

5.1. Clinical presentation and history

OAFHAs can result in a variety of clinical presentations like hip discomfort, joint stiffness, limited ROM, edema, tenderness and cracking of hip and muscular atrophy. The patient may experience dull or sharp pain in the hip joint that worsens with activity or weight-bearing, hip joint stiffness, particularly in the morning or after extended periods of inactivity, difficulty moving the afflicted leg through its complete ROM, edema and tenderness in the vicinity of hip joint, clicking or cracking in the hip joint during movement, and muscle weakness in the affected limbs (Katz et al., 2021).

In addition to the clinical presentations, a comprehensive patient history is essential for diagnosing AFs in conjunction with osteoarthritis. Patients are inquired for their symptoms including location, duration, and intensity of any pain or discomfort, previous hip joint injuries or interventions, medical history, certain occupations or activities may pose risk of hips injury.

5.2. Imaging modalities for diagnosis

Typically, imaging studies are used to corroborate the diagnosis of OAFHAs, carrying X-rays, CT-scans, MRI and arthroscopy. X-rays are typically first imaging study ordered, as they can reveal any hip joint deformities. X-rays can also reveal osteoarthritis symptoms, such as bone spurs and joint space constriction. CT scans provide more detailed images of hip joint than x-rays and can assist in determining the extent of bone or joint injury. MRI scans generate meticulous images of soft tissues, such as cartilage and ligaments, in hip joint. This imaging technique can help identify any cartilage or ligament injuries. In some instances, arthroscopy may be used to diagnose AFs. Through a small incision, a small camera is inserted into hip joint during arthroscopy, a minimally invasive procedure. This enables the visualization of joint, soft tissues and cartilage (Hayashi et al., 2018).

5.3. Differential diagnosis

Diagnosing the underlying cause of patient's symptoms requires differential diagnosis. A comprehensive patient history, physical examination, and imaging studies can assist in distinguishing between these conditions and determining the most appropriate treatment. These are:
Hip osteoarthritis is a degenerative joint disease that can cause joint discomfort, stiffness, and restricted ROM. Its symptoms resemble those of OAFHAs. However, osteoarthritis symptoms typically develop gradually, whereas acetabular fracture symptoms can occur abruptly. Labral tears are injuries to the labrum, which is a cartilage ring surrounding the hip joint. Labral tears can cause hip pain, joint stiffness, and cracking or clicking sounds in the hip joint. Trochanteric bursitis is an inflammation of the bursa, a pouch filled with fluid that cushions the hip joint. Trochanteric bursitis can cause hip discomfort, tenderness, and swelling in the outer hip region. Femoral neck stress fractures can induce hip pain, particularly during weight-bearing activities. Avascular necrosis is a condition characterized by the death of bone tissue and may manifest as hip discomfort, stiffness, and restricted ROM (Pianka et al., 2021).

6. Therapeutic Approach

Typically, a combination of non-surgical and surgical treatment options is used to treat OAFHAs:

6.1. Conservative management strategies

In cases where the fracture is stable and the osteoarthritis is mild, conservative management strategies may be used in treating OAFHAs, including pain management, physical therapy, assistive devices, modifications to lifestyle, corticosteroid etc (Lim et al., 2022).

Pain management is an integral part of conservative treatment to help manage the pain associated with this condition using over-the-counter or prescription pain medications. Physical therapy may be recommended to help strengthen the hip joint's ROM, strength, and function. Modifications of patient’s lifestyle may be advised to modify their daily activities to reduce tension on affected hip joint, involving avoiding high-impact activities like running and leaping and losing weight to reduce the load on the hip joint. In some instances, corticosteroid injections may be utilized to reduce inflammation and alleviate discomfort in the affected hip joint. Injections of hyaluronic acid may also be used to enhance joint lubrication and alleviate pain (Kemp et al., 2020).

7. Surgical Interventions

Surgical interventions for conditions affecting the hip can range from minimally invasive procedures to significant operations:

7.1. Total hip arthroplasty

Total hip arthroplasty (THA), is a surgical procedure, performed under general anesthesia, in which a damaged or arthritic hip joint is replaced with a metal, ceramic, or plastic artificial joint. During surgery, the damaged portions of the hip joint is removed and replaced with a prosthetic joint composed of a metal stem implanted in femur, a metal or ceramic ball attached to the tip of the stem, and a plastic or metal socket implanted in the hip bone. The new joint would restore stability, mobility, and function by mimicking the natural movement of the hip joint (Merola et al., 2019).

With a reported success rate of up to 95% in alleviating hip pain and restoring function, THA is a highly successful procedure. Infection, blood clots, dislocation, nerve injury, and implant failure are potential risks and complications associated with THA, as with any surgery (Table 1). To optimize outcomes, it is essential to thoroughly weigh the potential benefits and risks of THA and to adhere to all pre- and post-operative instructions.

Table 1: Characteristics of Patients Undergoing THA Who Have an Old Acetabular Fracture and Osteoarthritis

S. No	Sample size	Age (Years)	Fracture	Time since fractured (Years)	Follow up period (Years)	Reference
1	96	40.5	Posterior/anterior wall and columns, transverse fractures	1-10	1.5-2	Grubor et al., 2015
2	42	55-84	Posterior wall and posterior column	3-30	2-10	Brown et al., 2019
3	62	71.5	Anterior column and posterior hemi-transverse	5-7	4-5	Panteli et al., 2022
4	446	38	Posterior wall and posterior column	1-5	10	Cantrell et al., 2022
5	33	66	Posterior (2) and anterior fracture (16)	1-5	1-14	Lin et al., 2015
6	22	75.3	Transverse (9), anterior column (7), both column (6)	1-7	2.5	Herscovici et al., 2010

7.1.1. Indications and contraindications

THA is typically recommended for patients with significant hip pain and functional loss due to conditions such as osteoarthritis, arthritis rheumatoid, avascular necrosis, hip fractures and hip dysplasia. While, the contraindications involve Active infection in patients with severe osteoporosis, Patients with advanced age or substantial medical conditions, Allergy to implant materials of metals or plastics used in THA and Mental health conditions which can impede recovery phases (Günther et al., 2021).

7.1.2. Preoperative planning and evaluation (including patient selection and preoperative imaging)

THA efficacy is contingent on preoperative planning and postoperative evaluation. Typical preoperative planning stages include patient selection, preoperative imaging, and evaluation of the patient's medical history and comorbidities (Carmel-Neiderman et al., 2021).

Patient selection for THA is based on several factors, including age, degree of disability, pain intensity, and overall health. Patients who are younger and more physically active may be better candidates for THA, as they may experience greater surgical benefits.

Imaging is crucial for assessing the extent of hip joint injury and planning the surgical approach prior to surgery. X-rays, magnetic resonance imaging (MRI), and computed tomography (CT) scans are common imaging techniques utilized in preoperative planning for THA. These imaging studies can help pinpoint the location and

severity of joint injury, evaluate bone quality, and determine implant size and placement. The evaluation of a patient's medical history and comorbidities is essential for determining the most appropriate surgical approach and assessing the risks associated with THA. Certain medical conditions, including cardiovascular disease, diabetes, and pulmonary disease, may necessitate additional monitoring and care during and after surgery.

Additionally, patient's lifestyle, occupation, and expectations may also be considered during preoperative planning for THA. Patients who engage in high-impact activities, for instance, may require specialized implants or postoperative rehabilitation, whereas sedentary patients may benefit from simpler, less invasive surgical procedures.

7.1.3. Surgical technique and approach

THA is performed using a variety of surgical techniques and methodologies, including posterior, anterior and lateral approach (Table 2).

Posterior approach: In this technique, an incision is made on the back of the hip, enabling the surgeon to access the hip joint by slicing through the muscles and tissues on the side of the hip. This is the most common technique for THA and provides excellent exposure of the hip joint.

Anterior approach: This approach entails making an incision on the front of the hip, allowing the surgeon to access the hip joint by going between the muscles and tissues rather than cutting through them. Compared to the posterior approach, this technique may result in less muscle damage and a quicker recovery period.

Lateral approach: This approach entails making an incision on the side of the hip, allowing the surgeon to access the hip joint by cutting through the side of the hip's muscles and tissues. This method is utilized less frequently than the posterior or anterior approaches (Moretti et al., 2017).

Table 2: THA surgical techniques for patients with an old acetabular fracture and osteoarthritis

S. No	Surgical technique	Merits	Demerits	Reference
1	Antero-lateral approach	Provides excellent exposure of the acetabulum and femoral head, and if necessary, can be extended to a posterior approach.	Possibility of lateral femoral cutaneous nerve injury and hip instability due to disruption of anterior soft tissue structures.	Austin et al., 2009; Hasija et al., 2018
2	Posterior approach	Reduces the risk of injury to the lateral femoral cutaneous nerve and improves visibility of the posterior column and wall.	If not conducted carefully, can result in limited exposure of the acetabulum and femoral head, with the possibility of nerve damage.	Hu et al., 2017; Onyemaechi et al., 2014
3	Lateral approach	Avoids injury to the lateral femoral cutaneous nerve while providing adequate exposure of the acetabulum and femoral head.	Possibility of hip instability due to disruption of lateral soft tissue structures, resulting in limited exposure of the posterior column and wall	Goulding et al., 2010; Suzuki et al., 2013

7.1.4. Postoperative care and rehabilitation

Postoperative care and rehabilitation following THA are essential for a positive outcome and rapid recovery. Following are some general recommendations for postoperative care and rehabilitation following THA:

Pain is a common side effect of THA, and is managed through analgesics. Physical therapy is an essential component of THA rehabilitation along with the domestic exercises. Weight-bearing restrictions are imposed and patients are required to use a walker or crutches for several weeks or months, while progressively increasing the

amount of weight placed on hip joint. The incision site is kept sterile and dry to prevent infection and to prevent blood clots wearing compression stockings or taking blood thinners are recommended (Chen et al., 2021).

7.1.5. Outcomes and complications

THA is a highly effective surgical procedure that can alleviate pain and increase functions of hip joint. However, as with any surgical procedure, there are potential complications and outcomes of this technique:
One of the primary objectives of THA is to alleviate pain in the hip joint, thereby improving the patient's mobility, walking ability, and ability to conduct daily activities. It can restore mobility to hip joint, enabling the patient to engage in physical activities they were unable to perform prior to surgery. THA implants can last for many years, providing patients with hip joint disease with long-term relief (Ninomiya et al., 2018).

The notable complications included infection at surgical site, formation of blood clots in the extremities that can be fatal if they travel to lungs. Implant failure can loosen, deteriorate, or shatter, necessitating revision surgery, dislocation of the replacement hip joint, which is more likely to occur in first few months following surgery, nerve or blood vessel damage during surgery. Although uncommon, some patients may experience an allergic reaction to the materials used in the implant (Aqil et al., 2020).

7.2. Other surgical techniques

Osteotomy and arthrodesis are other surgical procedures used to treat conditions of the hip joint. Osteotomy is typically performed on younger patients with hip dysplasia or other conditions affecting hip joint alignment. Typically, it is not used to treat acute acetabular fractures (Millis et al., 2018). Arthrodesis is another surgical procedure that immobilizes the hip joint by fusing it together. Typically, it is reserved for cases of severe hip joint injury or chronic hip pain that cannot be managed by other surgical techniques.

In ORIF, an incision is made near the hip joint and metal plates are employed with screws or wires to hold the fractured bones in position. In percutaneous screw fixation, the fractured bones are held in position by inserting screws through small incisions or percutaneous punctures in the skin. Using bone grafts or metal mesh, the surgeon reconstructs the hip joint cavity during acetabular reconstruction.

8. Prognosis and Outcome of Old Fracture of Acetabulum Combined with Osteoarthritis

The prognosis and outcome of OAFHAs depend on a number of factors, including the severity and location of the fracture, the extent of the osteoarthritis, the patient's age and overall health, and the chosen treatment approach. It can result in chronic pain, stiffness, limited mobility and ROM. It can result in further joint injury and a worsening of symptoms if left untreated.

THA is a common surgical treatment option for acetabular fractures and osteoarthritis. It entails replacing the damaged hip joint with an artificial joint, which can provide significant pain alleviation, enhanced function, and improved life quality. THA efficacy depends on a number of factors, including the patient's age, overall health, and the durability of the implanted joint (Gautam et al., 2020). Depending on the specific circumstance, other surgical procedures, such as acetabular reconstruction, may also be considered. The prognosis and outcome of treatment for OAFHAs will depend on the severity and location of the fracture, the severity of the osteoarthritis, and the efficacy of the chosen treatment approach. Discussion given below in table which is conducted previously with different sample sizes follow up to different OAFHAs patients post-operatively in different part globally (Table 3) as we can see the result clearly shown that very few complications and revisions were recorded with passage of time and with higher HHS (Harris Hip Score) score which is a measure of dysfunction so the higher the score, the better the outcome for the individual. Results can be interpreted with the following :< 70 = poor, 70-80 = fair, 80-90 = good, and 90-100 = excellent.

Table 3: THA Outcomes in Patients with an Old Acetabulum Fracture and Osteoarthritis

S. No	Research	Sample size	Follow up (Years) Mean	Complications	Revisions	Harris Hip Score (Mean)
1	Grubor et al., 2015	96	1.5-2	Deep infection (n=4), respiratory (n=2), Dislocation (n=1)	5.3	87
2	Brown et al., 2019	42	5	Deep infection (n=1), Periprosthetic fracture (n=3), and Dislocation (n=3).	9.5	84
3	Panteli et al., 2022	62	4.5-5	Heteroscopic ossification (n=9)	16	85
4	Cantrell et al., 2022	446	10	Deep infection and dislocation	72	83
5	Lin et al., 2015	33	66	Pneumonia, urosepsis, hematoma, loss of fixation and line infection	6	77
6	Herscovici et al., 2010	22	75.3	Orthopedic surgery complications (10), UTI (2), ischemic attack (1)	18.2	74

9. Conclusion

An old acetabular fracture combined with osteoarthritis can result in chronic pain, stiffness, and limited mobility and surgical intervention may be required to better its functioning and alleviate the pain. THA is a common surgical treatment option for this condition, and it can provide significant pain relief and enhanced function. The significance of early diagnosis and intervention, the dependence of THA success on a number of factors, and the potential advantages of other surgical techniques, such as acetabular reconstruction, are among the most important considerations. Future research directions may include the development of patient-specific implants and the improvement of implant survival rates. Clinical implications and recommendations for the treatment of old acetabulum fractures accompanied by osteoarthritis include close collaboration with the healthcare team and selection of the optimal surgical technique based on patient-specific factors.

Conflict of Interest: None.

Ethics Approval and Consent to Participate: This manuscript is in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of First Affiliated Hospital of Xinjiang Medical University.

Consent for Publication: Not applicable.

Availability of data and materials: All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests: Authors declare that they have no competing interests.

Funding: Not applicable.

Authors' contributions: All authors contributed to the manuscript draft, conception and design. All authors read and approved the final manuscript."

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 14-24
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.300

Comparison Between Valproic Acid and Levetiracetam to Cognitive Function in Idiopathic Generalized Epilepsy

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Abstract
Epilepsy affects cognition through several mechanisms in a complex relationship. Valproic acid (VPA) and levetiracetam (LEV) are widely used due to their good efficacy and tolerability profiles. However, VPA may cause impairment of spatial working memory. There has not been much explanation regarding the negative cognitive side effects of LEV, few research suggests that LEV may even have a stimulating effect on cognition. Evidence of the comparative effects of anti-epileptic drugs on cognitive function is still limited. Objective: To investigate the effects of VPA monotherapy and LEV monotherapy on idiopathic generalized epilepsy patients. Methods: This was a cross-sectional observational study of patients with IGE taking either VPA monotherapy (n=28) or LEV (n=25). All patients underwent cognitive function assessment using MoCA-Ina, CDT, TMT A and B. Results: There was a significant association between 64.3% of patients taking VPA having MoCA-Ina score <26 vs. only 12% in patients taking LEV (OR 13.2, 95% CI 3.150-56.309, p<0.001), 35.7% of patients taking VPA vs. 0% in patients taking LEV on TMT-A score (p<0,001), and 46.4% of patients taking VPA vs. 4% in patients taking LEV on TMT-B score (OR 20.80, 95% CI 2.462-175.696, p 0,001). Neither patients with VPA monotherapy nor LEV monotherapy was statistically significant in CDT score (57.1% vs 36%, OR 0.422, 95% CI 0.139-1.277, p 0.170). Conclusion: This study showed patients with VPA have lower cognitive function than LEV. Further studies on cognitive function in epilepsy are recommended to provide information to assist in efficient drug selection decision-making for patients.

Keywords: Cognitive, Valproic Acid, Levetiracetam, Idiopathic Generalized Epilepsy

1. Introduction

Epilepsy is a neurological disease that is common in all age groups, races, social classes, and geographic locations. In developed countries, the annual incidence of epilepsy is estimated to be about 50 per 100,000 population and the prevalence is estimated to be about 700 per 100,000 population, the number is estimated to be higher in developing countries (Kusumastuti, 2019).

The goal of treating epilepsy with an anti-epileptic drug (AED) is to stop seizures without side effects that reduce the quality of life (Shih et al., 2013). AED is effective in reducing the risk of recurrent seizures, however, treatment does not alter the underlying disease and does not change the long-term prognosis. AED is associated with various side effects that should be considered during treatment. People with epilepsy are often affected by many other health problems. Seizures can cause morphological and functional changes in the brain, manifesting as cognitive and neuropsychological impairment. If epileptic seizures are not properly treated and controlled, they can lead to permanent cognitive dysfunction (Novak et al., 2022).

Cognitive impairment is a significant decline in the functioning of one or more domains of cognition (complex attention, executive function, learning, memory, language, perceptual-motor, or social cognition) from previous levels of performance (Asnakew et al., 2022; Aninditha, 2022). Difficulties with cognition are one of the most common problems that are more burdensome yet often overlooked. The most commonly reported cognitive problems associated with epilepsy are memory impairment, cognitive slowing, and attention deficits that negatively impact daily functioning, such as school work in children and driving ability in adults (Novak et al., 2022; Lodhi, 2012; Sayed et al., 2023).

Proper selection of AED can control epileptic seizures in almost 70% of epilepsy patients (Aninditha, 2022). Valproic acid is a widely used AED in both adults and children due to its good efficacy and tolerability profile with a broad spectrum of effectiveness for various seizures and epileptic syndromes (Romoli, 2019). However, it was found that clinically relevant doses of VPA can decrease spatial working memory (Pannangrong et al., 2019). Similar to valproic acid, levetiracetam (LEV) is widely used as it has a broad spectrum and has shown efficacy as monotherapy in patients newly initiated on the drug (El Sabaa et al., 2020). The consumption of valproate (VPA) and levetiracetam (LEV) has been reported to affect cognitive function, visuospatial memory to attention. The hippocampus plays an important role in learning, memory, and spatial navigation (Romoli et al., 2019; Pannangrong et al., 2019). Neuropsychological theories on hippocampal function have been related to inhibition, memory, and spatial function (Szabo, 2014). Neuropsychological assessment aims to assess the extent to which a particular skill is impaired and to determine the brain regions that may be damaged.

Although there are neuropsychological studies that have compared newer-generation drugs with older AEDs for high risk of cognitive impairment, the comparative effects of newer-generation drugs remain unclear (Khanna, 2019). However, evidence of the comparative effects of AED on cognitive function is still limited, while most recent studies have focused on comparing the efficacy and tolerability of AED (El Sabaa, 2020). Due to study limitations and the lack of research in Indonesia and specifically in Makassar that directly assesses this, a study was conducted to gain a better understanding of the comparative evaluation of valproic acid and levetiracetam as a single therapy for epilepsy on cognitive function. The main objective of this study was to determine the differences in cognition and memory tests through the MoCA-Ina, Clock Drawing Test (CDT), Trail Making Test (TMT) A and B questionnaires in the AED VPA and LEV groups.

2. Method

2.1 Research Design, Location and Time

This study was observational and cross-sectional study starting from August–December 2023. Subjects with epilepsy were recruited at Wahidin Sudirohusodo General Hospital Makassar, educational network hospitals, and private practices in Makassar, South Sulawesi, Indonesia.

2.2 Participant

Inclusion criteria are epilepsy patients who based on history, and/or EEG, have been diagnosed with idiopathic generalized epilepsy (IGE), are aged 12-60 years, can read and write, and consume AED monotherapy VPA for at least 6 months or LEV for at least 6 months. All of the patients provided their consent to participate in the research study. Exclusion criteria were IGE patients who changed AED more than twice, did not regularly control treatment, and had a history of stroke, brain infection, brain neoplasm, and moderate to severe head trauma.

2.3 Neuropsychological tests

Assessment of neuropsychological aspects consists of MoCA-Ina, Clock Drawing Test, and Trail Making Test A and B.

The Indonesian version of the MoCA test was used and validated in Indonesia for a population with cognitive impairment. MoCA-Ina evaluates cognitive domains such as memory, attention, concentration, executive functions, language, visuospatial abilities, capacity of abstraction, calculation, and orientation. The maximum score is 30, with a score below 26 suggesting cognitive impairment. In this study, the addition of 1 point was maintained for those patients with less than 12 years of schooling.

Clock Drawing Test (CDT) is a cognitive function instrument specifically for assessing visual memory and reconstruction, visuospatial skills, and executive function where the patient is asked to draw a clock showing a certain time. The normal score is 4, and further cognitive evaluation is needed if the score is <4.

Trail Making Test (TMT) is used to assess attention, executive and visuospatial skills, and psychomotor speed. The test consists of two parts (A and B). In the TMT-A test, subjects were asked to draw lines connecting 25 circles labeled with numbers; whereas in TMT-B, subjects were asked to alternately connect circles labeled with numbers and letters (1-A-2-B-3-C, etc.). The maximum time for TMT-A was 180 seconds, while TMT-B was 300 seconds.

2.3 Analyses

The research data was done using the SPSS version 27 program. Continuous variables were reported as medians (25th, 75th percentiles; IQR) for non-parametric data. The chi-squared and Mann–Whitney U tests were used to examine the differences between the VPA and LEV groups; a p-value < 0.05 was considered significant.

3. Results

3.1 Characteristics of the subjects

A total of 62 subjects were examined; of these, 3 did not meet the study criteria, and 6 refused to participate. The total sample analyzed was 53 subjects (Figure 1). Demographic characteristics based on age: the youngest age of epilepsy patients in this study was 12 years old, and the oldest was 57 years old, with a mean age of 23.75 ± 10.57 years. Based on gender, there were 24 male subjects (45.3%), while there were 29 female subjects (54.7%). The characteristics of the research subjects are summarised in Table 1.

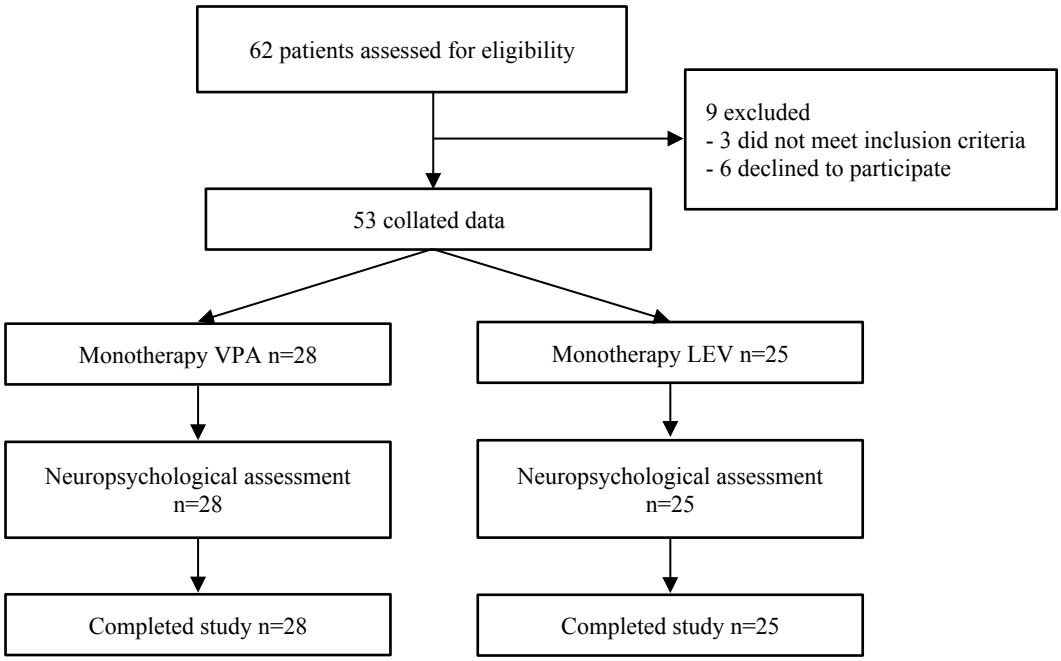

Figure 1: Patients' disposition study flow diagram

Table 1: Demographic profile and characteristics of patients in the VPA and LEV groups

Patient characteristics				
	Classification	**VPA (n=28)**	**LEV (n=25)**	**p-value**
Age (years)	12 – 16	8 (28,6%)	6 (24%)	0,162[a]
	17 – 30	14 (50%)	14 (56%)	
	31 – 45	6 (21,4%)	2 (8%)	
	> 45	0 (0%)	3 (12%)	
Sex	Male	17 (60,7%)	7 (28%)	0,035[a]
	Female	11 (39,3%)	18 (72%)	
Education level	Primary school	8 (28,6%)	4 (16%)	0,421[a]
	Middle school	5 (17,9%)	4 (16%)	
	Senior high school	11 (39,3%)	9 (36%)	
	High education	4 (14,3%)	8 (32%)	
Employment status	Employee	11 (39,3%)	4 (16%)	0,116[a]
	Unemployed	17 (60,7%)	21 (84%)	
History of illness	Febrile seizures	5 (17,9%)	9 (36%)	0,237[a]
	Mild head injury	3 (10,7%)	2 (8%)	1,000[a]
	Family history of epilepsy	1 (3,6%)	1 (4%)	1,000[a]
Type of IGE	GTCA	22 (78,6%)	18 (72%)	0,777[a]
	JME	2 (7,1%)	4 (16%)	
	CAE	1 (3,6%)	1 (4%)	
	JAE	3 (10,7%)	2 (8%)	

Values expressed in n (%)

[a]Chi-square test

3.2 MoCA-Ina test between the VPA group and LEV group

Table 2 presents the neuropsychological test results for the groups. This study found an association in the MoCA-Ina test where the cognitive function of the VPA group was significantly lower than that of the LEV group ($p<0.001$, 64.3% vs. 12%). Data is not normally distributed. Using the Mann-Whitney test, the median score in the VPA group was 25.00 (9.00-29.00), while the LEV group was 27.00 (23.00-30.00). On the MoCA-Ina domain, both groups showed indicators of cognitive impairment with worse performance on visuospatial ($p<0.05$), language ($p<0.01$), and delayed recall ($p=0.00$) task instruments as shown in Table 3.

Table 2: Cognitive performance in the VPA group and LEV group

Categories of differences in cognitive function							
		VPA (n=28)	LEV (n=25)	Total	OR	CI 95%	p-value
MoCA-Ina	Normal	10 (35,7)	22 (88)	32 (60,4)	13,2	3,150 – 56,309	0,000[a]
	Impaired	18 (64,3)	3 (12,0)	21 (39,6)			
CDT	Normal	12 (42,9)	16 (64)	28 (52,8)	0,422	0,139 – 1,277	0,170[a]
	Impaired	16 (57,1)	9 (36)	25 (47,2)			
TMT-A	Normal	18 (64,3)	25 (100)	43 (81,1)	-	-	0,000[a]
	Impaired	10 (35,7)	0 (0)	10 (18,9)			
TMT-B	Normal	15 (53,6)	24 (96)	39 (73,6)	20,80	2,462 – 175,696	0,001[a]
	Impaired	13 (46,4)	1 (4)	14 (26,4)			

[a]Chi-square test

Table 3: Cognitive domain scores in MoCA-Ina scores between VPA group and LEV group subjects

Parameter MoCA-Ina	VPA		LEV		p-value
	Min - max	Median	Min - max	Median	
Visuospatial	1,00 – 5,00	4,00	3,00 – 5,00	5,00	0,040[b]
Naming	1,00 – 3,00	3,00	2,00 – 3,00	3,00	0,075[b]
Attention	0,00 – 6,00	5,00	1,00 – 6,00	5,00	0,341[b]
Language	0,00 – 3,00	2,00	1,00 – 3,00	3,00	0,002[b]
Abstraction	0,00 – 2,00	1,00	0,00 – 2,00	1,00	0,852[b]
Delayed recall	2,00 – 5,00	4,00	2,00 – 5,00	5,00	0,000[b]
Orientation	2,00 – 6,00	6,00	5,00 – 6,00	6,00	0,609[b]
Total	9,00 – 29,00	25,00	23,00 – 30,00	27,00	0,001[b]

[b]Mann-Whitney test

3.3 CDT test between the VPA group and LEV group

The VPA and LEV groups did not have any significant differences in CDT scores (p-value of 0.170, p>0.05, 57.1% vs. 36%). Data is not normally distributed. According to the Mann-Whitney test, the median score for CDT in the VPA and LEV groups was 3.00 (0.00-4.00) compared to 4.00 (2.00-4.00).

3.4 TMT-A and TMT-B test between the VPA group and LEV group

In the TMT-A test, it was observed that the VPA group had a significantly lower level of cognition than the LEV group (p<0.001, 35.7% versus 0%). Data is not normally distributed in both TMT-A and TMT-B. The VPA and LEV groups had a median TMT-A score of 106.50 (30.00-243.00) and 82.00 (35.00-131.00) based on the Mann-Whitney test. The VPA group and the LEV had a significant difference in TMT-B scores (p = 0.001, 46.4% vs. 4%), as shown by similar results. The median scores for TMT-B in the VPA and LEV groups were 271.50 (48-643) versus 127.00 (55.00-347.00) using the Mann-Whitney test.

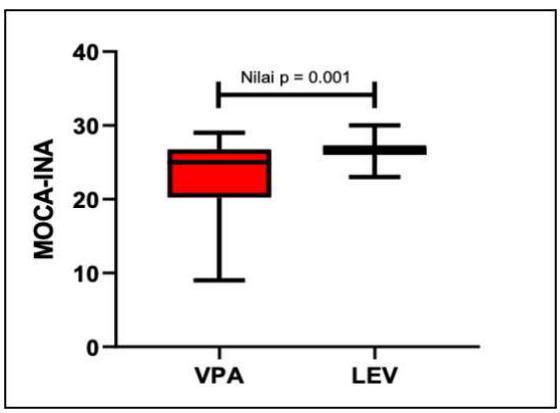

Figure 2: The median score of MoCA-Ina in the VPA group and LEV group

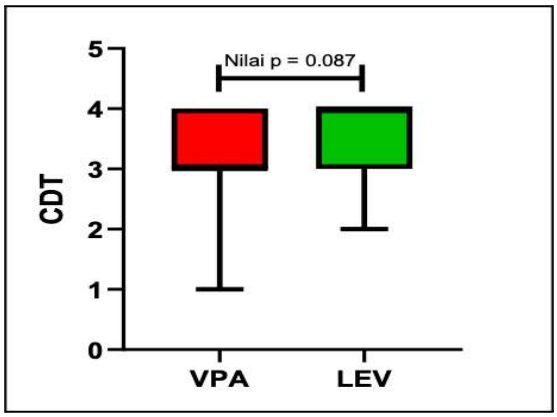

Figure 3: The median score of CDT in the VPA group and LEV group

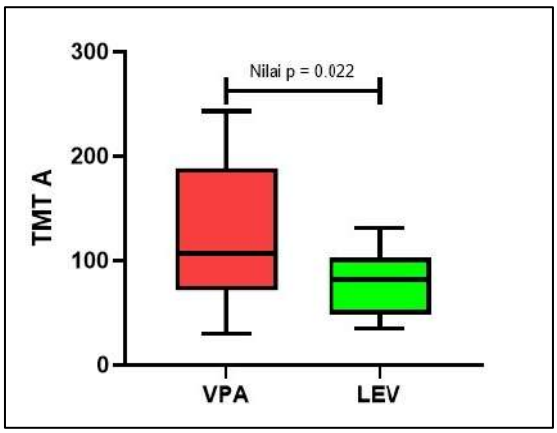

Figure 4: The median score of TMT-A in the VPA group and LEV group

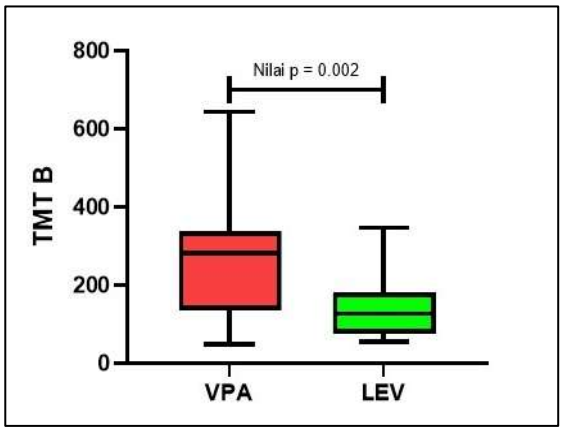

Figure 5: The median score of TMT-B in the VPA group and LEV group

4. Discussion

The study involved 28 subjects receiving VPA monotherapy treatment, and 25 patients receiving LEV monotherapy treatment. Several studies have demonstrated that the AED has negative effects on cognition (Novak et al., 2022; Lodhi, 2012). The age range in this study was between 12 and 57 years, with a mean age of 23.75 ± 10.57 years. The male-to-female ratio was 24:29, with a significant difference between the two (p 0.035). The use of age- and sex-corrected normative data prevented further analysis controlling for this difference. The two groups had no differences in education (p = 0.421).

The median MoCA-Ina score was 25.00 (9.00-29.00) in the VPA group and 27.00 (23.00-30.00) in the LEV group. In our study, 21 patients scored below the limit set in the MoCA-Ina questionnaire, of which 18 subjects (64.3%) were found to be impaired in the VPA group. Similar to previous studies, the use of VPA results in a decrease in MoCA-Ina scores. Romoli (2019) mentioned in animal studies that used location tests to evaluate spatial memory, there was a relationship between VPA and cognitive deficits thought to be caused by the suppression of hippocampal neurogenesis. In contrast to VPA, levetiracetam has had significant positive effects on the cognitive profile of epilepsy patients in different studies (Khanna, 2019; El Sabaa, 2020; Koo et al., 2013). According to this study, MoCA-Ina scores decreased by 12.0% for three people in the LEV group. In a randomized clinical trial, LEV was well tolerated and improved the performance of spatial memory and executive function tasks in patients with Alzheimer's disease and epileptiform activity (Vossel et al., 2021). In this study, cognitive impairment was reported mainly due to the use of VPA on several analyzed MoCA-Ina parameters. The domains of impairment were visuospatial (p 0.04), language (p 0.002), and delayed recall (p 0.00). Other findings in a cross-sectional study by Harahap (2022) of 155 patients with epilepsy, were reported similarly in our study with impaired cognitive impairment in several MoCA-Ina domains such as visuospatial and executive function, naming, attention, language, abstraction, delayed recall and orientation ($p<0.001$). While MoCA-Ina domain scores cannot fully replace neuropsychological tests, they can complement MoCA-Ina total scores in the systematic assessment of early neurocognitive disorders. This can help to conserve the use of neuropsychological tests for patients who are more likely to require further assessments.

A total of 25 subjects (47.2%) with CDT < 4 results requiring further cognitive evaluation with VPA group subjects was found to be more at 16 people (57.1%) than the LEV group 9 people (36%). Comparison of VPA and LEV groups was found to be not meaningful to CDT in this study ($p = 0.170$). Claudya (2018) with a similar study conducted a study with AED monotherapy carbamazepine and phenytoin the results there was no significant difference between the two groups. A case-control involving 80 epilepsy patients also reported no significant difference in the CDT examination ($p=0.060$) (Njamnshi et al., 2020). A control sample study involving 371 subjects reported a significant correlation between CDT and epilepsy duration (p 0.013) (Tedrus et al., 2020). Furthermore, a study by Yaksa (2018) showed a significant difference between CDT with the onset of seizure ($p < 0.05$). While the CDT scoring methods are valuable for their objectivity and ease of use, they cannot often assess specific characteristics of neurocognitive disorders in each phase of the task. This limits their usefulness in analyzing performance data.

In the TMT-A test, the mean value was 106.50 (30.00 - 243.00) in the VPA group and 82.00 (35.00 - 131.00) in the LEV group where there was a significant difference between the two ($p < 0.05$). Furthermore, the TMT-B test results with a mean value of 281.50 (48.00 - 643.00) in the VPA group and 127.00 (55.00 - 347.00) in the LEV group with a significant difference between the two groups (p 0.002). A previous study has shown the length of seizure duration was associated with poor TMT-B performance, and the use of AED polytherapy was associated with worse TMT-A outcomes (Hasegawa, 2023). Liu et al. (2016) associated interictal epileptiform discharges (IEDs) affecting cognitive performance with TMT-B outcome ($p=0.012$). The study by Hasegawa (2022) also revealed that minimal AED use and a higher education level were associated with a shorter time to complete TMT-A and TMT-B. This study supports the results of impaired executive function in this study.

There was a difference in significance between the CDT and TMT examinations (TMT-A and TMT-B), where the TMT results showed a significant difference between the VPA and LEV groups, while the CDT had no significant difference between the two groups. It should be noted that most neuropsychological tests do not only assess one particular domain or skill component. CDT is a brief test that permits the exploration of a wide range of cognitive processes including attention, understanding of instructions, planning, visuospatial ability, visual construction, programming and graphomotor performance, numerical knowledge, abstract thinking, symbolic representation, and semantic memory (Aguilar-Navarro et al., 2018). On the other hand, the TMT-A test results are related to cognitive domains such as visual scanning, attention, and processing speed, while TMT-B results are associated with more complex cognitive abilities, including working memory, complex set maintenance, switching, and mental flexibility (Du et al., 2022; Fellows et al., 2017). Similarly, hippocampal dysfunction does not cause a single deficit. The identification and quantification of cognitive function deficits obtained from

neuropsychological tests further enable the specification of dysfunctional processes that are characteristic of a particular disorder (Szabo, 2014).

Many other factors potentially contributing to cognitive dysfunction have been described, including age, disease duration, etiology, frequency of awakenings, and psychiatric disorders, but AED has been the focus of increased research attention as it represents a potentially modifiable risk factor (Novak et al., 2022; Njamnshi et al., 2022; Tedrus et al., 2020; Khalife et al., 2022). Along with the facilitation of the mitogen-activated protein kinase pathway, VPA modulates neurogenesis and blocks cognitive decline-induced hippocampal seizure activity (Romoli, 2019). It has been observed that VPA can lead to a reduction in spatial working memory. This effect is associated with a decrease in cell division required for neurogenesis in the hippocampus. The hippocampus is a crucial structure for spatial working memory and recognition that emerges as a main site of VPA action in causing cognitive decline (Pannangrong et al., 2019). Although some studies have shown a decrease in cognitive performance with VPA, other studies have reported that LEV has a favorable effect on cognition in attention, memory, and executive function (El Sabaa et al., 2020; Perkins et al., 2023). LEV reverses cognitive decline, behavioral abnormalities, hippocampal remodeling, and synaptic dysfunction (Sanchez et al., 2012). LEV is suggested to improve cognitive function, enhance cholinergic function, and prevent the formation of inflammation in neurons, neuronal apoptosis processes, and oxidative vulnerability. Administration of LEV can ameliorate the degeneration of cholinergic neurons due to inflammatory processes and oxidative vulnerability that can lead to several dysfunctions including impaired learning, memory, and attention (Mani, 2023). Data regarding AED-related cognitive dysfunction are widely reported involving the control of other confounding factors; however, cognition-related relationships are complex, and the contribution of AED cannot be easily separated from other factors (Foster et al., 2020). Thus, the outcomes of this research may not reflect or easily apply to actual clinical practice.

Enhancing the diagnosis and treatment, especially of elderly epilepsy patients requires a comprehensive understanding of cognitive decline and its associated risk factors (Miller et al., 2016). This study demonstrates the importance of early screening for cognitive impairment in epilepsy patients which should be done in conjunction with follow-up treatment, and this will improve the overall quality of life of epilepsy patients.

This study has several limitations. Firstly, the type of IGE, disease duration, length of AED consumption, and controlled seizures were not further differentiated. The data in this study may not be sufficient to determine certain effects that change over time. However, the design of this study provided an assessment of the effects of VPA and LEV monotherapy on cognitive function in IGE patients. Secondly, it should be noted that this study was not conducted as a randomized controlled trial. Thirdly, testing was done only once, although we applied advanced statistical methodology to look at confounding factors, which may have biased the results.

In conclusion, we have demonstrated that patients administered VPA exhibited lower cognitive function than those given LEV. Further research is recommended to provide information to assist in efficient drug selection decision-making for patients.

Author Contributions: Conceptualization, N.Y.N., A.D.W., and A.M.; Methodology, N.Y.N. and A.D.W.; Software, I.W.; Validation, A.D.W., A.M., M.A., and M.I.B.; Formal Analysis, N.Y.N. and I.W.; Investigation, N.Y.N.; Resources, N.Y.N. and A.D.W.; Data Curation, A.D.W. and M.I.B.; Writing – Original Draft Preparation, N.Y.N., A.D.W., and A.M.; Writing – Review & Editing, N.Y.N., A.D.W., A.M., M.A., and M.I.B.; Visualization, A.M. and M.I.B.; Supervision, A.D.W., A.M., M.A., and M.I.B.; Project Administration, N.Y.N. and A.D.W.

Funding: This research received no external funding

Conflicts of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics approval: All subjects gave their informed consent for inclusion before they participated in the study. The researchers have obtained ethical clearance from the Biomedical Research

Ethics Commission at the Faculty of Medicine, Hasanuddin University Makassar with No. 735/UN4.6.4.5.31/PP36/2023.

Acknowledgments: The author thank all of the participants who contributed to the study.

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Appendix A

The mean, SD, median, and range score of VPA group and LEV group to Neuropsychological tests

Group	VPA					LEV					p-value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
MoCA-Ina	23,50	4,44	25,00	9,00	29,00	26,80	1,61	27,00	23,00	30,00	0,001*
Visuospatial	3,79	1,20	4,00	1,00	5,00	4,44	0,65	5,00	3,00	5,00	0,040*
Naming	2,50	0,75	3,00	1,00	3,00	2,84	0,37	3,00	2,00	3,00	0,075
Attention	4,32	1,59	5,00	0,00	6,00	4,80	1,12	5,00	1,00	6,00	0,341
Language	1,71	1,12	2,00	0,00	3,00	2,60	0,58	3,00	1,00	3,00	0,002*
Abstraction	0,96	0,69	1,00	0,00	2,00	1,00	0,71	1,00	0,00	2,00	0,852
Delayed recall	3,61	1,07	4,00	2,00	5,00	4,56	0,87	5,00	2,00	5,00	0,000*
Orientation	5,82	0,77	6,00	2,00	6,00	5,96	0,20	6,00	5,00	6,00	0,609
TMT-A	126,11	65,93	106,50	30,00	243,00	79,24	30,61	82,00	35,00	131,00	0,022*
TMT-B	256,18	142,02	281,50	48,00	643,00	135,88	66,81	127,00	55,00	347,00	0,002*
CDT	3,14	0,93	3,00	1,00	4,00	3,56	0,65	4,00	2,00	4,00	0,087

SD: standard deviation

Mann-Whitney test

The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 25-29
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.301

Prevalence, Clinical Profile, and Outcomes of Diabetic Ketoacidosis in Pediatric Patients at the Intensive Care Unit of King Fahad Hospital, Al-Baha, Saudi Arabia

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Abstract
Introduction: Diabetic ketoacidosis (DKA) is a severe acute complication of type 1 diabetes mellitus (T1DM) leading to pediatric morbidity and complications. Objectives: Analyze the prevalence, clinical profiles, and outcomes of DKA in children. Methodology: This retrospective cohort study explored the diabetic ketoacidosis in type I diabetes mellitus at the Pediatric Intensive Care Unit at King Fahad Hospital at Albaha, Saudi Arabia, between January 2022 and December 2023. Participants included children aged < 14 years. Data were collected from medical records of all admitted patients. The main outcomes were the average time needed to recover from DKA, and patient survival rates. Results: Total of 180 DKA cases were reviewed, and observed that 68.3% were recurring cases of type 1 diabetes mellitus admitted to PICU due to poor treatment adherence. The remaining 31.7% were newly diagnosed as diabetes mellitus due to the onset of DKA. The average patient age was 8.9 ([4.0]) years, with females representing two-thirds of this cohort. The most frequent precipitating factors were non-adherence to treatment (90%) and previous infections (10%). Common symptoms included abdominal pain (78.3%), as the principal source of decompensation. Conclusion: Recognizing characteristic symptoms is vital for early diagnosis, emphasizing the importance of a timely and well-structured management approach for improved

outcomes, reduced morbidity, improved recovery times, and shortened hospital stays. Moreover, no deaths were reported in this study.

Keywords: Children, Diabetes Ketoacidosis, Type1 Diabetes Mellitus (T1DM), Pediatric Intensive Care Unit (PICU)

1. Introduction

Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune condition that leads to a total or partial loss of insulin-producing cells within the pancreas. Consequently, patients with T1DM require external insulin sources to manage their energy metabolism (Burcul, Ivana, et al. 2019). Notably, recent studies and literature reviews reveal an annual global growth of 3–5% in the incidence of T1DM among younger populations (McKenna, Amanda, et al 2021). The prevalence of diabetic ketoacidosis (DKA), a serious complication of diabetes, at the onset of T1DM in children and adolescents aged 0–18 years continues to increase, as observed in recent 2013–2014 survey data (Rabbone, Ivana, et al. 2020). Data collection was most extensive in the Europe (76%), while sub-Saharan Africa presented the least amount of data, 8% (Patterson, Chris, et al 2014). An alarming number of T1DM onset cases were reported annually in the United States (13,000), India (10,900), and Brazil (5,000) (Patterson, Christopher C, et al 2019). The rates of DKA at the time of diagnosis diverged greatly, varying from 12.8–80%. The highest rates were documented in the United Arab Emirates, Saudi Arabia, and Romania, whereas the lowest was found in Sweden, the Slovak Republic, and Canada (Forouhi, Nita Gandhi, and Nicholas J2010, Usher-Smith, J. A, et al. 2012). The European and North American countries reported high to intermediate DKA incidences; Africa demonstrated intermediate occurrences; and Asia reported low rates (Lee, Hye Jin, et al. 2017). Studies indicate an extensive range of reported DKA incidences linked to initial T1DM diagnosis, from 15–67% across differing geographic locations (Roche, Edna F., et al. 2016). Living in a high-incidence region or possessing a higher level of education was protective factors for DKA. Serious complications of DKA extend beyond cerebral edema to hyperchloremia, hypokalemia, hyponatremia, shock, acute kidney injury, arrhythmias, and thrombotic thrombocytopenic purpura (Peng, Wei, et al 2021). Enhanced understanding of the pathophysiology and improved implementation of care guidelines and pathways for DKA have been instrumental in the significant reduction of DKA-related mortality in recent years (Abbas, Qalab, et al. 2018). In Saudi Arabia, epidemiological studies spanning 1985–2016 suggest a temporal shift in pediatric DKA incidence, fluctuating between 37.7% and 79.8% (Al Shaikh, Adnan, et al. 2019, Hornstein, Henriette, et al. 2018). A recent study identified precipitating factors for severe DKA, which include upper respiratory tract infections (URTI), pneumonia, unhealthy lifestyle, and excessive sugar consumption (Danne, Thomas, et al. 2018).

2. Objectives

In this study, we aimed to determine the prevalence of DKA in the Albaha region, focusing on the clinical features of patients who were admitted to the Pediatric Intensive Care Unit (PICU) at King Fahad Hospital in Albaha. Moreover, symptoms and signs, laboratory results, management, and complications linked to the disease following the application of a standardized management protocol, were investigated.

3. Methodology

This retrospective cohort study explored the DKA in T1DM at the PICU of King Fahad Hospital at Albaha, Saudi Arabia, between January 2022 and December 2023. Participants included children aged < 14 years, who were either newly diagnosed with DKA or have T1DM and were admitted due to DKA. Patients older than 14 years or those diagnosed with type 2 diabetes mellitus, were excluded. To gather the required data, the patient's files were examined, extracting information on age, sex, weight, height, clinical indications and hydration status. Moreover, essential data such as various laboratory tests were collected, along with a confirmed history of insulin usage and other medication adherence. The complications associated with DKA were also recorded. The guidelines from the Saudi Ministry of Health (MOH) protocol and International Society for Pediatric and Adolescent Diabetes (ISPAD) were applied (Wolfsdorf, Joseph I., et al 2018). Clinical practice consensus was followed for diagnosing

DKA: blood glucose level > 11 mmol/L; presence of ketonemia and ketonuria; blood gas analysis pH < 7.3; and bicarbonate level (HCO3) < 15 mmol/L. Subsequently, DKA was classified into three degrees: (1) mild, arterial pH decreased to between 7.2 and 7.3 and serum bicarbonate level decreased to 10–15 mEq/L; (2) moderate, arterial pH of 7.1–7.2 and a bicarbonate level of 5–10 mEq/L; and (3) severe, arterial pH below 7.1 and a bicarbonate level < 5 mEq/L. Patient management followed the MOH protocol, employing strategies such as rehydration, insulin infusion, and correction of acidosis and electrolytes. Subsequently, the length of stay in the intensive care unit and patient survival rates were recorded. This study was approved by the Ethical and Research Committee of King Fahad Hospital Albaha and aligned with the principles of the Declaration of Helsinki. The data gathered was analyzed using Microsoft Excel 2020. A P value < .05 at 95% confidence interval was considered statistically significant.

4. Results

Our study included 621 patients admitted to the PICU, of which 180 were diagnosed with DKA, representing 29% prevalence (Table 1). The average age of the patients was 8.9±4 years, ranging from 1 month to 14 years. Female comprise 66.7% (n=120) of the participants, while male constitute 33.3% (60 patients). Notably, 31.7% (n=57) had DKA as the first presentation in newly diagnosed children, while 123 (68.3%) patients with an existing T1DM diagnosis presented at the PICU with DKA. The DKA severity showed that 39.4% (n=71) are moderate, 32.8% (n=59) are severe, and 27.8% (n=50) are mild. The primary symptoms observed upon presentation were abdominal pain (78.3%, n=141), vomiting (73.9%, n=133), nausea (32.2%, n=58), polyurea (28.3%, n=51), dehydration (15.6%, n=28), headache (15%, n=27), kussmaul breathing (11.7%, n=21), drowsiness (8.3%, n=15), weight loss (7.8%, n=14), and polydipsia (7.2%, n=13), which were significant (P=.005). The average blood sugar at admission was 430.2±160 mg/dL. Metabolic acidosis, another sign of DKA, was noted in varying degrees of severity across the patient pool. The average bicarbonate level was 10.5 mmol/L and the average osmolarity at time of diagnosis was 305.8 mOsm/Kg. An electrolyte check was conducted and revealed hyponatremia in 22.8% (n=41), hyperkalemia in 5.6% (n=10), and hypokalemia in 3.9% (n=7) of the patients. Majority of the known patients with T1DM (90%), had DKA developed due to medication non-compliance, while infection was identified in 10% as the trigger (P=.04). On average, patients recovered from DKA in 14±6.8hours. Newly diagnosed patients had the longest duration to recover from DKA at 24 hrs. Two patients were confirmed to have hypothyroidism. One patient who developed insulin-dependent diabetes mellitus at the age of 7 months, presented with severe DKA due to an autosomal recessive genetic variant in the LRBA gene (Alzahrani, Ali., et al. 2023). All patients received intravenous hydration before insulin administration. The treatment approach and outcomes showed no significant difference between newly diagnosed patients and those with known T1DM. No episodes of arrhythmia, cerebral edema, or death were recorded in this study.

5. Discussion

The prevalence of DKA in this study was 29%, which aligns with the previous findings from the Albaha region; however, it was significantly higher compared to the nationwide average prevalence of 9.4–14% (Al-Ghamdi, Ahmed Hassan, and Abdelhameed Ahmed Fureeh 2018). Our study demonstrated a conspicuous sex disparity, with nearly two-thirds of the patients (66.7%) being female while male accounts for 33.3%. This translates to a female-to-male ratio of 2, and corroborates the trend reported in previous studies (Satti, Satti Abdulrahim, Imad Yassin Saadeldin, and Ali Saeed Dammas 2013). A substantial 31.7% of the admitted patients presented DKA as the initial indicator of their diabetes diagnosis, while 68.3% of them were already known to have diabetes (P=.007; 95%CI [12.3-35.7]), similar to other studies. These variations extended beyond symptoms to include differences in initial presentation, delay before symptom recognition, and outcomes of conducted laboratory tests. Studies bearing equivalent prevalence rates are documented not only within the country but are also corroborated by studies conducted across Europe (Patterson, Chris C., et al. 2012). However, the present study varies relatively from the earlier findings in the region, where an immensely higher proportion (82.1%) of newly diagnosed patients was reported. This highlights the efficacy of fluid and insulin treatment in combating severe acidosis conditions (Robert, Asirvatham Alwin, et al. 2018). Among those who are newly diagnosed with diabetes, the median recovery time-lagged at approximately 24 hours, which was significantly longer than the recovery time at 15 hours for patients with pre-existing condition (p=.005). Moreover, the newly diagnosed group exhibited notable severity

in symptoms such as heightened hyperglycemia, advanced stages of acidosis, hyperosmolarity, and increased clinical complications, which aligns with the established research trends (Patterson, Chris C., et al. 2012, Robert, Asirvatham Alwin, et al. 2018). This study aligns with the general practices by employing a continuous infusion of smaller dosages of insulin (0.05–0.1 IU/kg/hr) to avert hypoglycemia. Despite the global guidelines advocating for subcutaneous boluses, additional studies are needed to ascertain the outcomes of this administration approach. Notably, 90% of the patients developed DKA due to missed or adjusted insulin dosages. Only a small proportion of DKA cases (10%) were associated with previous infections or febrile illnesses, supporting the findings of few studies, but contrasting that of a study in India, which highlight that infections are the most common DKA precursor (Usher-Smith, J. A., et al 2012). In terms of severity distribution, moderate DKA emerged as the most common presentation at 39.4% (n=71), followed by severe at 32.8% (n=59), and mild at 27.8% (n=50), which is consistent with the study by McKenna A et a 2021. Conversely, Peng et al., reported that mild DKA was the most prevalent (Peng, Wei, et al. 2021). Abdominal discomfort was the most common symptom (78.3% [n=141]), followed by vomiting (73.9% [n=133]), and nausea (32.2% [n=58]), corroborating the findings of other studies (Robert, Asirvatham Alwin, et al. 2018, Albuali, Waleed H., and Mohammad H. Al-Qahtani 2022). No mortality was reported in this study, which is attributed to the adoption of clear protocols for diagnosing and treating hospitalized patients. Given the discrepancies in the reported findings, further studies on T1DM and DKA are warranted.

6. **Conclusion**

DKA is a common and major complication of T1DM, resulting in substantial increase in PICU admissions and morbidity if not promptly detected and managed. Recognizing characteristic symptoms is vital for early diagnosis, emphasizing the importance of a timely and well-structured management approach for improved outcomes. The implementation of the MOH protocol in our unit not only enhanced the quality of care but also reduced morbidity, improved recovery times, and shortened hospital stays. Moreover, no deaths were reported in this study.

Table1: Categorizes different statistics related to admitted patients with DKA seen at the Pediatric Intensive Care Unit.

variable	**Pts number**	**percent**	**P value**
PICU admission	621		
DKA	180	29%	
Gender			.007
Female	120	66.7%	
Male	60	33.3%	
Age			.006
<5 yr.	19	10.6%	
5-10 yr.	45	25%	
>10 yr.	116	64.4%	
Diagnosis			.007
New	57	31.7%	
K/c	123	68.3%	
Severity			.08
Moderate	71	39.4%	
Severe	59	32.8%	
mild	50	27.8%	
Risk factors			.04
Infection	18	10%	
Doses	162	90%	

Pts: patients, DKA: Diabetes ketoacidosis, P value: Probability of chance

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: This study approved by ethical, research committee in King Fahad Hospital, Albaha, Saudi Arabia.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 30-36
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.302

The Value of Jejunal Tube in the Treatment of Severe Acute Pancreatitis

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Abstract
Background: Severe acute pancreatitis (SAP) is associated with high morbidity and mortality due to the development of pancreatic and an infection that follows extra-pancreatic necrosis, and multisystem organ failure (MOF). Objective: To determine the value of jejunal tube in the treatment of severe acute pancreatitis. Methods: A cross-sectional study was conducted at Saidu group of teaching hospitals, Saidu Sharif Swat, Pakistan, which was performed between July 2020 and March 2022. The total number of patients in our study was 112. The number of Male patients was 33 and females were 79. In 112 consecutive patients who underwent for blood tests and Procedures. We did CT scan for all patients to determine the grade of pancreatitis. Data was tabulated and analyzed by SPSS. Results: In a current study total of 112 patients were enrolled with mean±SD age of 52.61±5.54 years. The maximum age was 61 and minimum ages were 41. The mean±SD of serum lipase was 639.56±209.9. The maximum serium lipase was 1107 and minimum serium lipase was 299. The mean±SD of time of patients' recovery was 5.96±1.09. The maximum time of patient's recovery was 10 and minimum time of patient recovery was 5. The mean±SD of recovery days was 5.63±0.78. The maximum recovery days of patients were 9 and minimum recovery time was 5. Bar graph showing gender distribution in which female patients were 79 and male patients were 33. In this graph female patients were more as compared to male patients. The number of patients with abdominal pain was 109. The number of patients came to hospital with nausea was 86. The number of patients present with vomiting was 26. The patients who have gall stone were 51. The effectivenss of J-Tube in patients was 33. The complication was noted in 4 patients and the jejunal tubes were passed to 36 patients. Mild pancreatitis patients were 22%, moderate pancreatitis patients were 48% and severe pancreatitis patients were 30%. P- value effectiveness of J-Tube in age group was 0.477. P- value effectiveness of J-Tube in gender was 0.09. The P-value complication of the gender group were 0.18. Conclusion: The recovery time of patients from severe acute pancreatitis was 5 to 10 days. Jejunal tube is more effective in the patients who has more vomiting in severe acute pancreatitis. Jejunal tube is passed to the patient as soon as possible when patient is diagnosed with sever acute pancreatitis. In severe acute pancreatitis patients have more vomiting and abdominal pain. We can diagnose patient with sever acute pancreatitis on Serium lipase blood test. In our study females were more as compare to males.

Keywords: Severe Acute Pancreatitis (SAP), Multi Organ Failure (MOF), Acute Pancreatitis (AP), Enteral Nutrition (EN)

1. Introduction

Severe acute pancreatitis (SAP) is associated with high morbidity and mortality due to the development of pancreatic and an infection that follows extra-pancreatic necrosis, and multisystem organ failure (MOF) (Zerem 2014). The most frequent specific gastrointestinal diagnosis for inpatient hospitalization is acute pancreatitis (AP), with annual inpatient expenditures estimated to be $2.6 billion (Krishna et al., 2017). Even with the greatest standards of care being reached in the modern period, acute pancreatitis secondary to gallstones still poses a challenge to clinicians. Gallstones are the etiological cause in 30–50% of cases (Sangrasi et al., 2014). About 25% of patients with acute pancreatitis (AP) progress to severe acute pancreatitis (SAP) (Beger et al., 2007). Persistent alcohol misuse and gallstones continue to be the main causes of AP (Yang et al., 2020). The three most typical causes of AP are idiopathic, alcohol-associated, gallstone and biliary-related. The bulk of AP instances are caused by these three factors (Chatila et al., 2019). In our nation, the prevalence of pancreatitis is rising daily, and gallstone disease is one of the main causes of this condition (Ahmad et al., 2018). A patient presented with abrupt onset vomiting and nausea along with epigastric pain radiating to the back (Shah et al., 2018). Particular dietary difficulties arise from severe acute pancreatitis (Lodewijkx et al., 2016). Since it causes fewer infections, major problems, and fatalities than intravenous feeding, feeding liquid nutrition into the stomach or small bowel through a tube is the preferred method. Nonetheless, the best time to begin tube feeding is during the first 48 hours in order to maximize its effectiveness (Dutta et al., 2020). For the majority of patients, early enteral nutrition (EN) beginning within 24 to 48 hours is ideal. Due to its ability to reduce gastrointestinal dysmotility brought on by pancreatic inflammation, EN preserves the integrity of the gut barrier (Jabłońska et al., 2021). Two of the following three criteria form the basis of the diagnosis: (1) Serum lipase or amylase levels more than three times the upper normal range; (2) abdominal pain suggestive with pancreatitis; and (3) distinctive findings from abdominal imaging. The two most common causes of AP are alcohol (25–35%) and gallstones (40–70%) (Lakananurak et al., 2020). Therefore, early dietary management is crucial for Severe acute pancreatitis (SAP) patients. It has been discovered that enteral nutrition (EN) is superior at preserving the integrity and structure of the gut mucos (Song et al., 2018). Increased intestinal permeability combined with metabolic disturbances raises the risk of infections and multiorgan failure, which in turn leads to a worse prognosis and worse survival rates for SAP patients in the absence of early therapies (Ramanathan et al., 2019). The following criteria can be used to diagnose acute pancreatitis: (1) abdominal pain that is consistent with the illness (such as epigastric abdominal pain with potential radiation to the back); (2) lipase or amylase levels that are greater than three times the upper limit of normal; and (3) distinctive imaging features on CT, MRI, or ultrasound that indicate acute pancreatitis (Garber et al., 2018). Compared to USG, computed tomography (CT) is more sensitive and accurate at both diagnosing and demonstrating the extent of the condition. For the majority of patients, CT is an essential diagnostic technique for determining the etiology of endocrine and exocrine pancreatic insufficiency. Of all the gastrointestinal illnesses, pancreatitis is one of the most complicated and clinically difficult (Raghuwanshi et al., 2016). However, guidelines from the pancreatic and gastroenterology societies state that when patients cannot tolerate an oral diet for up to seven days, tube feeding is required, regardless of the severity of the diseas (Bakker et al., 2014). It is acknowledged that jejunal feeding is effective in treating severe acute pancreatitis (AP). Early oral feeding (EOF) is thought to be harmful during the initial stages of AP (Pupelis et al., 2006). When administered early, enteral feeding has the potential to shorten hospital stays in individuals suffering from acute pancreatitis (Vaughn et al., 2017). Maintaining the functional and anatomical integrity of the intestinal mucosal barrier appears to be just as crucial in the management of individuals with severe acute pancreatitis as obtaining "pancreatic rest." The largest immune system organ in the human body is the gastrointestinal tract. It makes up 80% of the tissue that produces immunoglobulins and 65% of the entire immune tissue (Ioannidis et al., 2008). Nutritional care is necessary for all Severe acute pancreatitis (SAP) patients, as they are at risk for malnutrition. One of the debilitating conditions that cause admission to the intensive care unit (ICU) is severe acute pancreatitis (SAP). For patients with SAP or pSAP, enteral feeding within 48 hours of admission is a safe and effective treatment option (Song et al., 2018). In patients with SAP, early enteral feeding via NG was not less effective than NJ (Singh et al., 2012). For patients with anticipated severe acute pancreatitis, enteral feeding reduces the incidence of infectious complications, pancreatic infections, and mortality in a statistically significant and clinically meaningful way. Ten percent or so of individuals with acute pancreatitis experience infectious complications (Petrov et al., 2008).

2. Materials and Methods

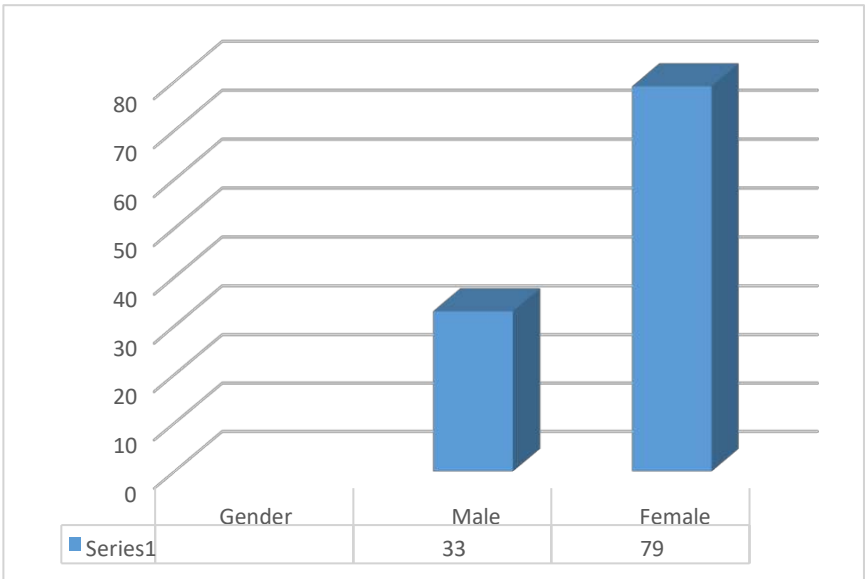
A cross-sectional study was conducted at Saidu group of teaching hospitals, Saidu Sharif Swat, Pakistan, which was performed between July 2020 and March 2022. The total number of patients in our study was 112. The number of Male patients was 33 and females were 79. In 112 consecutive patients who underwent for blood tests and Procedures. We did CT scan for all patients to determine the grade of pancreatitis. Data was tabulated and analyzed by SPSS.

3. Results

Table 1: Mean age, Serum lipase, Time of patient's admission and Recovery days of all the enrolled patients (*n=112*)

Variables	Minimum	Maximum	Mean±SD
Age (Years)	41	61.00	52.61±5.54
Serum lipase	299	1107.00	639.56±209.9
Time of patient's admission	5	10	5.96±1.09
Recovery days	5	9	5.63±0.78

Total of 112 patients were enrolled with mean±SD age of 52.61±5.54 years. The maximum age was 61 and minimum age was 41. The mean±SD of serum lipase was 639.56±209.9. The maximum serium lipase was 1107 and minimum serium lipase was 299. The mean±SD of time of patient's recovery was 5.96±1.09. The maximum time of patient's recovery was 10 and minimum time of patient's recovery was 5. The mean±SD of recovery days was 5.63±0.78. The maximum recovery days of patients were 9 and minimum recovery time was 5.



Bar graph showing gender distribution in which female patients were 79 and male patients were 33. In this graph female patients were more as compared to male patients.

Table 2: Patient characteristics of enrolled patients (n=112)

Gender	Frequency	Percentage
Male	33	29.5
Female	79	70.5
Abdominal Pain	109	97.3
Nausea	86	76.8
Vomiting	26	23.2
Pancreatitis Grade		
Mild	25	22.3
Moderate	54	48.2
Severe	33	29.5
Gall Stone		
YES	51	45.5
NO	61	54.5
Effectiveness of J-Tube	33	29.5
Complication	4	3.6
Jejunal Tube	36	32.1

Patient characteristics of enrolled patients in table 2 were (n=112). The frequency of male patients was 33 and its percentage was 29.5. The frequency of female patients was 79 and its percentage was 70.5. The frequency of abdominal pain in patients was 109 and its percentage was 97.3. The frequency of nausea in patients was 86 and its percentage was 76.8. The frequency of vomiting in patients was 26 and its percentage was 23.2. The frequency of mild pancreatitis was 25 and its percentage was 22.3. The frequency of moderate pancreatitis was 54 and its percentage was 48.2. The frequency of sever pancreatitis was 33 and its percentage was 29.5. The frequency of gall stone was present in 51 patients and its percentage was 45.5. The frequency of gall stone was not present in 61 patients and its percentage was 54.5. The effectiveness of J-Tube frequency was 33 and its percentage was 29.5. The frequency of complications in patients was 4 and its percentage was 3.6. The frequency of jejunal tube was 36 and its percentage was 32.1.

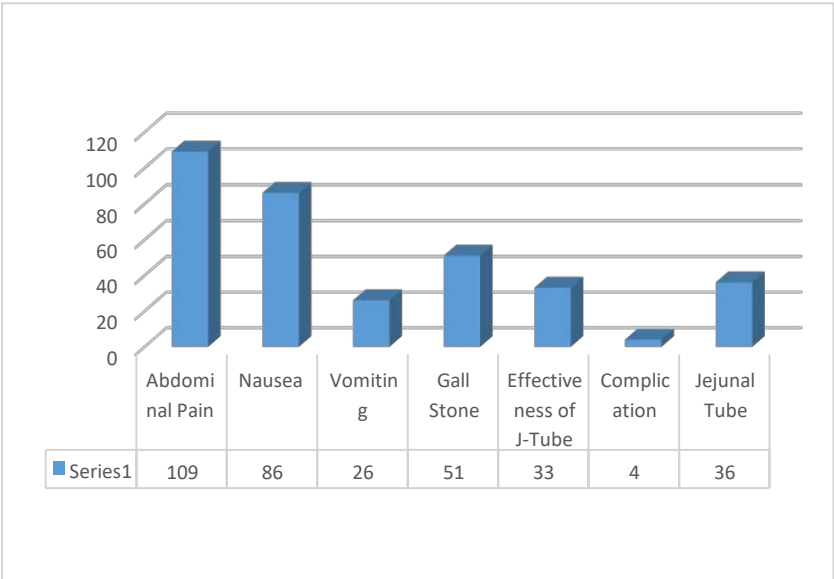


Figure 2: showing different characteristics of all patients

In figure 2 we can clearly see different characteristics. The number of patients with abdominal pain was 109. The number of patients came to hospital with nausea was 86. The number of patients present with vomiting was 26. The patients who have gall stone were 51. The effectiveness of J-Tube in patients was 33. The complication was noted in 4 patients and the jejunal Tube were passed to 36 patients.

Table 3: Effectiveness of J-Tube and its complications

Age groups	Effectiveness of J-Tube	p-value
41-50 years	11(33.3%)	
51-61 years	22(66.7%)	0.477
	Complication	
41-50 years	1(25.0%)	0.57
51-61 years	3(75.0%)	
	Effectiveness of J-Tube	
Male	6(18.2%)	0.09
Female	27(81.8%)	
	Complication	
Male	0(0.0%)	0.18
Female	100(100.0%)	

In table 3 the Effectiveness of J-Tube in age group of 41-50 years was 11(33%) and Effectiveness of J-Tube in age group of 51-61 years was 22(66.7%). Complication of J-Tube in age group of 41-50 years was 1(25%) and Complication of J-Tube in age group of 51-61 years were 3(75 %). P- value effectiveness of J-Tube in age group was 0.477.

Effectiveness of J-Tube in male patients was 6 (18.2 %) and Effectiveness of J-Tube in female patients was 27 (81.8 %). Complication of J-Tube in male patients were 0 (0.0%) and Complication of J-Tube in female patients were 100 (100.0%). P- value effectiveness of J-Tube in gender was 0.09. P-value complication of the gender group was 0.18.

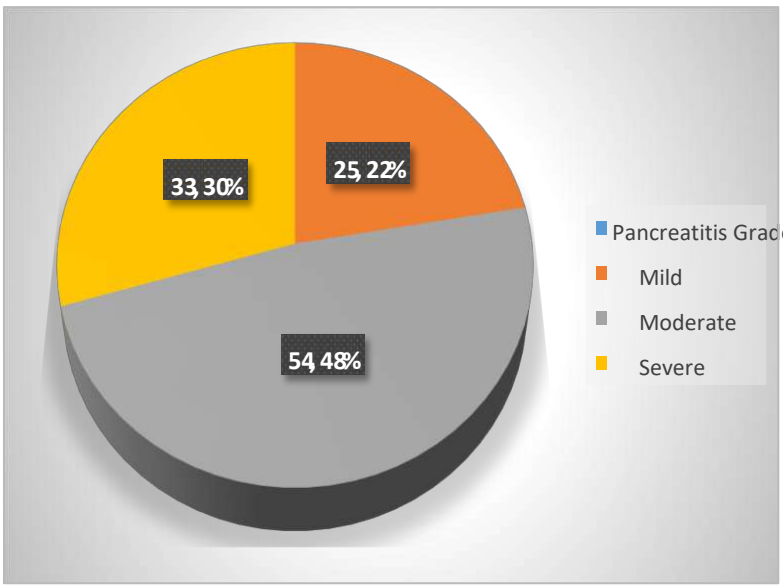


Figure 3: showing distribution of patients on the basis of pancreatitis Grade

In figure 3 distribution of patients on the basis of pancreatitis Grade, Mild pancreatitis patients were 22%, moderate pancreatitis patients were 48% and severe pancreatitis patients were 30%.

4. Discussion

When compared to parenteral nutrition, enteral feeding has been shown to reduce mortality and infection complications. Although it's unclear when enteral nourishment should be started, it seems safe and well-tolerated to start 48 hours early. Although nasogastric or even oral refeeding may be tolerated by certain individuals, the majority of trials have used nasojejunal feeding tubes. Healthcare professionals who treat patients with pancreatitis need to understand how important diet is in avoiding complications from the disease (Krishnan et al., 2017). With an increasing incidence, acute pancreatitis is one of the most prevalent GI diseases requiring immediate hospitalization. Numerous randomized controlled trials have yielded significant insights into the therapy of acute pancreatitis in recent years. Based on this evidence, the management of acute pancreatitis has evolved over time into a customized, interdisciplinary endeavor in which radiologists, surgeons, and gastroenterologists all play unique roles. This review highlights the data from randomized controlled trials when summarising the methods for diagnosing, categorizing, and treating individuals with acute pancreatitis (Van Dijk et al., 2017). The most common causes of acute pancreatitis are gallstones and binge alcohol consumption. There has been an increase in the incidence of acute pancreatitis reported worldwide. Despite improvements in access to care, imaging and interventional techniques, acute pancreatitis continues to be associated with significant morbidity and mortality (Greenberg et al., 2016).

5. Conclusion

The recovery time of patients from severe acute pancreatitis was 5 to 10 days. Jejunal tube is more effective in the patients who have more vomiting in severe acute pancreatitis. Jejunal tube is pass to the patient as soon as possible when patient is diagnose with sever acute pancreatitis. In severe acute pancreatitis patients have more vomiting and abdominal pain. We can diagnose patient of sever acute pancreatitis on Serium lipase blood test. In our study females were more as compare to males.

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: Not applicable.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 37-40
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.303

MRI Topometric of ACL Footprint on Femoral and Tibial Site in Indonesian Population

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Abstract
Anterior cruciate ligament (ACL) injuries are one of the most commonly injured ligaments of the knee. In the US, the incidence rate has reached 100,000 – 200,000 people per year based on the annual population. At Dr. Hasan Sadikin Bandung Hospital, the incidence has reached 32 cases from January 2020 – January 2021. This is a comparative analytical study with a cross-sectional approach that aims to determine whether there is a difference between the ACL footprint size that Monica has examined on the previous cadaveric knee and the ACL footprint size using the MRI knee. Measurement of ACL footprint on cadavers by Adisuhanto on the cadaveric ACL footprint length femoral site (12.05±1.18 mm), the width (8.65±1.02 mm). This size is compared with the results of the MRI measurement of the knee ACL footprint length femoral site (11.36±1.5 mm), a mean width (8.5±1.06 mm). Cadaveric ACL footprint length on the tibial site (12.11 ± 1.29 mm), the width (9.22±0.79 mm). These were compared to the MRI size of the ACL footprint length on the tibial site (13.18±1.32 mm), and the width (8.6±1.31 mm). This study was analogous to the study of measuring ACL footprint on cadavers so that this MRI ACL footprint study can represent cadaveric ACL footprint research with sufficient previous samples with p-value <0.05. The conclusion is that Indonesian ACL footprints were smaller than Thai, Chinese, and Americans.

Keywords: ACL Footprint, Indonesia, MRI, Topometry

1. Introduction

The Anterior Cruciate Ligament (ACL) contributes as the primary stabilizer of the knee joint. Insertion of ACL is located on the medial aspect of the anterior horn of the tibial plateau (LaBella, 2014). ACL tear has serious effect especially young population, acute ACL injury has an undesirable/unfavorable effect on knee joint function, and affect significantly quality of life (QoL), where the majority of the patient has osteoarthritis of the knee joint as one of late complication (Domnick, 2016).

ACL role as restraint of anterior tibial translation, and malrotation of the knee joint. ACL reconstruction is currently a challenge for orthopedic surgeons, it has difficulty restoring normal genu kinematics in patients with unstable ligaments. Abnormal genu kinematics are the primary cause of OA after anterior cruciate ligament reconstruction (Willinger, 2023).

The disturbance of knee function/disorders post ACL reconstruction has various consequences. This condition could be a consequence of the malposition of the anatomical placement of the graft. Inadequate positioning of the ACL footprint at the femur and tibial tunnel can increase graft pressure, altering graft length and tension. Based on previous research on cadaveric topography that has been carried out by Monica, the footprints of the cruciate ligament in Indonesian people are small. The selected single bundle technique can be applied as ACL footprint 13 mm as treatment of ACL reconstruction (Chien, 2020).

Therefore, it is necessary to carry out MRI measurements of ACL footprints in the femur and tibia to determine the placement and size of the graft by the number of samples that are representative of the Indonesian population. Therefore, it is necessary to conduct research with similar data on the Indonesian population for anatomical ACL reconstruction surgery.

2. Methods

The subjects of this study were all patients who underwent an MRI of the knee joint and went to the Orthopedic and Traumatology clinic of Dr. Hasan Sadikin General Hospital Bandung, Indonesia (RSHS). The design study was a comparative analytical study design, a cross-sectional to determine whether there is a difference between the size of the ACL footprint that has been studied by Monica previously and the size of the ACL footprint using knee MRI. This study is useful to determine the characteristics of the ACL footprint at its origin and insertion and the position of the ACL concerning the PCL and the anterior edge of the tibial condyle. The research sample was obtained using the Consecutive Sampling technique on treatment at the Orthopedic and Traumatology Clinic which will perform a knee MRI examination from January 14, 2021 – to March 04, 2021 period. There are 34 knee MRIs used in this study. The inclusion criteria consist of Indonesian citizens, aged 14-50, The patients with complaints of knee pain with ACL intact condition. The exclusion criteria consisted of patients with foreign national identity, knee pain with ACL rupture condition, and inflammatory arthritis with deformity. Ethical clearance was obtained, and the ethical clearance number is B.02.01/X.6.5/259/2020 from the Health Research Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung, Indonesia.

To choose hypothesis analysis, the researcher performs a normality data test. This normality data test for topometry MRI/ACL imprint and topography of the cadaveric ACL imprint on the femur and tibia in both length and width were normally distributed, respectively. The normality test was carried out to find out the distribution of the data with the Shapiro-Wilk test. In both samples, the cadaveric ACL topography and the ACL topography using MRI were each normally distributed so that parametric tests could be used. Thus, we used the Independent Sample T Test to see the Characteristics of the ACL Footprint based on the Length and Width of the ACL Footprint.

3. Results

There were 34 knee MRI examinations conducted, 23 men and 11 women, it was found that the intact ACL included 26 people and the remaining 8 people could not be included in this study because they did not meet the inclusion criteria. Sample who was not included in this study, 4 had an intact ACL, 1 patient was 4 years old, 2 patients had a history of fracture in the knee region, and 1 patient was diagnosed with a bone tumor in the distal femur. Table 4.1 lists the characteristics of the study subjects by sex, and ACL footprints on the femoral and tibial sites. The research subjects were male as many as 18 patients (69.2%) and female sex as many as 8 patients (30.8%). The cadaveric ACL topography and the ACL topography using MRI were each normally distributed so that parametric tests could be used. To test the difference can use the Independent Sample T Test.

Table 1 characterizes the long axis of the ACL footprints of the anteromedial bundle and posterolateral bundle on the femoral site. The mean length of the anteromedial bundle ACL footprint length axis on the femoral site was

4.42 mm while the mean posterolateral bundle ACL footprint length axis on the femoral site was 7.4 mm. Table 2 presents the characteristics of the variable length and width of the ACL imprint on the tibial site. The ACL imprint on the site of the tibia has an average length of 12.92 mm and an average width of 8.78 mm.

Table 1: Characteristics of the Length and Width of the ACL Footprint on the Femoral Site

Variable	**(n=26)**
ACL footprint length on femoral site (mm)	
Mean±STD	11.36 ± 1.5
median	11.69
Range (min-max)	6 (8.14-14.14)
Width of ACL imprint on femoral site (mm)	
Mean±STD	8.5 ± 1.06
median	8.26
Range (min-max)	3.38 (6.95 – 10.33)

Table 2: Characteristics of ACL Footprint Length and Width on the Tibial Site

Variable	**(n=26)**
ACL Footprint Length on Tibial Site (mm)	
Mean±STD	13.18 ± 1.32
median	12.92
Range (min-max)	5.33 (10.17 – 15.5)
ACL Footprint Width on Tibial Site (mm)	
Mean±STD	8.6 ± 1.31
median	8.78
Range (min-max)	3.97 (6.92 – 10.89)

The comparison results between Monica's 2017 study on the topography of the ACL imprint on the cadaveric knee and the ACL topometry on the MRI of the knee, it was found that there was no difference between the study of the ACL footprint size that Monica had studied on the cadaveric knee in 2017 and the ACL footprint size using the MRI of the knee. This knee MRI study can represent the previous research conducted by Monica on the cadaveric knee because of the sufficient number of measurement samples with p-value >0.05 (Monica, 2017).

4. Discussion

The arrangement of the ACL fibers is in the form of individual fiber bundles which are named according to their insertion site on the tibia (Morales, 2023). The ACL insertion is on the tibial plateau medial to the anterior horn of the lateral meniscus, in the sulcus in the anterolateral tibial spine anterior. The origin of the ACL is located in the femur, namely the medial wall of the condyle of the femur (Yonetani, 2019). This study aimed to measure the ACL footprints and boundaries of the tibial and femur, the length of the ACL, and the long axis of the anteromedial and posteriorlateral bundles of the ACL.

In this study, the ACL footprint data on the femoral site had an average length of 12.05±1.18 mm and an average width of 8.65±1.02 mm. This measure is similar to the data obtained in the Thai population (mean length 12.01±1.66 mm and mean width 9.52±1.37 mm) as well as in the Singaporean Chinese population (mean length 13.1±4.4 mm and mean width 9.7± 3.4 mm) (Pontoh, 2021).

The limitation of this study was MRI examination was unable to describe the bony structure, especially the 2 important structures used as landmarks of the ACL footprint on the femoral site, namely the lateral intercondylar ridge (resistant ridge) and lateral bifurcate ridge (cruciate ridge) so that researchers could not identify the existence of these 2 important structures as landmarks. To identify these important structures by obtaining a sample coverage that is as large as this study, a CT scan can be carried out (Tank, 2021).

There was a limitation to this study, researchers suggest further research to be conducted, it is a CT scan of the knee study, and it can identify important structures that are used as landmarks of the ACL footprint on the femoral

site, namely the lateral intercondylar ridge (resistant ridge) and lateral bifurcate ridge (cruciate ridge) to identify the existence of these 2 important structures as landmarks.

In conclusion, the comprehension of topography is expected to be a source of data that is used as a guide during ACL reconstruction to achieve more anatomical reconstruction results. Guidance in the placement of the tibial tunnel can use the characteristics of the distance between the anterior edge of the ACL imprint on the tibial site and the average anterior edge of the tibia 5.35±0.63 mm and the distance between the posterior edge of the ACL imprint on the tibial site and the anterior edge of the PCL imprint. on the tibial site an average of 13.37±1.16 mm. This data is useful if there is damage to the ACL insertion area, making it difficult to identify to determine the graft position. Insertion ACL of the Indonesian population is small (<13 mm).

Author Contributions: All authors contributed to this research.

Funding: This research received no external funding.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Dr. Hasan Sadikin General Hospital Bandung, Indonesia LB.02.01/X.6.5/259/2020

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 41-48
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.304

Current Practice of Internal and External Dental Whitening: Epidemiological Study Among Dentists in Morocco (Part I: Internal whitening)

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Abstract
Aim: To find out which whitening techniques and products are currently used by dentists in two cities, Marrakech and Khouribga-Morocco. Methods: Study type: Descriptive cross-sectional survey; Study population: 347 dentists practicing in the private sector, including 276 dentists in Marrakech and 71 in Khouribga; Study design: a questionnaire was drawn up to collect the data required for the study; Statistical analysis: data were analyzed using SPSS software at the FMDC Community Health Laboratory of Epidemiology and Biostatistics. Results: 205 responses out of 347 questionnaires distributed; External whitening was most widely used in Khouribga, and internal whitening most widely used in Marrakech; 35.7% of dentists used hydrogen peroxide at 35% as an internal whitening product; 35.9% of dentists used carbamide peroxide at 15% as an ambulatory whitening product; 67% of dentists made casts with reservoirs; 66% of dentists used 35% hydrogen peroxide for chairside whitening; 81.2% of practitioners used the lamp as a means of activation, while 37% used the whitening product for 30 minutes with the lamp. Conclusion: Dentists in Khouribga and Marrakech frequently employ the oldest high concentration whitening procedures. It is imperative that dentists in these two cities receive ongoing training. It must be regular, demanding and of high quality, as the therapeutics of each dyschromia and the specificities of internal and external bleaching protocols call for up-to-date knowledge.

Keywords: Bleaching, Discoloration, Tooth Whitening, Hydrogen Peroxide, Carbamide Hydroxide, Internal Bleaching, External Bleaching, Walking Bleach Technique

1. Introduction

The methodical use of whitening techniques, improved and simplified in recent years, makes it possible to deal with a wide range of clinical situations, and to attenuate and very often eliminate dental dyschromia, whether

external or internal. The quality and longevity of the result depend on the precision of the diagnosis, and the knowledge and expertise of the clinician. Dental whitening is widely used by Moroccan dentists. The aim of this study is to identify the techniques and products currently used by dentists in Marrakech and Khouribga.

2. Materials and methods

This descriptive cross-sectional epidemiological survey was conducted in the cities of Khouribga and Marrakech, in private practice dental offices, from November 2022 to February 2023. The study population included private practice dentists registered in the south regional council of the national dentists order in Khouribga or Marrakech who agreed to participate in the survey. Dentists specializing exclusively in orthodontics, pedodontics or periodontics were excluded. The total sample comprised 276 dentists in Marrakech and 71 in Khouribga.

To collect the data, a four-part questionnaire was used, covering the identification of practitioners, the practice of internal and external whitening, and the complications encountered. The study was carried out by two dental students at Hassan II University in Casablanca, one in Khouribga and the other in Marrakech.

Data processing was performed using SPSS (Statistical Package for the Social Sciences) software version 22.0 (SPSS, Chicago, Illinois), at the Laboratory of Epidemiology and Biostatistics of the Faculty of Dentistry of Casablanca, Morocco. Results for categorical variables were expressed as numbers and percentages.

3. Results

The response rate was 59.1%. The responses of 205 participants were collected from the 347 dentists surveyed. Practitioner profiles are shown in (Table 1).

- 93.7% of dentists performed whitening in Marrakech and 92.1% in Khouribga.
- 68.4% performed internal whitening in Marrakech and 60.3% in Khouribga.
- 98% of dentists performed whitening on patients aged over 18 in Khouribga and 99.2% performed it on patients aged over 18 in Marrakech (Table 2).

Table I Practitioner data

Variables	Number of employees (N)	Percentage (%)
Gender		
Female	99	48,3
Male	**106**	**51,7**
Age (years)		
< 30	55	26,8
Between 30 and 50	**102**	**49,8**
> 50	48	23,4
Origin of the diploma		
Casablanca	**164**	**80,0**
Rabat	13	6,3
Other	28	13,7
Duration of dental practice (years)		
< 5	54	26,3
Between 5 and 10	50	24,4
Between 11 and 20	46	22,4
> 20	**55**	**26,8**
Type of exercise		
General practitioner	**200**	**97,6**
Specialist	5	2,4

Table II Results of Internal Teeth Whitening Practice

Variables	Khouribga		Marrakech	
	N	%	N	%
Practice of whitening in-office	**58**	**92,1**	**133**	**93,7**
Type of whitening performed in-office				
- Internal	35	60,3	91	68,4
Practice of whitening in patients > 18 years	**48**	**98**	**118**	**99,2**
Practice of whitening in patients < 18 years	3	6,1	10	8,4

3.1. Indications and Contraindications for Internal Whitening

82.4% of dentists in Marrakech indicated internal whitening in cases of necrosis, and 72.5% of dentists contraindicated it in cases of root resorption. In Khouribga, 77.1% of dentists recommended internal whitening in cases of necrosis, and 82.9% of dentists advised against it in cases of root resorption. In Khouribga, 82.9% of dentists contraindicated internal whitening in cases of root resorption, and 77.1% in cases of cracks and/or fissures. The different percentages of internal whitening technique used by practitioners in the two towns are detailed in (Table 3).

Table III Practitioners' responses to the indications and contraindications of internal whitening

Variables	Khouribga (N=35)		Marrakech (N=91)	
	N	%	N	%
Indications				
- Discolouration due to intrapulpal bleeding	19	54,3	40	44
- Necrosis	**27**	**77,1**	**75**	**82,4**
- Defective endodontic treatment	12	34,3	21	23,1
- Asymptomatic root canal obliteration	8	22,9	13	14,3
- Presence of coronary restorative materials such as amalgam	11	31,4	34	37,4
- Discolouration due to eating habits and smoking	7	20	19	20,9
- Discolouration due marginal percolation	1	2,9	20	22
Contraindications				
- Dentinogenesis imperfecta	20	57,1	47	51,6
- Root resorption	**29**	**82,9**	**66**	**72,5**
- Severe coronary decay	22	62,9	53	58,2
- Bulky coronary restoration	12	34,3	35	38,5
- Crack and/or fissures	27	77,1	58	63,7
- Lack of patient motivation	19	54,3	42	46,2

3.2. Steps prior to internal whitening

Regarding the steps prior to internal whitening, 88.9% of dentists radiographically assessed the quality of endodontic treatment (density and length) and 82.5% took preoperative photographs. Regarding protection of the root canal filling, 84.1% of dentists protected the root canal filling before whitening, 84.3% used the glass ionomer cement to protect the root canal filling. Half of the dentists did not isolate the teeth with dental dam or modify the access cavity before whitening. 26% did not etch beforehand (Table 4).

Table IV Practitioners' responses to the stages prior to internal whitening

Variables	N	%
Preoperative Photography(N=126)	104	82,5
Radiographic evaluation of the quality of endodontic treatment	**112**	**88,9**
Isolation by rubber dam	62	49,2
Clinical evaluation of the quality of the root canal filling	86	68,3
Root canal retreatment before internal whitening	14	11,1
Removal of excess gutta-percha from the access cavity (N=124)		
- At the root canal entrance	31	26,7
- At the neck	8	6,9
- At 2 mm from cementoenamel junction	**77**	**66,4**
Rectification of the access cavity by removing pulp horns	66	52,4
Etching of the inner dentinal walls with orthophosphoric acid	33	26,2

3.3. Products Used for Internal Whitening

The most used product by Moroccan practitioners was hydrogen peroxide at 35 % in 35.7% of dentists. 22.2% of dentists used carbamide peroxide 15 to 16% (Table 5).

Table 5: Results of products used for internal whitening

Variables	N	%
Hydrogen Peroxide 6%	29	23
Hydrogen Peroxide 35%	45	**35,7**
Perborate de sodium	26	20,6
Carbamide peroxide 10%	14	11,1
Carbamide peroxide 15 to 16%	28	22,2
Carbamide peroxide 35%	17	**13,5**
Carbamide peroxide 40%	1	0,8
Heat-activated hydrogen peroxide	8	6,3
I don't know	4	3,2

3.4. Internal whitening product renewal

55.6% of dentists renewed the product once a week, while 20.5% renewed it once every 15 days. 74.6% determined the frequency of product renewal according to the intensity of dyschromia and 50% cited that it depended on the nature of the whitening product (Table 6).

Table 6: Product renewal Results

Variables	N	%
Frequency of product renewal (N=117)		
- 2 times / week	18	15,4
- 1 time / week	**65**	**55,6**
- 1 time / 15 days	24	20,5
- 1 time / 21 days	4	3,4
- 1 time /month	6	5,1
Determinant of frequency of product renewal (N=126)		
- Intensity of dyschromia	**94**	**74,6**
- Age of dyschromia	45	35,7
- Patient Habits	5	4
- Nature of the whitening product	63	50
- Patient cooperation	21	16,7

3.5. Temporary filling to seal access cavity

56.3% of dentists used glass ionomer cement and 23% used eugenol zinc oxide as a temporary restoration. Of the 120 dentists who responded to the question on permanent composite restoration after internal whitening:

- 39.2% performed restoration immediately after product disposal.
- 20% waited 1-3 days.
- 29.2% were waiting at least 1 week.
- 11.7% waited 2 to 3 weeks (Table 7).

Table 7: Results on the material used for the temporary filling to seal access cavity

Variables	N	%
Material used (N=119)		
- Zinc oxide eugenol	23	19,3
- Intermediate restorative material	4	3,4
- Glass ionomer cement	**67**	**56,3**
- Cavit	22	18,5
- Other	3	2,5

4. Discussion

Internal whitening consists of applying an oxidizing agent to the inside of the pulp cavity of a devitalized and discolored tooth, allowing the modification of its intrinsic color without altering its structure or resorting to prosthetic restorations (Clement et al., 2018).

Internal whitening requires essential preliminary steps, including pre-operative radiography to assess the endodontic filling, isolation of the tooth with a dental dam, rectification of the access cavity and removal of gutta percha up to 2 mm below the cementoenamel junction (Poyser et al.2004; Greenwallet-Cohen et al.2019).

Indeed, grinding the access cavity is essential prior to internal whitening. This step effectively removes residual coronal restorative materials and necrotic pulp tissue (sometimes under the pulpal horns) to prevent tooth discoloration (Timmerman et al. 2018). To improve treatment efficiency, 37% orthophosphoric acid can be used for 15 seconds for etching. It removes dentin sludge and opens the tubules, facilitating penetration of the whitening agent (Fagogeni et al. 2022; Wood et al. 2022).

The gutta-percha should be removed 2 mm below the enamel-cement junction and protected with an isolation base. Various materials can be used, including glass ionomer cement, intermediate restorative material or zinc oxide eugenol. Injectable glass ionomer cement is the most effective, thanks to its rapid melting and its mechanical and adhesive properties. It preserves the root canal filling by preventing penetration of the whitening agent, which is then applied in the access cavity against the vestibular wall, followed by a provisional hermetic coronal filling (Greenwallet al.; Timmerman et al.; Zimmerli et al.; Aboudharam et al.). In the interim, the provisional filling must be watertight to prevent bacterial penetration and avoid any problems with bleaching products leaking out or spreading to the gingiva (Irusa et al. 2022; Guerreiro et al. 2021).

4.1. Internal whitening products

This survey showed that 35.7% of practitioners used 35% hydrogen peroxide as an internal brightener, and 20.6% used sodium perborate.

A similar study carried out in Brazil (Demarco et al. 2013), also showed that hydrogen peroxide over 30% was the most widely used by dentists.

Hydrogen peroxide between 5% and 35% can be used for internal whitening, but it can be caustic and release free radicals at high concentrations (Plotino et al.; Kwon et al.). A low concentration of hydrogen peroxide is also effective in achieving satisfactory results (Pontes et al. 2020).

Since 2011, the European Union has regulated the use of hydrogen peroxide, limiting concentrations to 6% or less and reserved for dentists (Traviglia et al.2019).

Sodium perborate has been banned in the EU since 2015 due to its carcinogenic, mutagenic, and toxic properties (Pallarés-Serrano et al., 2022). This product is still marketed in Morocco.

4.2. Carbamide peroxide or hydrogen peroxide

35% carbamide peroxide and 35% hydrogen peroxide provide equal effectiveness for intracoronal bleaching. Carbamide peroxide has several advantages over hydrogen peroxide, namely its decomposition to the equivalent of only 12% hydrogen peroxide; its slower diffusion through dentin, as the presence of urea stabilizes the mixture and increases the duration of its efficacy as a bleaching agent; and its effect of inducing an alkaline pH in the tooth (Lim et al. 2004). Indeed, whitening efficacy is directly proportional to the increase in pH of the whitening agent, with maximum efficacy at pH=9 (hydrogen peroxide has pH=5 and carbamide peroxide has pH>8). Alkaline pH also reduces damage to tooth enamel and periodontal tissue (Torres et al. 2014; Sharma et al. 2017).

Products with low hydrogen peroxide concentrations and neutral or alkaline pH are therefore preferred for internal tooth whitening (Lilaj et al., 2019).

This study showed that only 13.5% of dentists used 35% carbamide peroxide as an internal whitening product, compared with 35.7% for 35% hydrogen peroxide.

For 56.2% of dentists, hydrogen peroxide offered better aesthetic results, and for 48.5% it was faster acting.

Regarding the frequency of whitening product renewal, half of the practitioners renewed the whitening product once a week. Renewal is usually a function of the intensity of the coloration and its average duration is 6 to 8 weeks (Greenwall-Cohen et al. 2019; Aboudharam et al. 2008).

It is advisable to see patients at least every two weeks to assess the tooth's response, manage possible complications, reassure and remotivate the patient, and replenish the whitening agent if necessary (Greenwall-Cohen et al. 2019).

Finally, it is mandatory to wait at least two weeks after the removal of the whitening product to place a definitive restoration to the composite (Greenwall-Cohen et al. 2019; Aboudharam et al. 2008). This step is necessary to ensure that the enamel does not contain any oxygen residues that may inhibit the binding of the composite to air and decrease the adhesion strength to the composite by 25 to 50%. In this study, 39.2% of practitioners immediately performed the final restoration once the whitening product was removed, and 29.2% waited at least a week.

5. Conclusions and recommendations for practitioners

Continuous training on whitening techniques is needed for dentists in Marrakech and Khouribga. However, there are a few recommendations that are very useful for practitioners:

- Delaying whitening after recent trauma.
- Check the quality of the endodontic filling before whitening.
- Isolate with dental dam.
- Rectify the access cavity: cervical boundary cleared (2mm below the cementoenamel junction)
- Protect the root canal filling with a cervical barrier (2mm glass ionomer cement)

- Recommend low concentrations without means of activation (heat, ultrasound or laser) to avoid cervical resorption.
- Preference should be given to whitening products based on carbamide peroxide rather than hydrogen peroxide.
- The final composite filling 2 weeks after the last whitening session.
- Follow-up

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: Not applicable.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 49-58
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.305

Current Practice of Internal and External Dental Whitening: Epidemiological Study Among Dentists in Morocco (Part II: External Whitening)

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Abstract
Aim: To find out which whitening techniques and products are currently used by dentists in two cities, Marrakech and Khouribga-Morocco. Methods: Study type: Descriptive cross-sectional survey; Study population: 347 dentists practicing in the private sector, including 276 dentists in Marrakech and 71 in Khouribga; Study design: a questionnaire was drawn up to collect the data required for the study; Statistical analysis: data were analyzed using SPSS software at the FMDC Community Health Laboratory of Epidemiology and Biostatistics. Results: 205 responses out of 347 questionnaires distributed. External whitening was most widely used in Khouribga, and internal whitening most widely used in Marrakech; 35.7% of dentists used hydrogen peroxide at 35% as an internal whitening product; 35.9% of dentists used carbamide peroxide at 15% as an at-home bleaching product; 67% of dentists made casts with reservoirs; 66% of dentists used 35% hydrogen peroxide in the dental office; 81.2% of practitioners used the light activation as a means of activation, while 37% used the whitening product for 30 minutes with the light activation. Conclusion: Dentists in Khouribga and Marrakech frequently employ the oldest high concentration whitening procedures. It is imperative that dentists in these two cities receive ongoing training. It must be regular, demanding and of high quality, as the therapeutics of each dyschromia and the specificities of internal and external bleaching protocols call for up-to-date knowledge.

Keywords: Bleaching, Discoloration, Tooth Whitening, Hydrogen Peroxide, Carbamide Hydroxide, Internal Bleaching, External Bleaching, Walking Bleach Technique

1. Introduction

The methodical use of whitening techniques, improved and simplified in recent years, makes it possible to deal with a wide range of clinical situations, and to attenuate and very often eliminate dental dyschromia, whether

external or internal. The quality and longevity of the result depend on the precision of the diagnosis, and the knowledge and expertise of the clinician. Dental whitening is widely used by Moroccan dentists. The aim of this study is to identify the techniques and products currently used by dentists in Marrakech and Khouribga.

2. Materials and methods

This descriptive cross-sectional epidemiological survey was conducted in the cities of Khouribga and Marrakech, in private practice dental offices, from November 2022 to February 2023. The study population included private practice dentists registered in the south regional council of the national dentists' order in Khouribga or Marrakech who agreed to participate in the survey. Dentists specializing exclusively in orthodontics, pedodontics or periodontics were excluded. The total sample comprised 276 dentists in Marrakech and 71 in Khouribga. To collect the data, a four-part questionnaire was used, covering the identification of practitioners, the practice of internal and external whitening, and the postoperative complications. The study was carried out by two dental students at Hassan II University in Casablanca, one conducted the study in Khouribga and the other in Marrakech. Data processing was performed using SPSS (Statistical Package for the Social Sciences) software version 22.0 (SPSS, Chicago, Illinois), at the Laboratory of Epidemiology and Biostatistics of the Faculty of Dentistry of Casablanca, Morocco. Results for categorical variables were expressed as numbers and percentages.

3. Results

93.7% of dentists performed whitening in Marrakech, and 92.1% performed it in Khouribga. 94.8% employed external whitening in Khouribga, and 91% employed it in Marrakech. Combined whitening technique was the least used in both cities due to practitioners' lack of knowledge of this whitening technique (Table1).

Table 1: Results of Internal Teeth Whitening Practice

Variables	Khouribga		Marrakech	
	N	%	N	%
Practice of whitening in-office	**58**	**92,1**	**133**	**93,7**
Type of techniques in-office				
- External	**55**	**94,8**	**121**	**91**
- Combined	7	12,1	30	22,6

3.1. Indications and Contraindications for External Whitening

Regarding the indications for external whitening, in Marrakech 92.6% of dentists indicated it in the case of coloration due to food and tobacco, while 57.9% indicated it in the case of coloration related to age. In Khouribga, 89.1% of dentists indicated it in the case of discoloration due to food and tobacco, while 61.8% indicated it in the case of coloration related to fluorosis.

Regarding the contraindications of external whitening, in Marrakech 93.5% of dentists contraindicated it in case of dentin hypersensitivity, while 86.8% contraindicated it in case of dental caries. In Khouribga, 90.9% of dentists contraindicated it in case of dentin hypersensitivity, while 85.5% contraindicated it in case of cervical resorption (Table 2).

Table 2: Results for the Indication and Contraindication of External whitening

Variables	Khouribga (N=55)		Marrakech (N=121)	
	N	%	N	%
Indications				
- Age-related coloring	28	50,9	70	57,9
- Fluorosis-related staining	34	61,8	66	54,4
- Staining due to tetracyclines	17	30,9	30	24,8
- Coloring due to food and tobacco	**49**	**89,1**	**112**	**92,6**
Contraindications				
- Dentin hypersensitivity	**50**	**90,9**	**113**	**93,5**
- Large or leaky coronal filling	35	63,6	83	68,6
- Very saturated dyschromia	36	65,5	59	48,8
- Cervical resorption	47	85,5	87	71,9
- Lack of motivation on the part of the patient	43	78,2	86	71,1
- Dental caries	44	80	105	86,8
- Tooth crack	41	74,5	96	79,3
- Under 18 years old	42	76,5	86	71,1

3.2. Steps prior to external whitening

As for the steps prior to external whitening, 96.6% performed tooth scaling and 91.5% treated dental caries. The other pre-operative steps are detailed in (Table 3).

Table 3: Results according to steps prior to external whitening

Variables	N	%
Tooth scaling	**170**	**96,6**
Tooth decay removal	161	91,5
Informing the patient about the possibility of the appearance of transient white spots	135	76,7
Diagnosis of tooth sensitivities, as well as their prevention with desensitizing toothpaste based on (N=116)		
- ACP(Amorphous calcium phosphate)	21	18,1
- Potassium nitrate	47	40,5
- Fluor	**48**	**41,4**
Preoperative Photography	136	77,3
Determination of hue with (N=144)		
- Shade guide	**139**	**96,5**
- Spectrophotometer	5	3,5
Repair or replacement of defective coronal restoration	113	64,2
Confection of dental gutters	120	68,2
Demonstration of the use and maintenance of dental gutters	108	61,4

3.3. Products Used for External whitening

66.7% of dentists used hydrogen peroxide 35% for in-office whitening, and 30.3% of dentists employed hydrogen peroxide 20% for home whitening technique.

48.2% used 35% carbamide peroxide for in-office whitening, while 35.9% used 15% for at home whitening technique (Table 4).

Table 4: Products Used for External whitening

Product Used / Concentration	In-office				At home			
	Hydrogen peroxide (N=123)		Carbamide peroxide (N=56)		Hydrogen peroxide (N=199)		Carbamide peroxide (N=78)	
	N	%	N	%	N	%	N	%
10%	5	4,1	5	8,9	18	18,2	18	23,1
15%	7	5,7	3	5,4	29	29,3	**28**	**35,9**
20%	9	7,3	4	7,1	**30**	**30,3**	21	26,9
25%	20	16,3	17	30,4	14	14,1	7	9
35%	**82**	**66,7**	**27**	**48,2**	8	8,1	4	5,1
70%	0	0	0	0	0	0	0	0

3.4. Techniques Used for External Whitening

For the techniques used for external whitening, 52.3% of practitioners associated both methods, at-home technique and in office technique. Regarding the means of activating the whitening product used in the dental office, 81.2% of practitioners used the light activation (Table 5).

Table 5: Positive results according to the techniques used for external whitening

Variables	N	%
Technique used: (N=174)		
- At-home technique	41	23,6
- In office technique	42	24,1
- Combined technique (In-office+ at home)	**91**	**52,3**
Means of product activation (N=133)		
- Light activation	**108**	**81,2**
- Laser	21	15,8

3.5. Confection of teeth gutters and duration of wear during at-home bleaching technique

64.7% of practitioners made casts with gutter tanks.
53.7% of practitioners recommended wearing the aligner for 4 hours a day.
62.8% of practitioners recommended wearing the aligner for 1 to 2 weeks (Table 6).

Table 6: Moulding and duration of wear of aligners during at-home bleaching technique

Variables	N	%
Confection of gutters with tanks (N=119)		
- Yes	**77**	**64,7**
- Not	11	9,2
- Not necessarily.	31	26,1
Duration of gutters wear per day (N=121)		
- 4 hours/day	**65**	**53,7**
- 6 hours/day	11	9,1
- 8 hours/day	7	5,8
- Nocturnal wear to sleep	38	31,4
Period of wear of the gutters N=113)		
- 1 to 2 weeks	**71**	**62,8**
- 2 to 4 weeks	30	26,5
- 4 to 6 weeks	9	8
- 6 to 8 weeks	3	2,7

3.6. Time to apply the whitening product in the dental office

36.8% of dentists used a 30-minute duration with a light activation, while 30.8% opted for a duration of 15 minutes (Table 7).

Table 7: Results of time to apply the whitening product in the office

Variables	N	%
15 minutes without light activation	25	18,8
30 minutes without light activation	31	23,3
60 minutes without light activation	2	1,5
15 minutes with light activation	41	30,8
30 minutes with light activation	**49**	**36,8**
60 minutes with light activation	11	8,3

3.7. Desensitizing products during external whitening

75.6% of dentists did not apply fluoride.
61.9% applied desensitizing gel or toothpaste postoperatively (Table 8).

Table 8: Positive results according to desensitizing products during external whitening

Variables	N	%
Application of fluoride is essential after whitening	43	24,4
Use of a desensitizing gel or toothpaste		
- Intraoperatively: alternating desensitizer with whitening product	40	22,7
- Intraoperatively: after temporary discontinuation of the product	37	21
- Post-operative	**109**	**61,9**

4. Discussion

External whitening is a technique that modifies the external dyschromia of the teeth using oxidizing agents, such as hydrogen peroxide or carbamide peroxide. These agents penetrate the enamel and dentin and break down the pigments responsible for tooth discoloration. The effectiveness of external tooth whitening depends on many factors, such as the concentration and pH of the whitening agent, the duration of application, the chemical additives, and the demineralizing agents used (Alkahtani et al.2020).

The indications for external whitening concern many pathological and natural discolorations. Age-related whitening of stains gives good results, but results can also be obtained in cases of pathological stains such as tetracycline poisoning (early stages 1 and 2), certain imperfect amelogenesis, fluorosis, white spots, hypo mineralization of the incisors and molars, and traumatic hypo mineralization (attenuation of the contrast between the lesion and the shade of the rest of the tooth). These pathological discolorations sometimes require a slightly longer treatment (Clement et al.2018).

Absolute contraindications are relatively rare. These include (Clement 2018):
• Teeth with significant wear or deep cracks;
• Teeth with cavities (polycarous patients);
• Restorations with major leaks;

• Mucous membranes with oral lesions, such as canker sores;
• Patients with untreated, unstabilized gingivitis/periodontitis;
• Lack of oral hygiene;
• Pregnant or breastfeeding women;
• Patients who are allergic to any of the different components of the products;
• Patients with dental sensitivities.

There are two main techniques for external whitening: at home and in-office techniques. At home technique involves the use of teeth gutters, into which the patient injects the product and then usually wears them at night for a few weeks. In contrast, in the dental office technique is performed directly by a practitioner, with high concentration whitening products, which can be combined with a light, thermal, or laser activation source (Alkahtani et al.2020, Buchalla et al 2007).

The results of our study showed that 52.3% used both external whitening techniques, 24.1% used only external in the dental office. In Brazil (Demarco et al. 2013) showed that at-home bleaching is the most commonly performed by 78.1% of dentists.

4.1. At-home bleaching technique

Regarding at-home bleaching products, the results of this study showed that 35.9% of practitioners used 15% carbamide peroxide, and 30.3% of practitioners used 20% hydrogen peroxide. These hydrogen peroxide concentrations are higher in comparison to the study conducted in Brazil (Demarco et al. 2013) which showed that 40.9% of practitioners used 10% carbamide peroxide while 11.7% used 30% hydrogen peroxide.

Furthermore, (Suntil et al.2022) In their randomized controlled clinical trial showed that the use of 37% carbamide peroxide or 10% carbamide peroxide for 3 weeks gave equivalent results. Also, (de Geus et al. 2018) demonstrated that the efficacy of whitening with 10% carbamide peroxide compared to 15% and 28% was similar with a lower risk and intensity of tooth sensitivity for the 10%. The effectiveness of whitening depends on the time the product is in contact with tooth surfaces and not on the concentration of the whitening product.

67% of practitioners reported using casts with gutter tanks. These do not have a significant effect on the effectiveness of whitening, regardless of the type of whitening agent used (Greenwall-Cohen 2019, Geisinger 2015). In addition, gutter tanks do not increase the longevity of tooth whitening (Martini et al. 2021). (Haywood et al. 2021) recommend the use of 10% carbamide peroxide 10% gutter (without tanks) as the first option considered for the treatment of various external dyschromia.
A low concentration of hydrogen peroxide between 7.5 and 15%, when worn at night for a period ranging from 3 days to 6 weeks, could be recommended for at home whitening (Geisinger 2015, Haywood et al. 2021- de Fátima Carvalho Vasconcelos et al. 2017).

4.2. In-office bleaching technique

Concentrations and Efficacy of Whitening Products

The results of our study showed that dentists employed hydrogen peroxide in high concentrations. 66% of practitioners used 35% hydrogen peroxide and 48% used 35% carbamide peroxide. In contrast to the study by (Demarco et al. 2013), where 40.9% of practitioners used 10% carbamide peroxide.

Although higher concentrations of hydrogen peroxide significantly improved tooth tint, there was no significant difference in efficacy compared to lower concentrations (Lilaj et al. 2019, Martin et al. 2015). Also, 6% hydrogen peroxide is just as effective as 25%, 30%, and 40% (Lilaj et al. 2019, Martin et al. 2015). In addition, dental whitening products used in-office and containing hydrogen peroxide at low concentrations (6% to 20%) or medium concentrations (between 20 and 30%) have a lower risk of sensitivity than those containing a high concentration

of hydrogen peroxide, with no difference in terms of effectiveness in changing the color of teeth (Maran et al. 2020).

4.3. Means of activation and time of application of the product in office

In our study, it was found that 81.2% of practitioners used the light activation as a means for in-office whitening technique. 37% used it for 30 minutes.

Activation by the light activation does not appear to improve tint change or sensitivity, regardless of the concentration of the whitening agent used. The diode laser gives better clinical results and better long-term tint stability (Tekce et al.2022). However, the same side effects, namely postoperative tenderness, and gingival irritation, are noted for both light activation and laser activation (Alshammery 2019- Yusof et al.2020).

(Ozdemir et al. 2021) showed similar results of 40% carbamide peroxide whitening without a light activation for 20, 40, and 60 minutes in continuous mode. According to this study, 40 minutes was the ideal application time. On the other hand, (Reis et al. 2011) propose the application of 35% hydrogen peroxide without a light activation in three 15-minute sessions instead of one 45-minute session. A prolonged session reduces the speed of whitening and slightly increases the intensity of tooth sensitivity.

Comparison of in office bleaching technique with 35% hydrogen peroxide with light activation for 15, 30 and 45 minutes in continuous mode, does not affect the effectiveness of the whitening (Ribeiro et al. 2022). Increasing the application time of hydrogen peroxide to 35% with light activation does not affect the whitening efficiency. The results of studies vary, with some suggesting that shorter, repeated sessions produce better results, while others advocate a longer session.

Nevertheless, the duration of application does not always affect the changes in the shade. Practitioners must therefore consider several factors to determine the best approach for each patient (Ozdemir et al. 2021, Ribeiro et al. 2022).

4.4. Comparison between in office dental technique and at-home bleaching

The efficacy and safety of both methods have been evaluated in several studies, but the results are inconclusive. Some studies (Buchalla 2007, Browning et al. 2011) have shown that both techniques are effective in achieving teeth whitening, with shade regression for both methods during the 3- and 6-month follow-up periods. However, color regression and tooth sensitivity after treatment were significantly higher for in-office bleaching (Mounika et al. 2018).

(Dourado Pinto et al. 2019) also demonstrated that both methods can treat dental dyschromia and offer stability over time. On the other hand, the at-home bleaching technique can cause more tooth sensitivity and gum irritation than in the dental office technique.

The application in dental office followed by at-home whitening, with the aim of improving and maintaining the whitening effect. This combination demonstrated the highest indices of tooth sensitivity, while producing a shade change effect similar to only at-home bleaching.

In conclusion, the choice of the best whitening technique depends on several factors, such as the patient's preferences, cooperation, expectations, compliance, oral health status.

4.5. Combined Whitening

This inside/outside whitening technique was first described by (Settembrini et al.1997) in the original American literature, and (Liebenberg et al. 1997) made a modification to this technique later. It consists of applying 10% carbamide peroxide to the inner and outer surfaces of the tooth. During treatment, the access cavity remains open

to allow for easy and regular change of the whitening product. The window tray at the adjacent teeth of the tooth to be treated is used to keep the whitening agent in and around the tooth (inside/outside open).

The whitening product should be changed inside the tooth and tray every two hours during the day, and the tray containing the product should be worn overnight (Poyser et al.2004). After the whitening session, the patient should clean the access cavities with a toothbrush. Injecting the viscous whitening product will naturally remove any remaining food residue.

Unlike the whitening of vital teeth, there is no limit to the number of times the material can be changed, as it is very unlikely that the patient will experience sensitivity. The more often the agent is changed, the faster the whitening will occur.

It is essential that the patient be cooperative. If the patient does not follow the instructions, it will result in a prolongation of the duration of the treatment and the discoloration may persist. Prolonged treatment means that the access cavity remains open longer (Poyser et al.2004).
The inside/outside closed technique has several advantages over other whitening techniques (internal, external, and inside/outside open), including reduced risk of infiltration, alteration of the coronal surface, and accumulation of food in the access cavity in the case of the inside/outside open technique (Greenwall-Cohen 2019).

4.6. Comparison between the effectiveness of Combined Whitening (Inside/Outside) and Internal Whitening

According to the results of our study, it was found that 60.3% of practitioners in Khouribga opted for internal whitening, while 12.1% practiced combined whitening. In Marrakech, these figures were 68.4% for internal whitening and 22.6% for combined whitening, respectively.

(Pedrollo et al. 2018) demonstrated that both techniques, internal whitening and combined whitening, were effective in producing a large and stable hue gain after two weeks, with no significant difference in brightness.

Zimmerli B et al. in 2010 suggest that combined whitening might be preferable to internal whitening because it avoids the use of sodium perborate, a product banned in the European Union due to its carcinogenic, mutagenic, and toxic effects. They also found that combined whitening could reduce the risk of external cervical resorption by using lower concentrations of whitening agents (Zimmerli et al. 2010).
We note a lack of knowledge of this technique by the practitioners included in our study.

5. Conclusions and recommendations for practitioners

- Use a protective barrier to protect gums and soft tissue.
- Make castings without gutter tanks.
- Wear dental gutter at night.
- Opt for at-homr rather than in the office technique.
- Prefer low-concentration products such as 6% hydrogen peroxide to avoid sensitivities.
- Avoid the use of activators such as LED lamps, heat, or lasers, and invest funds in other devices instead of the lamp itself.
- Prescribe a desensitizing toothpaste or gel.
- Regularly monitor patients to assess results and detect side effects.

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: Not applicable.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 59-71
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.306

Systematic Review on the Current Situation and Development of Local Antimicrobial Agents in Revision Arthroplasty for Periprosthetic Joint Infection (PJI)

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Abstract
Total joint arthroplasty is a common surgery to treat degenerative joint disease, and it significantly improves the lives of people suffering from conditions such as osteoarthritis. Moreover, it is very essential to know that the fact that the level of joint replacement surgery is discouraged by complications, therefore making the periprosthetic infection (PJI) to become a critical issue. As such PJI is full of significant negative results in a current pain, implant failure, and also as a systemic infection. Basically, the complex origin of PJI is usually involved in the formation of biofilms (protective communities of bacteria) which become resistant to the standard treatments. This capability to resist is able to highlight the urgency to look more into new strategies so as to particularly disrupt and to be able to prevent biofilm formation. In addition to that Topical antimicrobials that generally range from intraarticular antibiotic infusions and antibiotic-filled spacers, have therefore become the focus of this effort. In addition to this, the drugs are able to target the infection site directly, that probably leads to the minimization of systemic exposure and therefore increasing effectiveness of the treatment. Therefore, the knowledge of this challenges, this specific systematic review tends to aim so as to assess the current state and as well as advancements in local antimicrobial agents for the management of PJI. Moreover, by involving mechanisms, consideration of safety, in addition to its effectiveness, the review is able to give out insights that may shape more effective clinical approaches so as to fight Periprosthetic Joint Infection.

Keywords: Review, Local Antimicrobial Agents, Revision Arthroplasty, Periprosthetic Joint Infection

1. Introduction

Periprosthetic Joint Infection (PJI) is known a complication which associated with the revision arthroplasty. PJI being a complication causes a significant problem to patients and the healthcare providers. That condition hence leads to pain, implant failure, and also the systematic spread of infections. These infections later affect the entire body or multiple organ systems. These infections include sepsis whereby bacteria and other pathogens invade the bloodstream and cause inflammation and organ dysfunction and viral infections such as influenza which affect the overall quality of patient life and could lead to high mortality rates. These problems go below the usefulness of considering the management of PJI as an essential consideration in orthopedic surgery. This systematic review aims to assess the current state and ongoing developments in local antimicrobial agents in the context of revision arthroplasty for PJI.

The treatment and management of PJI is made more difficult by the formation of biofilm. Biofilms are arrangements of bacterial communities that attaches itself to prosthetic surface, in this case Biofilms prevents the treatment and diagnosis of PJI, therefore causing continuous infections around the implant. These findings show the complex relationship between Biofilms and PJIs, also giving out the benefits of creative ways to curb this resilient bacterial phenomenon. In addition, the study goes through the different treatment strategies which are likely to work and be more successful which are later considered and used to bring about good and improved clinical results. Most importantly, the aim of the study is to know more about function of local antimicrobial agents in managing Periprosthetic Joint Infection.

1.1. Biofilm Pathology

Biofilms are structured communities of bacteria intricately connected to the extracellular polymeric substances (EPS) (Waheed et al., 2022). Biofilm formation is a crucial factor in the pathogenesis of PJI. In the case of PJI pathogens attach themselves on the surface of prosthetic joint and in-turn create biofilms. Biofilms are difficult to eradicate and inhibit treatment of PJI bacteria. Bacteria in an established biofilm are up to 10,000 times more resistant to antibiotic therapy in comparison to their free-floating planktonic counterparts (Rabin et al 2015). The EPS matrix protects the bacteria from the patient's immune system and antibiotics that are administered making the pathogens extremely resistant to treatment. Biofilm-protected bacteria often course the recurrence of infections after initial treatment (Zimmerli & Sendi, 2010). This occurrence is because some protected bacteria might remain persistent even after treatment, making PJI treatment a long-term challenge.

Experts have and are exploring various strategies to prevent and disrupt formation of biofilms. Research into the topic is critical in PJI management. Preventive measures include the development of prosthetic materials that resist the formation of biofilm and research into implant coating with antimicrobial properties. Disruptive measures include the dispersion of enzymes such as B and DNase in treatment. Enzymes B and DNase have been studied for their ability to disrupt biofilm matrix (Hall-Stoodley et al, 2004) Thus making the bacteria more accessible to antibiotics. Medical personnel also use high-dose of prolonged antibiotic therapy as a disruptive measure against biofilms. Rifampin an example of an antibiotic has shown effectiveness against bacteria encased in biofilms (Zimmerli et al, 2004). Therefore the use of different combinations of antibiotics with different mechanisms of actions has been effective in enhancing the disruption of biofilms (Tande & Patel, 2014).

1.2. Local antimicrobial agents

The management of PJI leads to the need for a multifaceted approach and local antimicrobial agents have emerged as a very important component in the battle against this condition (Mustafa et al., 2023). The adoption of local antibacterial agents has effectively revolutionized the treatment of PJI this is by representing critical advancement in the management of the condition. Local antimicrobial agents make sure that antibiotics or antibacterial substances are targeted directly to the sites which are infected, optimizing treatment efficiency (Kalelkar et al., 2022). This is not like systemic administration which leads to diluted antibiotic concentrations and potential systemic side effects. Local agents of antibiotic delivery ensure that there is high local concentration while minimizing the risk of adverse reactions.

The importance of local antimicrobial agents depends in their inbuilt mechanisms that enables them to have the ability to fight against biofilm-encased bacteria effectively, penetrate the biofilm matrix, and reduce the risk of the same infections happening. The formation of biofilm is a key aspect of PJI development and a huge challenge in its management (Taha et al., 2018). There are various types of Local Antimicrobial agents which include intra-articular antibiotic infusion, antibiotic beads, antibiotic-loaded cement spacers, and antibiotic extended-release implants. There are various advantages of Local agents over traditional systemic antibiotic therapies, which include:

1. High local concentration – Local antimicrobial agents such as antibiotic loaded cement spacers or beads allow for delivery of antibiotics directly to the targeted site which results in significantly higher local concentration of antibiotics ensuring that they can effectively combat the infecting bacteria at the source (Bayramov, 2017).
2. Reduced systemic side effects - local antimicrobial agents are designed to deliver antibiotics directly to the infected site which reduces systemic exposure to antibiotics, minimizing the risk of adverse reactions and toxicities associated with high-doses in systemic antibiotic therapy.
3. Targeted and efficient therapy - Overall local antimicrobial agents provide highly targeted therapy (Koo, 2017). By delivering antibiotics directly to the infected there is a minimized risk of harming healthy tissues. This targeted approach enhances the effectiveness of treatment ensuring that antibiotics are concentrated where they are needed underscoring the chance of infection eradication (Spellberg, 2015).
4. Prevention of recurrence - PJI usually has a high risk of recurrence. The used of localized high concentration of antibiotics achieved with the agents is extremely effective in reducing the risk of recurrence by eradicating the infecting bacteria at the source, the agent can help the infection from reoccurring after treatment.
5. Minimized treatment complexity - The use of local agents simplifies the treatment of PJI. In some cases, such as the use of antibiotic loaded cement spacer, the spacer itself provides mechanical support for the joint while delivering antibiotics (Spellberg, 2015). This reduces the complexity of treatment by combining the role of mechanical support and drug delivery into a single intervention.

Local antimicrobial agent is delivered to the infection site using various mechanisms (ter Boo, 2015). Below is a table of mechanisms summarizing the mechanisms of action of different local antimicrobial agents in PJI.

Local Antimicrobial Agent	Mechanism of Action
Intra-articular Antibiotic Infusion	Direct delivery of antibiotics into the joint space to combat infection locally
Antibiotic-Loaded Cement Spacer	Antibiotics mixed with cement gradually elute into the surrounding tissues, providing sustained local coverage.
Antibiotic Beads	Small beads filled with antibiotics slowly release the drugs, maintaining high local concentrations.
Antibiotic Extended-Release Implants	Implants release antibiotics over an extended period, continuously targeting the infection site

2. Intra-articular antibiotic infusion

An intra-articular antibiotic infusion is a specialized approach to the management of PJI. The approach involves the direct delivery of high antibiotic concentrations into the joint spaces and targeting biofilm and pathogens. Various studies have shown and demonstrated the effectiveness of the method in eradicating PJI pathogens. The method is appreciated by medics not only because it is effective but also because it minimizes systemic exposure to antibiotics (McLaren & McLaren, 2016). A study by McLaren & McLaren (2016) showed a 92.9% clinical success rate and a 7.1% recurrence rate in the treatment of shoulder joint septic arthritis. A study also showed that there was 88.2% of patients achieved infection control and 11.8% recurrence in the knee and hip PJI (Piggott et al, 2019). The methods have various advantages and disadvantages.

2.1. Advantages

Intra-articular antibiotic infusion allows the delivery of exceptionally high antibiotics directly to the infected area. The localized therapy targets pathogens within the joint specifically addressing the source of infection efficiently (McLaren & McLaren, 2016). By limiting antibiotic exposure to the infected area, the method reduces the side effects associated with other broad-spectrum antibiotics. This advantage ensures that the patient experiences fewer adverse reactions, enhancing compliance and tolerability (Parvizi & Tarity, 2012). The approach also demonstrated the ability to penetrate biofilm which is a critical aspect in the management of PJI in a study done by Zimmerli & Sendi (2010). Biofilms in some cases shield the bacteria from antibiotics. This makes it important to penetrate the biofilms to ensure successful treatment,

2.2. Disadvantages

The intra-articular antibiotic infusion method carries some disadvantages. Firstly, the approach involves a surgical procedure. These procedures carry various risks and increase the overall complexity of treatment (Artz et al, 2015). In the treatment procedure, patients need to undergo anaesthesia, which may result in additional hospitalization. The method is effective against resistant or multi-organism infections (Kuiper et al, 2013). The method targets specific joint spaces and at times PJI infections occur at various locations, this occurrence necessitates a broader strategic approach which the method does not consider.

2.3. Safety

Intra-articular antibiotic infusion involves introducing antibiotics into the joint space to PJIs. Safety concerns include the risk of systemic effects, local tissue irritation, and adverse reactions (Cyphert, 2020). Generally, it is considered safe, however, careful antibiotic selection, dosing, and monitoring. Aseptic techniques during infusion are important in preventing additional complications (Horlocker, 2011). Patient-specific including allergies should be considered.

2.4. Feasibility

Intra-articular infusion is a feasible approach since it gives a practical application in that it delivers a localized treatment approach, feasibility depends on the accessibility of the joint, choice of antibiotic, and severity of the infection (Foster, 2023). Feasible methods of delivery include direct injection, drug-eluting implants, and joint lavage, the choice of approach relies on the surgeon's expertise and characteristics of PJI (Rodríguez-Merchán, 2021).

2.5. Effectiveness

Intra-articular antibiotic infusion provides targeted treatment which enhances the effectiveness of treatment by providing higher antibiotic concentration at infection point. The effectiveness of intra-articular antibiotic infusion may vary depending on the type and extent of the infection. The approach is often most suitable for early and less aggressive infections. As an example, research carried out by Ji et al. in 2019 showed that a single-stage revision with cement less reconstruction could be one of the treatment that could highly work for chronic infections in total hip arthroplasty (THA). This study, which included 126 patients which were from different ethnicities and different characteristics and found that 89.2% of the participants were not infected after an average assessment of 58 months (Day et al., 2021).

In another study, Ji et al. (2020) looked into the level of desired success of single-stage revision using intra-articular antibiotic infusion in finishing culture-negative PJI. Thus, the results found considered that this method could be very important in managing culture-negative PJI as it is in culture-positive cases.

However, a study carried out in 2022 by Ji et al. went through the usefulness of single-stage revision using intra-articular antibiotic infusion this is due to multiple unsuccessful surgeries for PJI. The researchers found out that

this method could deliver a high concentration of antibiotics in the synovial fluid, thereby being able to overcome challenges such as reduced vascular supply and biofilm formation. Therefor this alternative method of administration could be a potential treatment option for PJI, more so particularly in cases where previous surgeries have failed to resolve the infection.

These studies has showed that intra-articular antibiotic infusion could be a promising treatment strategy for PJI, even in advanced cases such as culture-negative infections and instances involving multiple prior surgeries which are not successful. However, more research is needed to validate these results and to refine the application of this treatment method.

3. Local Antibiotic Carriers

The use of antibiotic carriers acts as an alternative approach that allows for the maintaining of high local concentrations of antibiotics without systemic exposure, local antibiotic carriers incorporate an antimicrobial to prolong its half-life as well as provide predictable elution characteristics while at times they may play assistance role such as filling dead space and providing mechanical support for limb alignment (Engin et al, 2019). The most effective carrier is one that provides prolonged antibiotic concentrations at an effective level and achieves complete antibiotic release to reduce subtherapeutic elution time, is extremely versatile and has compatibility with the desired antibiotics, and is fully resorbable with minimized risks of allergies, local and systemic adverse effects (Le et al., 2021).

4. Hydrogels

Hydrogels are three-dimensional networks of hydrophilic polymers that can absorb and retain significant amounts of water or other fluid within their structure. Hydrogels have a unique ability to respond to changes in environmental conditions such as pH, temperature, and ionic subsequently triggering swelling or deswelling (Xie et al, 2022). In the context of PJI hydrogels offer a unique and innovative approach to the management of the condition by acting as effective delivery systems for antibiotics and antimicrobial agents.

The treatment process using hydrogels involves impregnating the hydrogel with the desired antimicrobial substance through chemical bonding, entrapment, or physical mixing (Gonçalves et al., 2019). The hydrogel is then placed into contact with bodily fluids or the surrounding environment where it absorbs water or biological fluids causing it to swell causing the hydrogel to release the loaded antimicrobial agents in a controlled and sustained manner. The advantages of hydrogel include controlled and sustained release, biofilm penetration, and reducing the risk of adverse reactions and toxicity (Xie, et al, 2022). One of the limitations is complexity, the preparation and application of hydrogels is extremely complex, especially in comparison to local antimicrobial agents this entails the need for specific expertise and equipment. Another limitation of hydrogels is that they suffer from biodegradation and may need to be replaced or replenished periodically this can introduce practicality challenges.

4.1. Safety

Hydrogels safety varies depending on the specific composition and the function made for. In addition most hydrogels are biocompatible and show low toxicity, this makes them safe in the treatment of PJIs (Atkin et al., 2022). However, there are reactions for example allergic reactions and inflammatory responses (Osmon et al., 2013). It is very essential to carry out biocompatibility and safety studies before administering hydrogels to patients (Lei et al., 2022).

4.2. Feasibility

The use of hydrogels in the management of PJI is capable of being done (Evans et al., 2023). Hydrogel can be transformed to come up with a supportive environment for drug delivery, allowing for the sustained release of

antibiotics at the target site (Chakrapani et al., 2022). Hydrogels ability to adapt to different such as injectables or coating for prosthetic components makes them very easily capable to be done (Karczewski et al., 2021).

4.3. Effectiveness

The effectiveness of hydrogels in the treatment of PJIs is determined by their ability deliver antibiotics locally therefore providing targeted and sustained therapeutic effects. Hydrogels also plays a role as carriers for antimicrobial agents and contribute to infection control (Samuel & Gould, 2009). More over the incorporation of hydrogels leads to controlled antibiotic release, there for overcoming challenges associated with systemic administration (Zheng et al., 2023). In order to ensure overall effectiveness it is important to regulate their mechanical properties to ensure that there is stability in the joint environment and to bring about the desired drug release kinetics (Li et al., 2023).

5. Antibiotic-Loaded Cement Spacer

This is an essential component in the management and revision of arthroplasty, Most especially in PJI. The Antibiotic-Loaded Cement spacers are temporary prosthetic material that are created using bone cement that is accumulated with antibiotics. These spacers have two major functions in PJI management which are maintaining joint space and functioning and delivering antibiotics locally. Antibiotic-loaded cement spacers have various positive outcomes in the treatment and management of PJI. They offer highly concentrated and targeted antibiotics at the site of infection specifically targeting at the pathogens responsible for the infection.

This method is However useful since most bacteria in PJI are encased in biofilms. In addition the spacers also allow the patient to maintain joint stability and functionality during the duration of the treatment, this is to be able to improve mobility and comfort during the crucial period. Moreover, various studies carried out in the last twenty years have shown that spacers reduce the risk of recurrent infection (Valle, 2004). These studies give further evidence of the efficiency of the spacers.
One of the most significant limitations of spacers is that they are temporary equipment. This temporality creates a need for subsequent surgery for the removal of spacers and the introduction of permanent implantation. The need for additional surgery increases the risk factor for patients with PJI (Parvizi, 2012). Additionally antibiotic spacers at times may be ineffective against highly resistant and multi-organism infections that call for broader systemic antibiotic therapy.

Over the years several studies into antibiotic-loaded cement spacers in PJI management. Anagnostakos et al in 2018 reported that the use of an antibiotic loader in two-stage revision in infected total knee arthroplasty resulted in an infection control rate of nighty seven percent. Moreover, Kuiper et al in 2013 showed that spacer had a success rate of eighty-seven percent in two-stage hip revision surgery.

One of the most extensively used Antibiotic-Loaded Cement Spacer is PMMA Polymethylmethacrylate commonly referred to as bone cement. PMMA cement is impregnated with antibiotics before it hardens and acts as a mechanical spacer to maintain joint stability and a local drug delivery system to treat PJI. The mechanism and consideration in the use of PMMA as an Antibiotic-Loaded cement spacer involve several steps such as the aforementioned impregnation with antibiotics, these involve mixing antibiotics with the PMMA, the choice of antibiotics usually varies depending on the factors previously mentioned in the paper, sometimes antibiotics can be pre-mixed with PMMA by manufacturer or this can be done at the time of surgery to allow for customization based on the specific patient needs and the pathogens.

This process is usually an intricate balancing act as high concentrations of antibiotics, though can improve bacterial eradication could destroy the structural integrity of the cement compromising its mechanical strength. Once cured, the PMMA cement forms a load-bearing spacer. The spacer is inserted after debridement during the first of a two-stage exchange procedure.

The spacer ensures joint stability, and bone alignment and aids in weight-bearing, mobility, and pain management. Antibiotics mixed with the PMMA cement release directly at the site of infection. This is an effective method for treating localized infection in PJI. The release of antibiotics from PMMA cement occurs in two steps an initial burst followed by a slow decline in concentration. Elution can be improved by shaping smaller beads with a larger surface area which can release a higher percentage of contained antibiotic over time. Below is a reference diagram showing the process.

5.1. Safety

In general antibiotic-loaded cement spacers are considered safe this is because they deliver high concentrations of antibiotics at specific targeted points of infections while also still providing mechanical support (Iarikov et al., 2012). As they are very effective against bacteria on the downside to their safety there is a significant challenge of developing antibiotic resistance. The longer use of antibiotics may lead to the development of resistant strains which brings to careful consideration regarding the use antibiotic and the amount of time to be used (Sabater-Martos et al., 2023).

5.2. Feasibility

The ability of antibiotic-loaded cement spacers being feasible lies in their ability to deliver high concentrations of antibiotics to the target site (Fu et al., 2020). The local delivery reduces the systemic side effects that are related with prolonged oral or intravenous antibiotic therapy. Cement spacers play also a role in providing mechanical stability which allows for the preservation of joints as well as mobility during treatment, this especially makes them feasible for example in cases where the infected prosthetic may need to be temporarily removed (Lunz et al., 2022).

5.3. Effectiveness

Antibiotic-loaded cement spacers are very effective in the complete eradication of joint infection. The main function is that they can release high concentrations of antibiotics for over an extended period at a specific infection point Thus being able to improve overall chances of complete infection eradication (van Vugt et al., 2019). In addition the use of spacers offers only a temporary solution, which undercuts its effectiveness. Medical personnel most of the time consider the approach during a staged approach; There are two stages involved , the first stage which involves the removal of the infected prosthesis implanting antibiotic-loaded spacer and also administering systemic antibiotics. In the second stage the spacer is later removed, and finally a new prosthesis is implanted (Fu et al., 2020).

6. Antibiotic Beads

Antibiotic beads help in the management of PJI, especially in cases where systemic antibiotics are unreliable (Ricciardi, 2020). Antibiotic beads are small biodegradable beads that are injected with antibiotics and are directly placed at the site of infection (Tzeng et al., 2015). Some of the most crucial advantages that make the approach highly feasible include localized antibiotic delivery, biofilm penetration, and reduced risk of systemic toxicity which have been discussed as advantages of intra-articular antibiotic infusion. However, the latter offers to resolve one of the challenges identified earlier in the paper which is the increased risk of antibiotic resistance by biofilm encased PJI bacteria (Getzlaf et al, 2016).

The strategy also has various disadvantages for example, the strategy offers a temporary solution since they are biodegradable, this calls for a subsequent revision strategy for the implantation of the permanent prosthesis, which entails surgery on the infected further enhancing the risk and inherent complexities of surgeries to patient. Furthermore, the small beads are targeted towards a specific pathogen which makes them highly ineffective in cases of multi-organism infection (Kozlowski et al., 2022). Moreover, there is a significant of the beads migrating from the infected spaces they can comprehensively compromise their effectiveness. Furthermore, there is limited

data on the clinical success rate of the beads. This calls for investigating further into their long-term effectiveness (Neuberger et al., 2017).

6.1. Safety

Antibiotic beads are able to reduce systemic exposure and therefore minimize the risk of the systemic side effects. Hence as a result of this, they are highly considered to be safe, Since they provide the safety this is by providing localized antibiotic delivery which are specifically directed to the infected site (van Vugt et al., 2019). However, those beads do not completely cover the area infected and ending up having a probability of risk of infection persistence (Wouthuyzen-Bakker et al., 2018).

6.2. Feasibility

In additionally ,The major factor that enables antibiotic beads to be feasible is that they can be able to placed precisely at the surgical point there for this is for allowing for targeted antibiotic to be released (van Vugt et al., 2019). The beads are also feasible this is because they are also capable of reducing the risk of patients facing systemic complications .Also the local release of antibiotics from beads is able to reduce the use for prolonged antibiotic therapy (Steadman et al., 2023).

6.3. Effectiveness

The antibiotic beads are also effective in the control of infections this is by being able to release high concentrations of antibiotics which are specifically directed into the infected area (van Vugt et al., 2019). Additionally, they also may be used to complement treatment as in cases where the systemic antibiotics may be not enough and may be used as an additional component to surgical procedures (Steadman et al., 2023).

7. Antibiotic Extended-Release Implants

For this strategy which is applied in the treatment of PJI infections is relatively new this is when comparing to the other strategies that have been discussed in the paper (Cataldo et al, 2010). The implants' inner workings are what makes them to be able to be different to the rest in that it is also formulated to be able to provide a sustained and controlled antibiotics release aimed directly into the infection site. This approach gives out significant challenges which are associated with the treatment of PJI and additionally overcomes the disadvantages experienced by other devices (Shoji et al, 2020).

Firstly, the development of the implants focuses on prolonged antibiotic release thus making them highly sustainable when comparing to other methods (Szyk et al, 2023). The long exposure of antibiotics on the sites that are infected ensures that a therapeutic concentration of antibiotics is present at the infected point thus enhancing the implant effectiveness (Anagnostakos et al, 2010). To add up , the implants also directly target the infected joint as is mentioned in other devices discussed previously . Moreover, while the antibiotic-loaded cement spacers and beads in various cases require additional surgical procedures for replacement and removal thus increasing the complexity in treatment of PJI , antibiotic extended-release implants is much more efficient, In that Once the implant is in place the patient does not need to undergo another surgery to remove it (Ma et al, 2018). Additionally, the treatment procedure can effectively fight the re occurrence of antibiotics due to the sustained release strategy (Xiong et al, 2014).

7.1. Safety

Firstly, Antibiotic extended-release implants are made up for a localized antibiotic which are able to make them a safe option this is because they reduce systemic exposure and potential side effects that are brought about by intravenous or prolonged oral antibiotic use (Le Vavasseur & Zeller, 2022). The negative side to this is that there is a risk of infection persistence especially if the implants do not fully cover the extended area (Le Vavasseur & Zeller, 2022).

7.2. Feasibility

For feasibility of extended-release implants it lies in their ability to give out targeted antibiotic delivery to the infected joint space and also the ability to control the release of antibiotics for a long duration Thus reducing the need for frequent intervention (Le Vavasseur & Zeller, 2022). Also the feasibility of the implants heavily depends on ease of surgical placement, implant design, and compatibility with joint anatomy (Baddour & Chen, 2022).

7.3. Effectiveness

The extended-release implants are important in maintaining sustained antibiotic levels at the infection site thus leading to better outcomes (Le Vavasseur & Zeller, 2022). In addition they are also effective in a way that they limit antibiotic exposure to the infection site; thus helping reduce the risk of systemic side effects (Le Vavasseur & Zeller, 2022).

7.4. Comparative analysis

So as to help medics formulate informed decisions on the choice of local antimicrobial agents, it is essential to create a comparative analysis this is by highlighting the advantages and disadvantages of each agent in terms of safety, effectiveness, and feasibility.

7.5. Safety

Intra-articular Antibiotic Infusion (IAI) use is considered safe this is by reducing systemic antibiotic exposure; however, it possesses the risk of secondary surgical procedures which has inherent risk (Li et al., 2021). The antibiotic-loaded Cement Spacer (ALCS) use is also considered safe but has spacer-related complications including dislocation and fracture are factors that make it unsafe (Li et al., 2023). Antibiotic Beads (AB) use might be considered the most unsafe due to variuos factors such as a risk of bead migration which could compromise safety. It entails that a secondary surgery may be needed to mitigate the risk (van Vugt et al., 2019). The Antibiotic Extended-Release Implant (AERI) is developed for the safety since it provides long term antibiotic release and does not lead to additional secondary surgical need (Le Vavasseur & Zeller, 2022).

8. Discussion

The Single-stage revision having intra-articular antibiotic infusion has come up as a future fruitful treatment option for periprosthetic joint infection (PJI) (Ji et al., 2019). Various studies carried out have regularly demonstrated its desired result, with their success level ranging from 84% to 99% even in complex cases involving culture-negative PJI, multidrug-resistant organisms, and multiple failed surgeries (Li et al., 2022). The incorporation of the approach offers several mentioned advantages over traditional two-stage revision, which includes reduction in surgical burden, decrease in hospitalization times, and improvement in functional outcomes.

As evident to the study that was conducted in 2019 by (Ji et al.,), it is evident that the function is to investigates the use of single-stage revision with cement less reconstruction as a treatment for chronically infected total hip arthroplasty (THA). In addition, far from the traditional two-stage approach, which is involved in removing the infected implant, and treating the infection, then later re-implant a new joint.

The following had 126 patients who had different characteristics, thus representing a wide range of candidates than typically correct for single-stage processes (Li et al., 2022). The findings were encouraging, having one of them being a high success rate: At an average follow-up of 58 months, 89.2% of patients remained infection-free. There was high success rate for patients with challenging conditions like multidrug-resistant organisms (84.2%) (Li et al., 2022).

Improved mobility and function: For example Patients reported significant improvements in hip function as according to the Harris hip score, thus reaching an average of 79.6 points at the final assessment (Chahal et al, 2015).

Cementless reconstruction benefits: The use of cementless implants may bring about to the positive results. The cementless implants gives way for better bone integration and potentially minimizes the risk of loosening and infection associated with cement (Matthias et al, 2021). These studies suggest that single-stage revision with cementless reconstruction can be a viable and effective option for treating chronic hip infections. This approach has more benefits over the two-stage method, which includes reduced hospital stays, faster recovery times, and potentially lower costs. However, it is essential to point that this study has limitations. Extended follow-up and comparing with the other treatment options are needed to confirm the long-term success of this approach (Elliott et al, 2011).

Most importantly, high doses of antibiotics are poured directly into the joint space, bathing the site and potentially eradicating the unseen enemy. The outcomes are promising when Comparing to a control group of culture-positive patients, the "infused" group achieved a similarly impressive 90.2% infection-free rate after over four years (Li et al., 2022). The findings suggest that even without knowing the exact foe, a targeted combat can be of full function. Of course, there are caveats. Extended research and larger studies are needed to solidify these results. This research is able to open the door to a potentially faster, single-stage treatment option for a particularly frustrating type of PJI. In conclusion by delivering antibiotics directly to the desired target, intra-articular infusion may offer a valuable support in the fight against invisible joint invaders (Li et al., 2022).

9. Conclusion

In a nutshell, management of Periprosthetic Joint Infection (PJI) during arthroplasty revision is a complicated problem that requires comprehensive detailed research and data-driven decision-making (Ji et al., 2022). This article underperforms the importance of accurate diagnosis, a multidisciplinary use, and the utilization of several local antimicrobial agents in PJI management. Therefor the focus on agents like intra-articular antibiotic infusion, antibiotic-loaded cement spacers, beads, and extended-release implants is emphasized, which aims to reduce systemic side effects and recurrence. The paper pushes for future research into local antimicrobial agents, this is by considering safety, effectiveness, feasibility, and individual patient characteristics.

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: Not applicable.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 72-79
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.307

Clinical Study and Surgical Management of Alveolar Echinococcosis (AE)

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Abstract
Background: Hepatic alveolar echinococcosis (HAE) is a serious zoonotic infection that affects humans. It may have a tumor-like appearance at times. Percutaneous treatment of HAE patients is extremely relaxing for them. HAE is a significant human zoonotic infection caused by the fox tapeworm Echinococcus Multilocularis larvae. It possesses the characteristics of an invasive tumor-like lesion due to its infiltrative growth pattern and protracted incubation period. The disease is endemic over central Europe, Asia, and North America. Objective: To determine the clinical study and Surgical management of alveolar Echinococcosis (AE). Methods: A cross-sectional study was conducted at the First Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, P.R China, which was performed between September 2018 and December 2023. The total number of patients in our study was 142. The number of Male patients in our study was 67 and female patients were 75. In 142 consecutive patients who underwent for blood tests and surgical Procedures. We took preoperative and postoperative blood tests for all operated patients. I take PNM staging for all patients and we took a brief history from all patients. Data was tabulated and analyzed by SPSS version 25. Results: A total of 142 patients were enrolled with a mean±SD age of 37.32±13.90. The mean±SD of Preoperative WBC was 6.85±1.76. The mean±SD of Preoperative NE was 6.85±1.76. The mean±SD of Preoperative HB was 1.33.7±23.5. The mean±SD of Preoperative Platelets was 288.21±94.1. The mean±SD of the frequency of PNM staging P1N0M0 was 21 and its percentage was 14.8. The frequency of PNM staging P2N0M0 was 59 and its percentage was 41.5. The frequency of PNM staging P3N0M0 was 29 and its percentage was 20.4. The frequency of PNM staging P4N0M0 was 33 and its percentage was 23.2. The frequency of Jaundice before surgery was 19 and its percentage was 13.4. The frequency of Laparoscopic / Laparotomy in abdominal dissection was 119 and its percentage was 83.8. The frequency of laparoscopy was 23 and its percentage was 16.2. In all cases, P-value was <0.05. Conclusion: Hepatic resection is considered safe and the only curative treatment for Hepatic alveolar echinococcosis (HAE), when the lesion can be removed completely. The advantages of this technique for AE treatment need to be compared further with the classical open approach. Laparoscopy appears as a feasible and safe approach for patients with PNM stages alveolar echinococcosis without impact on early disease recurrence. Hepatic alveolar echinococcosis will improve the treatment results by avoiding non-radical surgery associated with the development of complications after further radical surgical treatment. Liver resection remains the gold standard for AE. In our study females were more as compared to males. PNM staging of P2N0M0 patients was more in our study as compared to other stages. In our study, there was no major complication noted after the surgical procedure.

Keywords: Hepatic Alveolar Echinococcosis (HAE), PNM Staging, Alveolar Echinococcosis (AE)

1. Introduction

China is one of the countries seriously affected by hepatic alveolar echinococcosis (HAE), accounting for 91% of the global burden of new HAE cases every year. One of the worst zoonoses, human hepatic alveolar echinococcosis (HAE), is very common in rural Western China (Torgerson et al., 2010; Zhang al et al., 2015). The larval stage of Echinococcus multilocularis is the cause of human hepatic alveolar echinococcosis (HAE) (McManus et al., 2011). Because of its distinctive infiltrative growth, hepatic alveolar echinococcosis (AE), a chronic proliferative parasite illness, has a poor natural prognosis (Torgerson et al., 2010). After ten to fifteen years of diagnosis, death in individuals with AE who are not treated or are not treated enough has been reported to reach 90% (Vuitton et al., 2020; Aji al et al., 2018; McManus al et al., 2012). HAE is sometimes known as "parasitic liver cancer" since it typically shows signs of malignant progression. HAE progresses slowly; it may take up to ten years. Although there is a substantial chance of recurrence, radical hepatic resection at the early and middle stages of the disease can produce excellent results (Wen et al., 2019). The only treatments available are liver transplantation or palliative medication therapy if the lesion spreads, in which case there is a significant risk of mortality (Giraudoux et al., 2013). The first organ impacted by a larval invasion is the liver. In seven out of ten instances, hepatic lesions are limited to the right hepatic lobe; in forty percent of cases, there is also involvement of the liver hilus. Out of 10 instances, only two have an infestation in both hepatic lobes (Kern et al., 2006). Usually, in the early stages of the infection, patients have no symptoms. Cholestatic jaundice and upper abdomen discomfort are possible initial symptoms. There is a five to fifteen-year incubation period (Heyd et al., 2000). In advanced stages of the disease, complications such as portal hypertension, bleeding esophageal varices and biliary obstruction have been reported. These complications are attributed to the invasive expansion of the E. multilocularis lesion in the liver (Craig et al., 2003). Endoscopic retrograde cholangiopancreatography (ERCP) is a commonly used treatment for biliary fistulae. Cystic echinococcosis, which is caused by E. granulosus, has an incidence of 1% to 25% and can result in biliary complications like intrabiliary rupture in conjunction with obstructive jaundice (Sezgin et al., 2005; Erzurumlu al et al., 2005). The rate of curative resection can only be increased by early discovery, which is verified by serologic markers and imaging techniques (Sharma et al., 2012; Buttenschoen al et al., 2009). endoscopic and percutaneous procedures as therapeutic alternatives for those for whom surgery has intolerable risks or for whom it is not possible to completely remove the AE lesion (Kern et al., 2000; Kern al et al., 2010).

An uncommon and dangerous parasite disease called human alveolar echinococcosis (AE) is caused by infection with the echinococcus multilocularis larval stage (Cakmak et al., 2013). When paired with the outcomes of immunodiagnosis (specific serology) and epidemiological data, imaging techniques including ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and 18F fluorodeoxyglucose (FDG)-positron emission tomography (PET) are used to diagnose AE lesions (Kern et al., 2017; Kratzer al et al., 2015). More precisely than ultrasonography, CT scans can show the characteristic calcifications and can also indicate the form, number, size, and location of lesions (Schweiger et al., 2012). When total resection is possible, early diagnosis is thought to be the most crucial aspect in improving the prognosis of HAE (Reuter et al., 2001). It is still debatable how to treat severe HAE, particularly when it comes to the need for aggressive procedures like orthotopic liver transplantation (OLT) and palliative resection (Farrokh et al., 2015; Kawamura al et al., 2011).

If the parasite mass can be removed completely, then curative surgery for AE may be possible. R0 resectability is more common at early stages. Because medical treatment alone produces excellent long-term effects, the usefulness of palliative surgery is questionable. Necrotic tissue, however, is susceptible to bacterial superinfection, which can result in sepsis that is potentially fatal. When alternative methods are ineffective for treating issues, palliative surgery becomes a viable choice (Qin et al., 2016).

2. Materials and Methods

A cross-sectional study was conducted at 1ST Affiliated Hospital of Xinjiang Medical University, Urumqi, Xinjiang, P.R China, which was performed between September 2018 and December 2023. The total number of patients in our study was 142. The number of Male patients in our study was 67 and female patients were 75. In 142 consecutive patients who underwent for blood tests and surgical Procedures. We took preoperative and postoperative blood tests for all operated patients. We took PNM staging for all patients and we took a brief history from all patients. Data was tabulated and analyzed by SPSS version 25

3. Results

Table 1: Mean value of different characteristics of all the enrolled patients (*n=142*)

Variables	Mean±SD
Age (Years)	37.32±13.90
Preoperative WBC	6.85±1.76
Preoperative NE	56.05±9.7
Preoperative HB	133.7±23.5
Preoperative Platelets	288.21±94.1
Preoperative protein	38.6±4.16
Preoperative T-Bil	17.17±25.2
Straight forward	6.39±14.12
Preoperative AST	40.40±53.06
Preoperative ALT	47.44±68.2
Operative time (mint)	345.38±132.8
Intra Operative blood loss (ml)	464.08±506.41
WBC on the 1ST day after surgery	15.52±4.57
HB on the 1ST day after surgery	120.29±26.14
Platelets on the 1ST day after surgery	263.55±271.13
AST on the 1ST day after surgery	399.63±420.0
ALT on the 1ST day after surgery	397.73±366.94
T BIL on the 1ST day after surgery	28.76±27.97
PROTEIN on the 1ST day after surgery	31.62±4.73
WBC on 3rd postoperative day	8.859±2.54
NE on 3rd postoperative day	75.11±7.11
HB on 3rd postoperative day	106.52±21.3
PLATELETS on 3rd postoperative day	205.69±70.72
AST on 3rd postoperative day	104.87±101.7
ALT on 3rd postoperative day	220.20±196.4
T BIL on 3rd postoperative day	28.13±28.56
PROTEIN on 3rd postoperative day	31.50±5.24

Post-Operative Time (days)	1.57±0.61
Extubation Time	8.49±8.1
Expenses (yuan)	68517.8±25742.6
Post-operative hospital stays	10.64±7.51

Total of 142 patients were enrolled with mean±SD age of 37.32±13.90. The mean±SD of Preoperative WBC was 6.85±1.76. The mean±SD of Preoperative NE was 6.85±1.76. The mean±SD of Preoperative HB was 1.33.7±23.5. The mean±SD of Preoperative Platelets was 288.21±94.1. The mean±SD of Preoperative protein was 38.6±4.16. The mean±SD of Preoperative T-Bil was 17.17±25.2. The mean±SD of straight forward was 6.39±14.12. The mean±SD of Preoperative AST was 40.40±53.06. The mean±SD of Preoperative ALT was 47.44±68.2.

The mean±SD of operation time (min) was 345.38±132.8. The mean±SD of Intra operative blood loss (ml) was 464.08±506.41. The mean±SD of WBC on the ist day after surgery was 15.52±4.57. The mean±SD of HB on the ist day after surgery was 120.29±26.14. The mean±SD of Platelets on the ist day after surgery was 263.55±271.13. The mean±SD of AST on the ist day after surgery was 3.99.63±420.0. The mean±SD of ALT on the ist day after surgery was 397.73±366.94. The mean±SD of T-BIL on the ist day after surgery was 28.76±27.97. The mean±SD of protein on the ist day after surgery was 31.62±4.73. The mean±SD of WBC on the 3rd postoperative day was 8.859±2.54. The mean±SD of NE on 3rd postoperative day was 75.11±7.11. The mean±SD of HB on 3rd postoperative day was 106.52±21.3. The mean±SD of platelets on 3rd postoperative day was 205.69±70.72. The mean±SD of AST on 3rd postoperative day was 104.87±101.7.

The mean±SD of ALT on 3rd postoperative day was 220.20±196.4. The mean±SD of T-BIL on 3rd postoperative day was 28.13±28.56. The mean±SD of Protein on 3rd postoperative day was 31.50±5.24. The mean±SD of Post-operative time (day) was 1.57±0.61. The mean±SD of Extubation time was 8.49±8.1. The mean±SD of Expenses in (Yuan) was 68517.8±25742.6. The mean±SD of Post-operative hospital stay was 10.64±7.51.

In all cases P-value was <0.05.

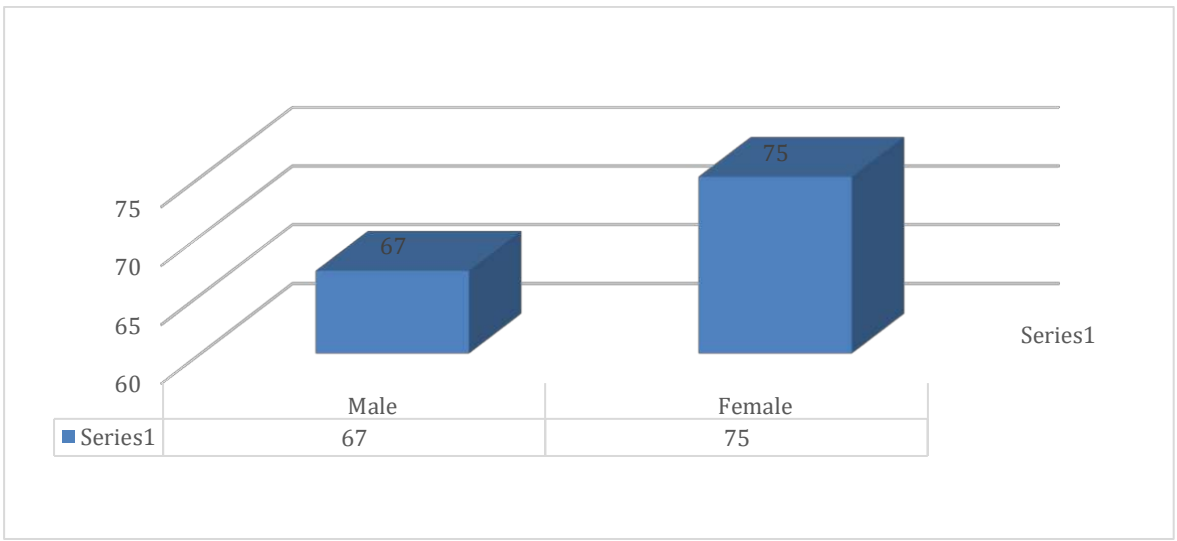

Figure 1: Bar graph showing gender distribution

Figure 1, Bar graph showing gender distribution in which female patients were 75 and male patients were 67. The total number of patients was 142 in our study. In this graph, female patients were more as compared to male patients.

Table 2: Patient characteristics of enrolled patients (n=142)

Variables		
Gender	Frequency	Percentage
Male	67	47.2
Female	75	52.8
Number of Lesions		
Nil	3	2.1
1	123	86.6
2	12	8.5
3	3	2.1
4	1	0.7
PNM Staging		
P1N0M0	21	14.8
P2N0M0	59	41.5
P3N0M0	29	20.4
P4N0M0	33	23.2
Jaundice before surgery	19	13.4
Post-operative complication	110	77.5
Abdominal/pelvic effusion		
not worn	98	68.3
puncture	43	30.3
conservative treatment	2	1.4
Pleural Effusion		
not worn	129	90.8
puncture	13	9.2
Survival	142	99.3
postoperative outcome		
Multiple bone metastases	1	0.7
Bile leakage	1	0.7
get better	136	95.8
liver transplantation	1	0.7
jaundice	1	0.7
Cholangitis	1	0.7
Smoking	5	3.5
Laparoscopy/laparotomy		
abdominal dissection	119	83.8
Laparoscopy	23	16.2

Patient characteristics of enrolled patients in Table 2 were (n=142). The frequency of male patients was 67 and its percentage was 47.2. The frequency of female patients was 75 and its percentage was 52.8. The frequency of number of lesion Nil was 3 and its percentage was 2.1. The frequency of number of lesions 1 was 123 and its percentage was 86.6. The frequency of number of lesions 2 was 12 and its percentage was 8.5. The frequency of number of lesions 3 was 3 and its percentage was 2.1. The frequency of number of lesions 4 was 1 and its percentage was 0.7.

The frequency of PNM staging P1N0M0 was 21 and its percentage was 14.8. The frequency of PNM staging P2N0M0 was 59 and its percentage was 41.5. The frequency of PNM staging P3N0M0 was 29 and its percentage was 20.4. The frequency of PNM staging P4N0M0 was 33 and its percentage was 23.2.

The frequency of Jaundice before surgery was 19 and its percentage was 13.4.

The frequency of Post-operative complications was 110 and its percentage was 77.5. The frequency of Abdominal / Pelvic effusion not worn was 98 and its percentage was 68.3. The frequency of Abdominal / Pelvic effusion puncture was 43 and its percentage was 30.3. The frequency of conservative treatment was 2 and its percentage was 1.4. The frequency of pleural effusion was not worn in 129 patients and its percentage was 90.8. The frequency of pleural effusion was puncture were in 13 patients and its percentage was 9.2.

The frequency of survival in our study was 142 and its percentage was 99.3.

The frequency of postoperative outcome in multiple bone metastases was 1 and its percentage was 0.7.

The frequency of postoperative outcome in bile leakage was 1 and its percentage was 0.7. The frequency of postoperative outcome in get better was 136 and its percentage was 95.8. The frequency of postoperative outcome in liver transplantation was 1 and its percentage was 0.7. The frequency of postoperative outcome in Jaundice was 1 and its percentage was 0.7. The frequency of postoperative outcome in smoking was 5 and its percentage was 3.5. The frequency of Laparoscopic / Laparotomy in abdominal dissection was 119 and its percentage were 83.8. The frequency of laparoscopy was 23 and its percentage were 16.2. In all cases, P-value was <0.05.

4. Discussion

Surgical planning with precision and accurate anatomical evaluation is important factors in choosing the most effective treatment for human hepatic alveolar echinococcosis (HAE). (Buttenschoen et al., 2009; Dong al et al., 2013).

Thus far, ultrasound, CT, and magnetic resonance imaging (MRI) have been the primary methods used for preoperative diagnosis and evaluation of hereditary anemia (HAE). An estimated assessment of the lesion position and a preliminary diagnosis are typically obtained through ultrasound examination. It is frequently necessary to use CT and MRI in conjunction with image post-processing techniques (such as CTA) to further diagnose and assess the invasion of conduits both inside and outside the liver by lesions. Due to the limited 2D presentation of these tests, surgeons must use their clinical expertise and understanding of liver anatomy to recreate 3D spatial images. The extent of lesions ultimately determines the surgical course of treatment (Chen et al., 2010; Fang al et al., 2010). Lesions from AEs nearly always occur in the liver. This infiltration into biliary and circulatory systems is clinically significant in addition to lesion size (Xie et al., 2013).

Despite the fact that radical resection was thought to be the best option for treating HAE, many cases were not identified until the lesion had progressed to the point where it was no longer possible to entirely remove it because of the lengthy clinical latency. There is disagreement over how to treat advanced HAE, particularly over the need for aggressive surgeries (Kawamura et al., 2011).

One of the causes for the decrease in intraoperative bleeding and blood transfusion was the ability to judge and recognize hepatic conduits with greater precision at the same time, allowing for a shorter operation duration. Patients' serum albumin levels varied between the two groups, although not significantly. The incidence of lesion recurrence and surgical complications (He et al., 2015).

5. Conclusion

Hepatic resection is considered safe and the only curative treatment for Hepatic alveolar echinococcosis (HAE), when the lesion can be removed completely. The advantages of this technique for alveolar echinococcosis (AE) treatment need to be compared further with the classical open approach. Laparoscopy appears as a feasible and safe approach for patients with PNM stages alveolar echinococcosis without impact on early disease recurrence. Hepatic alveolar echinococcosis will improve the treatment results by avoiding non-radical surgery associated with the development of complications after further radical surgical treatment. Liver resection remains the gold standard for alveolar echinococcosis (AE). In our study females were more as compared to males. PNM staging

of P2N0M0 patients was more in our study as compared to other stages. In our study, there was no major complication noted after the surgical procedure.

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: Not applicable.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 80-84
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.308

Compliance Level and Side Effects in the Treatment of Tuberculosis Patients: A Study from Indonesia

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Abstract
Indonesia has the second largest Tuberculosis (TB) burden in the world. One of the solutions to reduce this prevalence is medication compliance and avoiding side effects. However, compliance level and side effects data on TB patients in Indonesia are still limited. Therefore, the study aimed to determine compliance levels and medication side effects in tuberculosis susceptible drugs patients. Medication Morisky Adherence Scale-8 (MMAS-8) and Naranjo algorithm scale were used to determine the compliance level and the side effects, respectively. Seventy-six patients were involved in this study (male 64.47%, mean age 45.68 y.o, and 98.68% living with family). The compliance level of low, medium, and high were 5.28%, 40.79%, and 53.93%, respectively. Thirty-five (46.05%) patients experienced side effects, which involved a high probable category (37.15%) was tingling, a probably category (42.85%) was nausea, itch, myalgia, and tingling, and a possible category (20.01%) was cough and myalgia. We didn't find any correlation between compliance with age, sex, education level, and occupations. However, education level slightly correlated with compliance (p 0.066). The compliance level is still low, provides an education and side effects prevention and treatment may increase the compliance level. These compliance and side effects data give a solution to reduce the prevalence of TB in Indonesia.

Keywords: Compliance, MMAS-8, Naranjo Algorithm, Side Effects, Tuberculosis

1. Introduction

Tuberculosis (TB) is a disease caused by the *Mycobacterium tuberculosis* and the second cause of mortality from infectious diseases group (WHO, 2022). The prevalence worldwide people fell ill of TB reached 10.6 million (WHO, 2021). Until recently, TB is still a global burden, especially for a developing country, including Indonesia, which placed the second largest contributor after India (WHO, 2023). In Indonesia, the TB incidence rate for drugs susceptible (non-MDR-TB) reached 354 per 100.000 populations and 10 per 100.000 populations for MDR-TB (WHO, 2022). Compliance with the medications is one of the determinant keys to eradicating TB and reducing the incidence of multidrug-resistant TB (MDR-TB) (Sveinbjornsdottir., et al. 2024). However, this compliance will be reduced by the side effects of the TB medications (Awofeso, 2008; Lolong et al., 2023). Unfortunately, the

compliance level and side effects studies for TB medications are still limited in Indonesia. Therefore, we conducted a study on the compliance level and TB medication's side effects in Indonesian susceptible-drug TB patients.

2. Method

The study is a prospective cross-sectional study through direct interviews with the patients using the Medication Morisky Adherence Scale-8 (MMAS-8) for compliance and the Naranjo algorithm for drug side effects (Laghousi et al., 2023; Belhekar et al., 2014). This study was conducted in Ciamis General Hospital from January-April 2023. The patient sampling method used was purposive sampling. The inclusion criteria for the patients were diagnosed with TB susceptible drugs, outpatients, age ≥ 18 y.o, and agreed to be a respondents by signing informed consent. All the procedures of this study were approved by the Ethical Research Health Committee of Bakti Tunas Husada University with number 034/E.01/KEPK-BTH/III/2023. The data was analyzed using SPSS version 22 with the Chi-square method. The significant level is at a P value of 0.05.

3. Results

Seventy-six patients were involved in this study with domination of males, 46-65 y.o, elementary school education, unemployment, and living with family members (Table 1). Moreover, 13.6% of this population has no health insurance to cover the medications cost. The results of the compliance level for low, moderate, and high adherence were 5.26%, 40.79%, and 53.95%, respectively (Table 2). Moreover, no correlation between compliance with age, sex, education level, and occupation. However, education level slightly correlated with the compliance (p 0.066) (Table 3). Based on the Naranjo algorithm, myalgia, itchy, shortness of breath, and tingling are highly probable side effects category due to TB medications. Meanwhile, nausea and cough side effects involve probable and possible categories, respectively (Table 4).

Table 1: Patients Demographic

Patients Characteristic		**number**	**%**
Age	19-25 y.o	14	18.42
	26-35 y.o	9	11.84
	36-45 y.o	7	9.21
	46-55 y.o	17	22.37
	56-65 y.o	16	21.05
	≥ 66 y.o	13	17.11
Sex	Male	49	64.47
	Female	27	35.53
Living with family	Yes	75	98.68
	No	1	1.32
Education	Elementary school	28	36.84
	Junior High School	22	28.95
	Senior High School	17	22.37
	Bachelor	8	10.53
	Postgraduate	1	1.32
Occupations	Goverment Employees	6	7.89
	Enterpreneur	33	43.42
	Teacher	1	1.32
	Farmer	3	3.95
	Housewife	14	18.42
	Unemployment	19	25.00
Insurance ownership	Yes	66	86.84
	No	10	13.16
Total		76	100

Table 2: Compliance Level Based on MMAS-8 Questionnaire

No	Compliance Level	number	%
1	Low adherence	4	5.26
2	Moderate adherence	31	40.79
3	High adherence	41	53.95
Total		76	100

Table 3: Relationship between Compliance Level and Patients Characteristic

	Characteristic	Compliance Level			p-value (95% CI)
		Low adherence (%)	Moderate adherence (%)	High adherence (%)	
Age	19-25 y.o	0.00%	13.16%	5.26%	0.315
	26-35 y.o	1.32%	2.63%	7.89%	
	36-45 y.o	1.32%	3.95%	3.95%	
	46-55 y.o	1.32%	5.26%	15.79%	
	56-65 y.o	1.32%	9.21%	10.53%	
	≥66 y.o	0.00%	6.58%	10.53%	
Sex	Male	2.63%	27.63%	34.21%	0.767
	Female	2.63%	13.16%	19.74%	
Living with family	Yes	5.26%	40.79%	52.63%	0.649
	No	0.00%	0.00%	1.32%	
Education level	Elementary school	2.63%	14.47%	19.74%	0.066
	Junior High School	0.00%	10.53%	18.42%	
	Senior High School	0.00%	14.47%	7.89%	
	Bachelor	2.63%	1.32%	6.58%	
	Postgraduate	0.00%	0.00%	1.32%	
Occupations	Goverment employees	0.00%	0.00%	7.89%	0.401
	Enterpreneur	1.32%	23.69%	18.42%	
	Unemployment	2.63%	9.21%	13.16%	
	Teacher	0.00%	0.00%	1.32%	
	Farmer	0.00%	2.63%	1.32%	
	Housewife	1.32%	5.26%	11.84%	
Insurance	Yes	3.95%	34.21%	48.69%	0.127
	No	1.32%	6.58%	5.26%	

Table 4: Side effects based on Naranjo algorithm

Category	Side Effects	n	%
Possible	Myalgia, cough	7	20
Probable	Nausea, tingling, itchy, myalgia	15	42.85
Highly Probable	Myalgia, itchy, shortness of breath, tingling	13	37.15

4. Discussion

The demographic data indicates that 98.68% of TB patients live with family members such as their father and mother, as well as other family members (Table 1). This is a dominant factor in the rapid spread of TB in Indonesia, necessitating a reorganization of population density in areas to reduce the acceleration of TB transmission (Narasimhan et al., 2013). Additionally, TB patients predominantly have low education levels and are unemployed

(Table 1). Low education levels result in limited critical thinking skills and can hinder the effectiveness of disseminating TB prevention information and compliance with TB treatment (Nezenega et al., 2020). Meanwhile, unemployment leads to smokers, alcohol abuse, and the inability to meet the nutritional needs of the community, resulting in decreased immunity or community health and making individuals more susceptible to infection (Przybylski et al., 2014). Improving human resources through increased access to education and facilitating access to suitable employment is fundamental in addressing this issue. Another factor impacting the increase in TB is the lack of health insurance for TB patients (Table 1), requiring individuals to bear the treatment costs themselves. Based on these factors, TB treatment becomes the primary focus as an eradication measure by covering all treatment costs for TB patients.

In the compliance study, the findings are that the compliance rate is only about 53.95% (Table 2), with the remaining TB patients experiencing forgetfulness in taking medication, which can affect the success of treatment. The most significant factor influencing this non-compliance is the level of education (Table 3). Therefore, increasing education through facilitating access to education and comprehensive TB-related information is crucial in improving patient compliance with medication (Nezenega et al., 2020; Yani et al., 2022).

In the study on side effects, the findings are that muscle pain or stiffness, skin itching, tingling, and shortness of breath are the main side effects of treatment for drug-sensitive TB (not MDR). Approaches to preventing side effects such as providing pyridoxine for tingling are essential (Mafukidze et al., 2015; Bhargava & Bhargava., 2018), and consuming plenty of water or eating bananas can prevent nausea or vomiting (Central TB Division, 2016). Meanwhile, treatment approaches are used for side effects that cannot be prevented, such as using antihistamines or topical corticosteroids for mild to moderate itching, and using topical pain relievers for myalgia (Central TB Division, 2016). Providing information or guidance in the form of a pocketbook regarding side effects and self-management techniques is crucial to be provided to patients.

Author Contributions: Concept – Y.P.S. ; Design – Y.P.S., N.R., M.H.; Resources – Y.P.S, N.R, M.H.; Materials – Y.P.S., N.R., M.H.; Data Collection and/or Processing – M.H.; Analysis and/or Interpretation – Y.P.S., N.R., M.H.; Literature Search – Y.P.S., N.R., M.H.; Writing – Y.P.S., N.R., M.H.; Critical Reviews – B Y.P.S., N.R., M.H.

Funding: This research received no external funding

Conflicts of Interest: The authors declared no conflict of interest.

Informed Consent Statement/Ethics approval: All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Bakti Tunas Husada University with number 034/E.01/KEPK-BTH/III/2023.

Acknowledgments: The authors thank to University of Bakti Tunas Husada for the encourage, all the healthcare professional in General Hospital of Ciamis, and all the participants.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 85-94
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.309

Risk Factors of Severe Acute Malnutrition among Under-five Children in Al-Nohud Western Kordufan State: Cross-Sectional Study

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Abstract
Background: Malnourishment is still conceder a severe public health and progress issue, not just in evolving populations but everywhere in the world. Because it outcomes in the losses of 3.5 million kids less than five, each year, it is a major issue. Its severity is still greatest in Sudan and western Kordufan, where it is public health problems. Objectives: Identification of risk factors and immediate contributors to malnutrition among kids less than five years old was the goals of the study. Methodology: The study's methodology was prospective descriptive. This study included all children under the age of five who were admitted to Al-Nohud Hospital and were diagnosed with unembellished critical malnutrition, which is identified as weight for height quantity of 70% of the median or > 3 SD below the mean World Health Organization situation values or the occurrence of consensual fighting oedema of nutritious origin. The World Health Organization arrangement of kids from 0-59 months of time for height (HFH -3 z-score, or Mid-Upper Arm Circumstances 115 mm) served as the foundation for this investigation. A large proportion of kids (66.7%) had a Mid-Upper Arm Circumstances of below 11cm (110mm), exhibiting acute malnourishment, and (28.6%) had a Mid-Upper Arm Circumstances of between 11 and 12cm, showing adequate malnourishment. According to interpretation of Mid-Upper Arm Circumstances in the research, Weight in relation to height, which represents the majority, is (-3SD). Results: Maternal illiteracy, mother's age, families' economic situation, exposure to infectious infections, and diarrhoea were all factors in under-five malnutrition. Conclusion: By educating mothers on the value of healthy eating for their children's growth and development, we can raise their level of education. All expectant mothers should get antenatal care, and existing programs on child care, infection control, and breastfeeding should be reinforced.

Keywords: Risk factor, Malnourishment, Under Nutrition, Stunting, Wasting

1. Introduction

One of the most important measures recommended by WHO to achieve health equity are kids malnourished measure. The term malnutrition generally describes under nutrition and over nutrition (Picbougoum et al., 2023; Uthman, 2009). The most important anthropometric indicators used to measure malnutrition in the communities

less than 5 years, are stunting, wasting, underweight. Low weights reflect the relationship of height to age as well as weight to age, and it also reflects the accumulation of cases of acute nourishments. (Janevic et al., 2020).

The Millennium Development Goals (MDGs) state as the first goal "to halve between 1990 and 2015 the proportion of people who suffer from hunger" (Bliznashka et al., 2021) Various studies have proven that the problem of malnutrition is large, and that the groups most vulnerable to it are kids and women who suffer from the persistence of malnutrition related to malnourishment, for example food security.

Malnourishment is a severe issue since it kills 3.5 million kids less than 5 years, each year globally and ranks third in the world for the problem of disease in this group (Onis et al.,2008). Equal though babyhood malnourishment decreased somewhat internationally through the 1990s; its occurrence grew in Africa equal throughout that year. (Blössner et al., 2005). Around 143 million kids less than 5 years in the evolving world—more than 25% of all children—are malnourished. Nearly three-quarters of the 143 million undernourished kids living in just 10 Sub-Saharan African countries, and above 25% of kids less than 5 years are undernourished. (Huang & Yang, 2020).

When only nations with stunting prevalence rates of at least 20% were taken into account, thirty-six present nations calculated for 90% of all stunted kids worldwide (Pediatrics Week, 2017). Children in underdeveloped nations experience moderate severe undernourishment in about nine percent of sub-Saharan African children, 19% of South Asian children (State of the World's Children, 2012). And severe undernourishment in tow percent of kids (Onis et al.,2008). This equates to roughly 60 million children who are moderately acutely malnourished and 13 million who are severely acutely malnourished at any given time (Jamro et al., 2012).

Until now, malnutrition is considered a health problem that represents a major challenge to public health and development as a result, not alone in evolving populations, however likewise globally (Uthman, 2009). Formerly, kid's malnourishment continues to be problem for public health, primarily in progressing nations like Ethiopia (GUPTA et al., 1991).

The federal ministry of health for Sudan (2014) (Ahmed et al., 2020). Stated that Sudan's rate of childhood malnutrition has risen beyond the global average. One in 20 Sudanese children is severely starving, according to the deputy secretary of the ministry of health, who revealed that half a million kids in the country are distress from prolonged malnourishment. 12.6% of kids under the age of five continue to experience severe wasting and stunting due to malnutrition (International Food Policy Research Institute, 2014). Utilizing anthropometric measurements, often weight and length (or height), children's health is frequently assessed as an outcome of growth (Gebretsadik et al., 2021). Both in Sudan and the research area, child malnourishment is still a severe public health problem. Identifying the reasons for malnourishment is necessary to fighting it, which is exactly it was critical to identify the root causes of poor malnourished in kids of less than five years.

2. Method

Research was done in Al-nohoud town. It is capital of western kordufan state. We accompanied a community-built cross sectional research which was cast-off to measure the threat factors linked with severe acute malnutrition amongst 6-59 months' kids live in the area. Using Mid-Upper Arm Circumstances dimension, the kids were measured for their nourishing grade. Kids with strictly undernourished is with Mid-Upper Arm Circumstances <115 mm.

Research was done with a sample of normal household living in the research area. The study population of research was kids less than 5 years. For newborn and young child nourishing had alarmed to 6-23 months old.

The sample size was determined using formula that calculates the base of occurrence of 50% and design effect of 1.5.

$$n = DF * \frac{Z^2_{1-\alpha/2}P(1-P)}{E^2} \text{ or } n = 1 + \rho(m-1) * \frac{Z^2_{1-\alpha/2}P(1-P)}{E^2}$$

n = required minimum sample size
DF = design effect=1+ρ(m-1)
ρ = intracluster correlation
m = number of individual in each cluster
P = the estimated prevalence of an indicator
α = Level of significance
Z_α = the z-score corresponding to the degree of confidence
E = Desired Precision

Total section comprised 576 kids in study area. The selected specimen methods is systematic three phase clusters random selection, the first step concentrating on choosing neighborhoods with in topographical area of region of Al-Nole population of the chosen blocks was enrolled. As much as practicable, a comparable number of households within the unit (block) was chosen. Using the systemic random selection approach, the necessary number of households in each block was chosen. In every designated home, all kids less than 5 years involved in research even if they are from deferent mothers. Children aged less than 5 years not from selected home and refusal were not involved in the study.

Data were gathered via a survey. The survey that will be used to gather information from families was educated on by public health authorities and vaccination professionals.
The survey was initially written in Arabic, and then distributed by tow previously trained investigator. Everyone of volunteer was accompanied by district godmother to simplify the conversation. All mothers or caregivers of kids asked to reply to a questionnaire. The survey included questions about mothers' care, kid healthiness and care practices, social indicators, and socio-demographic and economic aspects and household statistics.

After training, the practical use of the processes and equipment was examined by administering a prior test to comparable eligible study children from the nearby census region. According to the outcome of the pre-test, the survey was revised.

Throughout the whole time of gathering data, the lead scientist and coordinators carried out strict site supervision. Before being handed over to the gatherers of data, completed surveys were carefully examined and cross-checked each day. Both the interview portion and the anthropometric measures were included in the questionnaire

A motorized infant suspending weight with a 15 g payload was used to assess body weight for kids who were unwilling to get up. But a Japanese-made motorized panel balance with a 130 kg capability was utilized for larger youngsters. All kids were measured twice and weighed to the nearest 0.1 kg in casual clothes and without footwear. Before and after the investigation began, the measuring instruments were accuracy-checked, and they were then frequently rechecked.

Height and length were meticulously restrained to the nearest 0.1 cm spending an inelastic determining tape. Children who were more than 24 months old and taller than 85 cm were restrained standing up, kids younger than one year of age or less than 85 cm tall were measured while lying on their beds.

Children’s rulers were used to determine MUAC in centimeters, and results were accurate to within 0.1 cm. When the upper body rested, a reading was obtained on the leftward at the theme among the elbow and the shoulder.

Data were entered using Statistical Package for Social Sciences (SPSS) version 22 for analysis. Formerly recoded, characterized and arranged to simplify its examination. For ordinarily disseminated constant variable, standard deviation was associated using unpaired t-test. Descriptive analysis was used to define the proportions and amount

circulations of the sample size by socio-demographic features and other related variables in the research. Differences in proportions were compared by using Chi-squire test. A possibility of less than 0.05 was measured statistically significant. The power of relationship of selected associated/risk factors for acute malnutrition was determined by assessing odds ratios (ORs) and their 95% confidence intervals (CIs).

Agreement was gained from the individual parent previous to the survey.

3. Results

Table 1: Socio-demographic Characteristics of children assessed for malnutrition from Alnohoud locality (N=768)

Demographic characteristics	Response category	No	%
Age of children Overweight	less than 12 month	221	28.8
	12-24 month	469	61.1
	25-36 month	48	6.3
	37-48 month	12	1.6
	49-59 month	18	2.3
sex of children	male	406	52.9
	female	362	47.1
age of mothers	=25	311	40.5
	26-30 years	323	42.1
	31-35 years	67	8.7
	=36	67	8.7
social status	Marred	616	80.2
	separate	95	12.4
	widow	57	7.4
Mothers educational level	Illiterate	122	15.9
	primary school	251	32.7
	secondary and high school	246	32.0
	university	126	16.4
	post graduate	23	3.0
maternal occupation	farmer	166	21.6
	laborer	54	7.0
	Employee	157	20.4
	house wives	391	51.0
Monthly family income	=2000	474	61.7
	2001-5000 SP	233	30.3
	= 5000 SP	61	7.9

A number of 768 mothers of children who were selected as a sample were included in the study for analysis. The study proved, as shown in the table, that the average age of the children was 1.87 (0.78%) months. More than 400 children are male (52.9%). The study also showed that the majority of mothers participating in the study, 616 (80.2%), were married. Regarding the educational level, the study showed that more than half of the mothers had low education (64.7%) and that half of them were housewives (51%). The study showed that nearly two-thirds of the participants had a low level of income.

Table 2: Environmental health conditions which are factors under five children age Malnutrition in Alnohoud locality. n=768.

Risk factors	Response category	No	%
Washing hands	Before feeding the baby	314	40.9
	before breast feeding	234	30.5
	after cleaning baby's bottom	145	18.9
	before food preparation	75	9.8
Waste disposal	pit latrine	479	62.4
	improved pit latrine	224	29.2
	septic tank	30	3.9
	No facility/bush/field	35	4.6
sources of drinking water	deep well	278	36.2
	public network	360	46.9
	Rain water	74	9.6
	Surface water	56	7.3
Means of water transmission	Jericans	308	40.1
	tankers	293	38.2
	Carriages	167	21.8
Numbers of meals during a day	Two meals	117	15.2
	three meals	523	68.1
	more than three meals	128	16.7

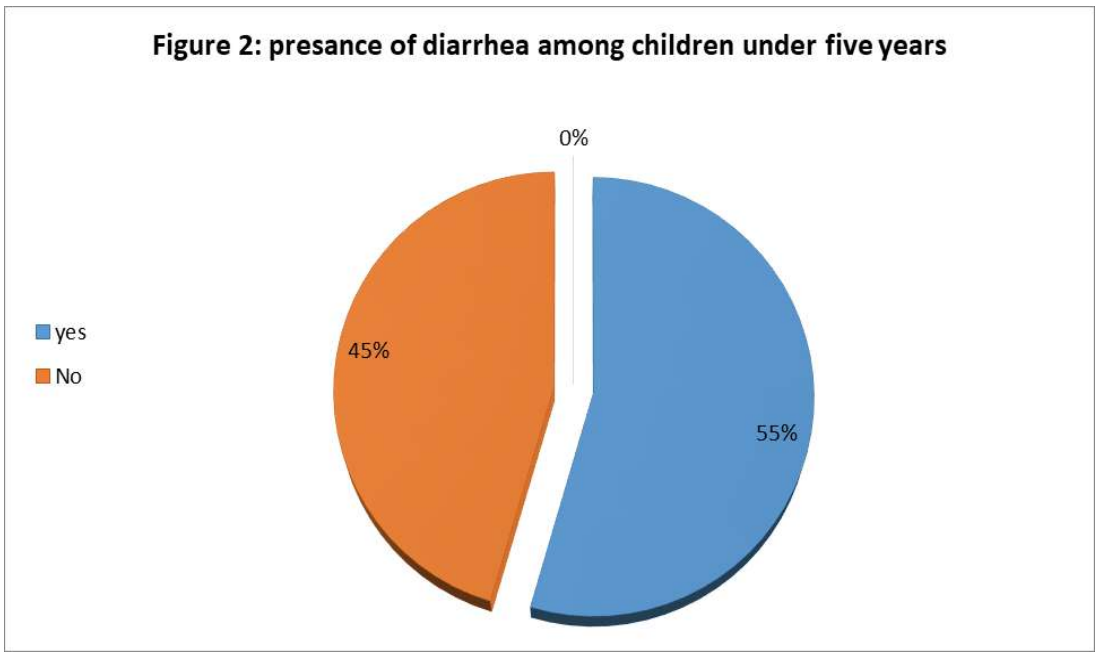
Concerning environmental and behavioral risks, the study showed that mothers' behavior regarding personal hygiene (washing hands with soap and water before feeding children) was poor, which had a negative impact on the children's health.

The study also proved that more than 60% of the study samples habit pit baths to dispose of human discarded, which makes the environment susceptible to the breeding of disease vectors. Our study showed that the tools used to bring drinking water are primitive, lack hygiene, and do not guarantee the safety of drinking water, especially since the main source of water is the public network and underground wells.

Table 3: Factors associated with malnutrition among children less than five years' age in Alnohoud locality.

Demographic characters	category	Malnutrition category					
		wasting No (%)	stunting No (%)	Underweight No (%)	Total No (%)	X2	p-v
Age of mothers	= 25	40(5.2)	31(4.0)	38(4.9)	109(14.2)	57.40	.000
	26-30 years	63(8.2)	55(7.5)	66(8.6)	184(24.0)		
	31-35 years	12(1.6)	7(0.9)	11(1.4)	30(3.9)		
	= 36	20(2.6)	11(1.4)	13(1.7)	44(5.7)		
	Total	135(17.6)	104(13.5)	128(16.7)	367(47.8)		
Education of mothers	Illiterate	22(2.9)	14(1.8)	15(2.0)	51(6.6)	41.00	.004
	primary school	40(5.2)	34(4.4)	36(4.7)	110(14.3)		
	secondary and high school	46(6.0)	38(4.9)	49(6.4)	133(17.3)		
	university	26(3.4)	10(1.3)	21(2.7)	57(7.4)		
	post graduate	1(.2)	8(1.0)	7(0.9)	16(2.1)		
	Total	135(17.6)	104(13.5)	128(16.7)	367(47.8)		
Family income size	= 2000	72(9.4)	57(7.4)	71(9.2)	200(26.0)	32.74	.000
	2001-5000 SP	50(6.5)	39(5.1)	51(6.6)	140(18.2)		
	> 5010 SP	13(1.7)	8(1.0)	6(0.8)	27(3.5)		
	Total	135(17.6)	104(13.5)	128(16.7)	367(47.8)		

The factors associated with acute malnutrition were: mother's ages (p-value = 0.000), which conceder strongly significant association, mother's educational levels (p-value = 0.004), and family's income (p-value = 0.000). The study showed that the children of mothers whose children are less than 30 years old are more likely to suffer from malnutrition than the children of mothers who are in the age groups above 30 years old, our research found that families with fewer resources (2000) had a higher likelihood of malnutrition.



The number of kids who said they had diarrhea in the three weeks before the discussion served as the numerator, and the total figure of kids in the sample served as the denominator, to estimate the occurrence of diarrhea between kids less than 5 years. The prevalence of diarrheal cases over the three weeks before to the interview was 55% overall.

Table 4: Socio-demographic Characteristics of children associated with nutritional status, Alnohoud locality. (N=768)

Demographic characteristics	Response category	Nutritional status			Total	p-v	X^2
		Acute malnutrition (No/%)	Moderate malnutrition (No/%)	Well nourished (No/%)			
Age of children	less than 12 month	38(4.9))	145(18.9)	38(4.9)	221(28.8)	48.38	.000
	12-24 month	146(19.0)	232(30.2)	91(11.8)	469(61.0)		
	25-36 month	3(0.4)	32(4.2)	13(1.5)	48(6.3)		
	37-48 month	0(0.00)	8(1.1)	4(0.5)	12(1.6)		
	49-59 month	2(0.3)	6(0.8)	10(1.3)	18(2.3)		
	Total	**186(24.6)**	**423(55.1)**	**156(20.3)**	**768(100)**		
sex of children	male	86(11.2)	225(29.3)	95(12.4)	406(52.9)	8.17	.017
	female	103(13.4)	198(25.8)	61(7.9)	362(47.1)		
	Total	**189(24.6)**	**423(55.1)**	**156(20.3)**	**768(100)**		
age of mothers	= 25	52(6.8)	180(23.4)	79(10.3)	311(40.5)	42.81	.000
	26-30 years	114(14.8)	158(20.6)	51(6.6)	323(42.1)		
	31-35 years	6(0.8)	48(6.2)	13(1.5)	67(8.7)		
	=36	17(2.2)	37(4.8)	13(1.5)	67(8.7)		
	Total	**189(24.6)**	**423(55.1)**	**156(20.3)**	**768(100)**		
social status	Marred	169(22.0)	346(45.1)	101(13.2)	616(80.2)	47.18	.000
	separate	10(1.3)	42(5.5)	43(5.6)	95(12.4)		
	widow	10(1.3)	35(4.6)	12(1.6)	57(7.4)		
	Total	**189(24.6)**	**423(55.1)**	**156(20.3)**	**768(100)**		
Mothers educational level	Illiterate	28(3.6)	71(9.2)	23(3.0)	122(15.9)	25.95	.001
	primary school	43(5.6)	146(19.0)	62(8.1)	251(32.7)		
	secondary and high school	78(10.2)	133(17.3)	35(4.6)	246(32.0)		
	university	38(4.9)	58(7.6)	30(3.9)	126(16.4)		
	post graduate	2(0.3)	15(2.0)	6(0.8)	23(3.0)		
	Total	**189(24.6)**	**423(55.1)**	**156(20.3)**	**768(100)**		
maternal occupation	farmer	46(6.0)	96(12.5)	24(3.1)	166(21.6)	8.19	.415
	laborer	12(1.6)	28(3.6)	14(1.8)	54(7.0)		
	Employee	32(4.2)	91(11.8)	34(4.4)	157(20.4)		
	house wives	99(13.0)	208(27.1)	84(10.9)	391(51.0)		
	Total	**189(24.6)**	**423(55.1)**	**156(20.3)**	**768(100)**		
Monthly family income	= 2000	103(13.4)	268(34.9)	103(13.4)	474(61.)	7.17	.127
	2001-5000 SP	68(8.9)	126(16.4)	39(5.1)	233(30.3)		
	= 5000 SP	18(2.3)	29(3.8)	14(1.8)	61(7.9)		
	Total	**189(24.6)**	**423(55.1)**	**156(20.3)**	**768**		

A sociodemographic factor associated with nutritional Status were: age of children (p-value = 0.000), age of children (p-value = 0.000), Mothers educational levels, (p- value = 0.001), which conceder strongly significant association, our study revealed no correlation amongst nourishing Grade and sex of kids, (p-value= 0.017), maternal occupational (p- value =0.415) and families' income (p-value =0.127).

4. Discussion

There is once again a need to look into the contributions of many factors impacting malnutrition in order to properly address the issues with under-five malnutrition in Sudan generally and in the current research areas in particular. In order to incorporate as many risk variables as feasible, this study has attempted to examine the elements that contribute to malnutrition in the study area.

Kids younger than 12 months were shown to be more probable to be underweight throughout the research time. This conclusion is reinforced by research conducted in Ethiopia using the EDHS report. (Gelana et al., 2017. Hailemariam et al., 2017] was in conflict with a 2009 study done in Kenya (Gelana, 2014. Talukder, 2017).

Our research found a strong correlation between maternal illiteracy and a child's chance of developing malnourished before the age of five. The same results were made in Machakel Woreda, Northwest Ethiopia, and North Gondar, where the risk of developing hunger raises threefold and above (Gebretsadik et al., 2023) However, we identified larger magnitudes of stunted growth, which may be due to survey site variance.

The findings of this research demonstrated that maternal education had an important beneficial effect on kids stunted growth; children whose parents had secondary or higher education were about 32–50% less likely to continue to be in the most severe nutritional conditions than children whose parents had no formal education. This result is in agreement with a number of earlier research (Nahar et al., 2010. Musa et al., 2017. Jeyaseelan et al., 1997. Lenka, 2015). Similar studies show that the children's nutritional status was influenced by the mother's literacy. Kids of uneducated moms were more likely to be underweight, stunted, or wasteful. Malnurched in kids less than 5 years was highly correlated with mothers a lack of education indicating that one way to intervene to lower child malnutrition might be to increase mothers' education or literacy. (Dube et al., 2014. Khor et al., 2003. Hong, 2007. Tette et al., 2015. Chirande et al., 2015. Zhang et al., 2011).

Our research showed the connection between malnutrition and a monthly household income of 2000 pence (about 25 dollars) and the significance of poverty in the etiology of malnutrition in this context. This is comparable to earlier research from Khartoum and Northern Sudan that revealed that the income of low-income families was a hazard feature for unembellished critical malnourishment. Another Ghanaian research indicated that persistent undernutrition is closely related to economic inequality (Yisak et al., 2015) It is also comparable to a study conducted in Nigeria, which discovered that malnutrition was linked to mother monthly income of $20 and monthly household food spending of $55 (Johri et al., 2016. Heidkamp et al., 2015).

Our research discovered, the practice of undefended basis of consumption water improved the danger of malnourishment triple and beyond than threatened water foundation. The population in the desert does not have access to pure and safe drinking water, and we find that the main environmental risk factors that lead to the spread of common diseases are unsanitary practices. Percentages of Sudanese who have insufficient access to clean water in rural, town, and national settings are 21%, 84%, and 30%, respectively (Nassur et al., 2022) The occurrence of water borne disorders like diarrhea, which subsidize to malnourishment, is intimately associated to admission issues and unprotected potable drinking water (Gudu et al., 2020).

Lack of food is three times more common among mothers who neglect hand soaping at every opportunity than in child care providers or mothers who just wash their hands after using the restroom. According to our research, more than forty of mothers cleansed fingers before feeding kids. In Sudan, an identical result was made. When a kid is six months old, extra nourishment is crucial, but inadequate eating habits can also be detrimental to the nutritional well-being of young infants. Advanced occurrence of malnourishment (94.2%) detected in kids of mothers didn’t practice hand hygiene after conduct garbage. It is important to wash hands well after touching any surfaces or doing any activates, and then dealing with kids. For health practitioners, practice of hand hygiene is important to break the connection between food and the spread of infection. health practitioners need to clean their hands with soap and water before preparing food, before feeding children, and after visiting the toilets or cleaning kid’s stools (Gewa, 2010. Menalu et al., 2021. Tekile et al., 2019. Anonymous, 2016. Sambo et al., 2022).

5. Conclusions

Severe Acute Malnutrition is establishing to be related with low Mothers’ educational level, age of mother, families' economic status, exposure to infectious diseases and diarrhea.

In this research, Mid-Upper Arm Circumstances, founded to be a great broadcast method. Thus, it is preferable to measure the mid-upper arm circumference periodically as part of the medical evaluation for all children who are

admitted to treatment hospitals and health centers to see a doctor and for different age groups. Priority must be given to interventions that limit the spread of malnutrition diseases and control the factors that help in the spread of malnutrition.

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: Not applicable.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 95-105
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.310

Transcranial Doppler Findings in Myeloproliferative Diseases (Polycythemia Vera and Essential Thrombocytosis): A Systematic Review

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Abstract
Background and aims: Myeloproliferative neoplasms (MPN) are rare hematologic diseases that require early diagnosis to prevent thrombotic events. Only a few studies have investigated transcranial Doppler (TCD) ultrasonography among these population groups. Following the PRISMA Guidelines, we reviewed the utility of TCD in Polycythemia vera (PV) and Essential Thrombocytosis (ET) patients in the context of cerebral blood flow and detection of microembolic signals (MES). Methods: This systematic review focuses on the application of TCD in MPN. By incorporating findings from one observational study, one prospective study, and three case reports, the review establishes that while TCD is not a primary tool for diagnosing PV and ET, it plays a crucial role in monitoring cerebrovascular complications, assessing thrombotic risk, evaluating treatment responses, and facilitating research related to these conditions. Results: This review incorporates findings from a total of 63 patients. 3.2% had ischemic stroke and 1.6% had transient ischemic attack with a total of 4.8% stroke risk. High-intensity transient signals (HITS) were common in 22% of patients wherein they had elevated hemoglobin, hematocrit, and platelet values. Following treatment and normalization of blood panels, 31.7% had improved cerebral perfusion with normal flow velocities. 3.2% had elevated flow velocities linked to blood flow obstruction. There was significant clinical improvement among the study population, with 17.5% becoming asymptomatic with the disappearance of MES. Conclusions: The judicious use of TCD can enhance a comprehensive diagnostic and monitoring strategy, complementing traditional clinical and laboratory assessments in the management of MPN specifically PV and ET.

Keywords: Transcranial Doppler, Cerebral Hemodynamics, Microembolic Signals, Polycythemia Vera, Essential Thrombocytosis

1. Introduction

Myeloproliferative neoplasms (MPN) are a group of hematologic disorders arising from the aberrant proliferation of one or more terminal myeloid cell lineages in the peripheral circulation. The three classic *BCR-ABL1* negative MPNs include essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) (Arber et al, 2016). These diseases are also characterized by JAK2 mutation, leading to sustained activation of the JAK2

kinase, subsequently causing excess blood cell production independent of erythropoietin (Lu et al, 2023). This mutation is correlated with increased risk of cerebrovascular complications, predominantly due to the hypercoagulability state that is observed in these individuals.

The prevalence of MPNs is uncertain due to limited incidence estimates and a lack of consistent, repeatable data. Both PV and ET are diagnosed at a median age of sixty years. PV predominantly affects males than females (male to female ratio: 1.8: 1) with an annual incidence estimates that range between 0.4% and 2.8% per 100,000 individuals. Meanwhile, ET has higher prevalence among females, with a male-to-female ratio of 1:2, and an annual incidence estimate ranging between 1.2 and 2.5 per 100,000 individuals (Srour et al, 2017). Due to the lower prevalence of PMF, this current review would only include ET and PV patients.

A meta-analysis of 13,436 newly diagnosed patients with MPN revealed that thrombosis (20%) and hemorrhage (16.2%) are frequent initial manifestations of the disease. The disease is associated with a higher risk for arterial or venous thrombosis than the general population. Additionally, the study revealed that the combined prevalence of arterial and venous thrombosis in PV was 28.6%, while that of bleeding was 6.9%. In contrast, the pooled prevalence in ET was 20.7% and 7.3% for arterial and venous thrombosis and hemorrhage, respectively (Rungjirajittranon et al, 2019).

While complications abound in the context of PV and ET, particularly involving ischemic cerebrovascular events, a complete understanding of the mechanisms behind these complications remains elusive (Spivak, 2002; Elliott & Tefferi, 2005; Barbui et al., 2013; Falanga & Marchetti, 2014). Consequently, transcranial Doppler (TCD) has become a valuable instrument for observing cerebral blood flow and identifying initial indications of cerebrovascular dysfunction. TCD is a relatively inexpensive, non-invasive, repeatable procedure that provides rapid and real-time measures of cerebrovascular function (Purkayastha & Sorond, 2012). TCD is used to assess cerebral hemodynamics, including cerebral blood flow velocity and pulsatility indices. It is also used to investigate cerebrovascular autoregulation and the presence of microembolic signals (MES) or high-intensity transient signals (HITS).

Exploring the cerebrovascular impact of PV and ET and their connection with TCD findings has important treatment implications. Yet, limited articles delve into the relationship between TCD findings and these conditions. This systematic review seeks to investigate this link and aims to uncover connections between specific blood parameters and TCD results, aiming to provide insights into the mechanisms contributing to cerebrovascular complications in patients with PV and ET. Understanding these correlations can enhance our comprehension of how changes in blood composition relate to cerebrovascular events. The study also aims to evaluate the ability of TCD to predict the occurrence of cerebrovascular events in patients with PV and ET. By determining whether TCD findings can serve as predictive markers, the study aims to contribute valuable information for clinicians in identifying individuals at an elevated risk of cerebrovascular complications. This insight could impact the management and preventive strategies for these patients.

2. Methodology

2.1. Search strategy

Searches were conducted in the following scientific databases: PubMed, the Cochrane Library, and Google Scholar. The keywords used were "polycythemia vera," "essential thrombocytosis," and "transcranial Doppler" to search titles and abstracts. Duplicate terms included "TCD" and "polycythemia rubra vera."

During the search on these databases, the following filters were applied: type of study (observational studies, prospective studies, cohort studies, clinical studies, and case reports), language (English), and study subjects (individuals >18 years of age). The reference lists of the included papers were also manually reviewed for any additional eligible studies.

However, despite the thorough and intensive search, minimal studies were shown to meet the inclusion and exclusion criteria. PV and ET are relatively rare conditions, and specific clinical scenarios or complications associated with these diseases may not be well documented in large-scale clinical studies or trials involving TCD. Case reports can highlight these rare or unusual occurrences, offering a deeper understanding of the diverse clinical presentations and outcomes associated with PV and ET. Case reports often emphasize clinical relevance and real-world applicability; they showcase specific patient experiences and outcomes, which may benefit clinicians seeking guidance on properly managing similar situations.

In the context of PV and ET, which both have multifaceted complications, case reports can illustrate less common cerebrovascular complications, which may have yet to be extensively studied. They can expound on knowledge about these complications, helping clinicians and researchers recognize them in practice.
While case reports can contribute valuable information to a systematic review, it is essential to acknowledge their limitations. They are anecdotal and may lack the scientific rigor of controlled studies. Therefore, their inclusion in this study was balanced with critically evaluating their quality and relevance to the research question. Including case reports in this study was done judiciously.

2.2. Eligibility criteria and clinical case definitions

Included studies were those that described cerebral hemodynamics using TCD among patients diagnosed with PV and ET done among patients aged 18 years and older of both sexes and any ethnicity. They were published from database inception up to April 30, 2022. Study outcomes included TCD parameters (including mean flow velocity and MES monitoring) and hematocrit, hemoglobin, and platelet values.

Studies with other hematologic conditions or severe cardiovascular disease were excluded Studies with pregnant patients and those with severe coexisting medical conditions were also excluded. Studies not in English, animal studies, unfinished and unpublished trials, and those not from primary literature such as review articles, editorials, commentaries, or meta-analyses were likewise excluded.

2.3. Selection process

Upon removing duplicates, studies resulting from the initial search were screened for eligibility through their titles and abstracts by the investigator. Studies that were not relevant to the objectives of this review were excluded. A second round of screening was performed based on the complete text, and the list of studies to be included in the systematic review was finalized after the fact. References identified during the second round of screening were again screened for a third time. For comprehensiveness, the reference lists of included studies and other previously published meta-analyses were cross-checked for additional studies that could meet the eligibility criteria.

2.4. Outcomes assessed

Data items that were extracted included the following: general information (author, year of publication, country) and study characteristics in terms of study design, population, sample size, age and sex of study participants, and a diagnosis of polycythemia vera or essential thrombocytosis. TCD parameters of interest included any of the following: cerebral mean flow velocities (MFV) in the middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), basal cerebral artery (BA), and MES or high-intensity transient signals (HITS).
Other study outcomes included changes in TCD parameters and hematocrit, hemoglobin, and platelet values.

2.5. Data analysis

A pre-specified electronic data collection sheet was used for all included studies to retrieve pertinent information. Descriptive statistics in frequency and percentages were used to analyze study outcomes and will be computed using Microsoft Excel.

3. Results

3.1. Characteristics of the retrieved studies

After a thorough selection process across five databases (Science Direct, Google Scholar, PubMed, Cochrane Library, and Journal Storage), six articles (three retrieved from PubMed and three from Google Scholar) matched all the characteristics outlined in the inclusion and exclusion criteria. Studies that did not meet the inclusion criteria based on age and diagnosis were excluded from the review. Moreover, animal studies, unfinished and unpublished trials, and those not from primary literature, such as review articles, editorials, commentaries, or meta-analyses, were also excluded after the removal of duplicates and exclusion of studies with meta-analyses. Five articles were screened based on their title and the contents of their respective abstracts. All five articles passed the eligibility criteria and were subsequently included in the study. Fig. 1 illustrates the search strategy for selecting studies for the review.

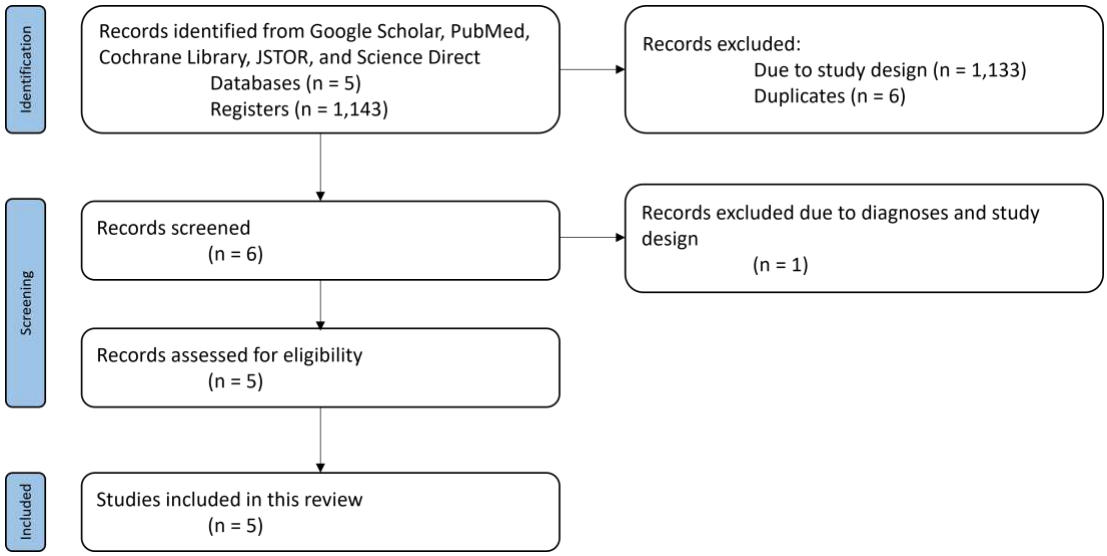

Figure 1: Search strategy for the selection of studies using PRISMA Method

Table 1 shows the summary of results from the articles collated, which includes details of the authors, year published, study design, Doppler machine used, and outcomes assessed in the respective papers.

Table 1: Summary of Studies

Author & Year Published	Study Population	Study Design	Doppler machine used	Outcomes Assessed
Fiermonte et al. (1993)	PV	Observational study *(N = 20)*	CW Doppler Velocimeter D800; TC 2-64b	• Mean flow velocities (MCA, ACA, PCA and BA)
Del Sette et al. (1995)	PV	Case report *(N = 1)*	TCD 64 EME	• Mean flow velocities (MCA) • MES in MCA
Segura et al. (2000)	PV	Case report *(N = 1)*	DWL-multidop X4	• Mean flow velocities (MCA) • MES in MCA
Blaser et al. (2001)	ET	Case report *(N = 1)*	*Not specified*	• MES in MCA
Cinar et al. (2020)	ET	Prospective study *(N = 40)*	Sonara TCD system Care Fusion, San Diego, CA, USA	• Mean flow velocities (MCA) • MES in MCA

Table 2 shows the pre- and post-therapy clinical features of the study population, the neuroimaging and treatment employed.

Table 2: Clinical features of PV and ET patients

Author and Year	Pre-therapy clinical features	Neuroimaging	Treatments employed	Post-therapy clinical features
Fiermonte et al. (1993)	Hypertension, headache, asthenia, itching, splenomegaly (2-5cm), scotomas, blushed face, cyanosis, vertigo, gouty arthritis, paresthesia, confusional state	*None*	• Phlebotomies • Pipobromanum 50-75mg • Dipyridamolum 150-225mg	Hypertension, periodic headache, splenomegaly (1cm), gouty arthritis
Del Sette et al. (1995)	Left-sided headache Right brachiorural paresis	Left hemispheric infarction with hemorrhagic transformation in the area of the lenticulostriate arteries and posterior branches of the right MCA	• Isovolemic hemodilution • Pentoxifylline 800mg • LMW Dextran 500ml • Heparin 24,000 IU • Busulfan 4mg • Ticlopidine 500mg	Mild right hemiparesis
Segura et al. (2000)	Left brachial paresis	Right hemispheric infarction of the posterior division of the MCA	• Ticlopidine • Acenocumarol INR	Asymptomatic
Blaser et al. (2001)	Recurrent right-sided paresthesia of the extremities and face, blurred vision on the right, dizziness, headache	Normal	• ASA 100mg/day • Hydroxycarbamide	Asymptomatic
Cinar et al. (2020)	*Not specified in the study.*	*None*	• Low dose aspirin • Hydroxyurea • Anagrelide	*Not specified in the study.*

Of the five studies reviewed, three were case reports wherein there were two cases of PV and one case of ET (Del Sette et al., 1995; Segura et al., 2000; Blaser et al., 2001), one was an observational study with a sample size of 20 newly diagnosed PV patients (Fiermonte et al., 1993), and another was a prospective case-control study with a sample size of 40 ET patients, age and sex-matched with 40 healthy controls (Cinar et al, 2021). In total, 63 patients were included in this review; 27 were male, and 36 were female. The median age of the participants is 58.89 years.

In utilizing transcranial Doppler, readings were performed using various Doppler models, including the following: CW Doppler Velocimeter D800 and TC 2-64b, TCD 64 EME, DWL-multidop X4, and Sonara TCD system Care Fusion. One study did not specify the TCD machine used (Blaser et al, 2001). There was no mention of the credentials of sonographers in any of the investigations.

Polycythemia vera was diagnosed according to the criteria of the Polycythemia Vera Study Group (PVSG) (Fiermonte et al., 1993), or confirmed through bone marrow examination (Segura et al., 2000) or through hematological screening (Del Sette et al., 1995).

Meanwhile, essential thrombocytosis was diagnosed according to the WHO 2008 diagnostic criteria for ET (Cinar et al, 2021). Platelet function tests, such as template bleeding time, platelet glass retention, quantitative clot retraction, and induced platelet aggregation by ADP, were also performed (Blaser et al, 2001).

The outcomes measured across three studies investigating patients with PV were in congruence with each other. The blood velocities in the MCA were measured in 62 patients from all the studies, except one (Blaser et al, 2001), which only investigated MES. 20 subjects from Fiermonte et al.'s study also measured the blood velocities in the ACA, PCA, and BA.

All five studies described the TCD findings and blood parameters outlined in Table 3. Elevated hematocrit and hemoglobin values in all 22 PV cases (Del Sette et al., 1995; Segura et al., 2000; Fiermonte et al., 1993) and an elevated platelet value in one ET patient have improved to normal levels after treatment (Blaser et al, 2001). However, in 40 ET patients, only the baseline platelet value was reported (Cinar et al, 2021). These alterations in blood parameters—erythrocytosis and thrombocytosis—are correlated with changes in cerebral blood perfusion as measured by mean flow velocities and the detection of MES.

Table 3: Mean flow velocities and Blood parameter values

Author & Year	Mean flow velocities (cm/s)		Hematocrit, %		Hemoglobin, g/dl		Platelet	
	Pre-tx	Post-tx	Pre-tx	Post-tx	Pre-tx	Post-tx		
Fiermonte et al. (1993) [13]	MCA = 39.40 ± 9.34 ACA = 34.05 ± 10.25 PCA = 31.46 ± 5.97 BA = 27.47 ± 7.42	MCA = 47.00 ± 10.85 ACA = 42.10 ± 9.66 PCA = 34.92 ± 5.89 BA = 32.00 ± 5.95	55.78 ± 3.65	46.97 ± 3.45	18.18 ± 0.96	15.44 ± 1.30	N/A	
Del Sette et al. (1995) [10]	MCA_1 = 80 MCA_{14} = 78 MCA_{28} = 80		Hct_1 = 66.1 Hct_{14} = 54.8 Hct_{28} = 49.2		Hb_1 = 23.0 Hb_{14} = 18.4 Hb_{28} = 17.2		**Pre** 300 x 1000/mm^3	**Post** 311 x 1000/mm^3
Segura et al. (2000) [11]	**R** MCA_1 = 41 MCA_8 = 43 MCA_{60} = 107 MCA_{120} = 167	**L** MCA_1 = 39 MCA_8 = 40 MCA_{60} = 61 MCA_{120} = 65	Hct_1 = 57 Hct_{60} = 42.5		Hb1 = 19 Hb_{60} = 13.4		234 x10^9/l	350 x10^9/l
Blaser et al. (2001) [12]	N/A		N/A		N/A		682 x10^9/l	*Normal**
Cinar et al. (2020) [14]	**R MCA** Peak-R = 73.4 ± 26.6 EDV-R = 23.7 ± 8.6	**L MCA** Peak-R = 77.5 ± 30.1 EDV-R = 25.7 ± 11	N/A		N/A		436 K/mL** (378-1046)	

Tx: treatment; **MCA:** middle cerebral artery; **ACA:** anterior cerebral artery; **PCA:** posterior cerebral artery; **BA:** basal artery; **R:** right; **L:** left; **Peak**: peak systolic flow velocity, **EDV:** end-diastolic flow velocity
Digits in subscript are days after admission/treatment
** No value specified in the study*
*** Patients detected with MES*

20 subjects from Fiermonte et al.'s study had decreased MFV (MCA = 39.40 ± 9.34) compared to the control group, which significantly improved following treatment (MCA = 47.00 ± 10.85). In another patient, the MFV in the MCA remained elevated in spite treatment (Del Sette et al., 1995). This was explained by the persistent stenosis of the MCA trunk, which was thought to be caused by the migration of clots to the distal branches. One patient had normal basal MFV but subsequently increased on repeat TCD studies (Segura et al., 2000). The authors confirmed the development of stenosis by magnetic resonance angiography (MRA) with absence of flow in the right ICA, and severe stenosis of the proximal right MCA. They hypothesized that this was likely due to microemboli discharge from the carotid siphon, which contributed to the formation of stenosis in the distal MCA. One study did not specify the MFV (Blaser et al, 2001). However, 40 ET patients reported significantly elevated MFV despite treatment compared to the control group (Cinar et al, 2021). The authors explained that high platelet values may form aggregates and cause obstruction by preventing blood cell passage which was subsequently measured as high MFV.

TCD detected MES in four studies (Del Sette et al., 1995; Segura et al., 2000; Blaser et al., 2001; Cinar et al., 2021) with three reporting bilateral findings (Segura et al., 2000; Blaser et al., 2001; Cinar et al., 2021) and one study documenting unilateral MES (Del Sette et al., 1995). A total of 14 patients (22%) had MES monitoring,

showing an average of 132 HITS on the right and 38 HITS on the left in 30 minutes to 1-hour monitoring of MCA. However, the study of Cinar et al. only specified the number of cases with HITS (R-MCA N=8, L-MCA N=5).

Two PV studies repeated MES monitoring and demonstrated a declining trend of HITS (Del Sette et al., 1995; Segura et al., 2000). In contrast to the findings of Del Sette et al., which documented the absence of HITS within the initial month, Segura's study only observed the absence of HITS on the left and 20 HITS per hour on the right MCA on day 60 post-treatment. After a period of four months, no HITS were detected (Segura et al., 2000). Both cases have associated these findings with normalization of blood parameters (hemoglobin 13.4 - 18.4 g/dL and hematocrit 42.5 - 54.8%).

Among the 63 subjects, 3.2% had ischemic stroke and 1.6% had transient ischemic attack with a total of 4.8% stroke risk. Significant improvement, as assessed through clinical evaluation, was observed among the study population after the initiation of treatment. 11 patients (17.5%) became asymptomatic (Segura et al., 2000; Blaser et al., 2001; Fiermonte et al., 1993). Five patients (8%) had a notable decrease in the size of the splenomegaly. Four patients (6%) had persistence of hypertension (Fiermonte et al., 1993); another case had mild right hemiparesis (Del Sette et al., 1995); another had periodic headaches; and another had persistent gouty arthritis (Fiermonte et al., 1993). There was one case with an unvaried outcome (Fiermonte et al., 1993). Clinical improvement was not specified in 40 cases (63%) by Cinar et al.

Table 4 shows the MES monitoring results in the respective studies examining patients with PV and ET. Table 5 and 6 shows the summary of the mean flow velocities and microembolic signals pre- and post-treatment, respectively.

Table 4: MES monitoring results

Author & Year	Cases	MES-Right MCA	MES-Left MCA
Del Sette et al. (1995)	1	recorded per 30 minutes: 0_1 0_{14} 0_{28}	recorded per 30 minutes: 80_1 36_{14} 0_{28}
Segura et al. (2000)	1	recorded per hour: 250_1 360_8 20_{60} 0_{120}	recorded per hour: 30_1 8_8 0_{60} 0_{120}
Blaser et al. (2001)	1	recorded per hour: 14	recorded per hour: 4
Cinar et al. (2020)	11	N=8*	N=5*

MES: Microembolic signals
Digits in subscript are days after admission
**No data regarding number of MES recorded per case*

Table 5: Mean Flow Velocities

		Pre-treatment MFV			Post-treatment MFV	
		Normal	**Decreased**	**Elevated**	**Normal**	**Elevated**
MPN (n= 63)	PV (22 subjects)	1 (1.5%)	20 (31.7%)	1 (1.5%)	20 (31.7%)	2 (3%)
	ET (41 subjects)	-	-	40 (63.5%)	-	-
TOTAL		1 (1.5%)	20 (31.7%)	41 (65%)	20 (31.7%)	2 (3%)

Table 6: Microembolic signals

Cases		Pre-treatment MES	Post-treatment MES
MPN (n= 63)	PV (22 subjects)	2 (3%)	None
	ET (41 subjects)	12 (19%)	None*
TOTAL		14 (22%)	None

**The study of Cinar et al. did not examine post-treatment MES; only the study of Blaser et al. with 1 subject reported absence of HITS after treatment initiation*

An illustrative case of recently diagnosed polycythemia vera manifesting as an acute ischemic stroke with hemorrhagic conversion is depicted in Fig. 2 and 3. TCD exhibited bilateral multiple HITS, which resolved eventually following treatment initiation.

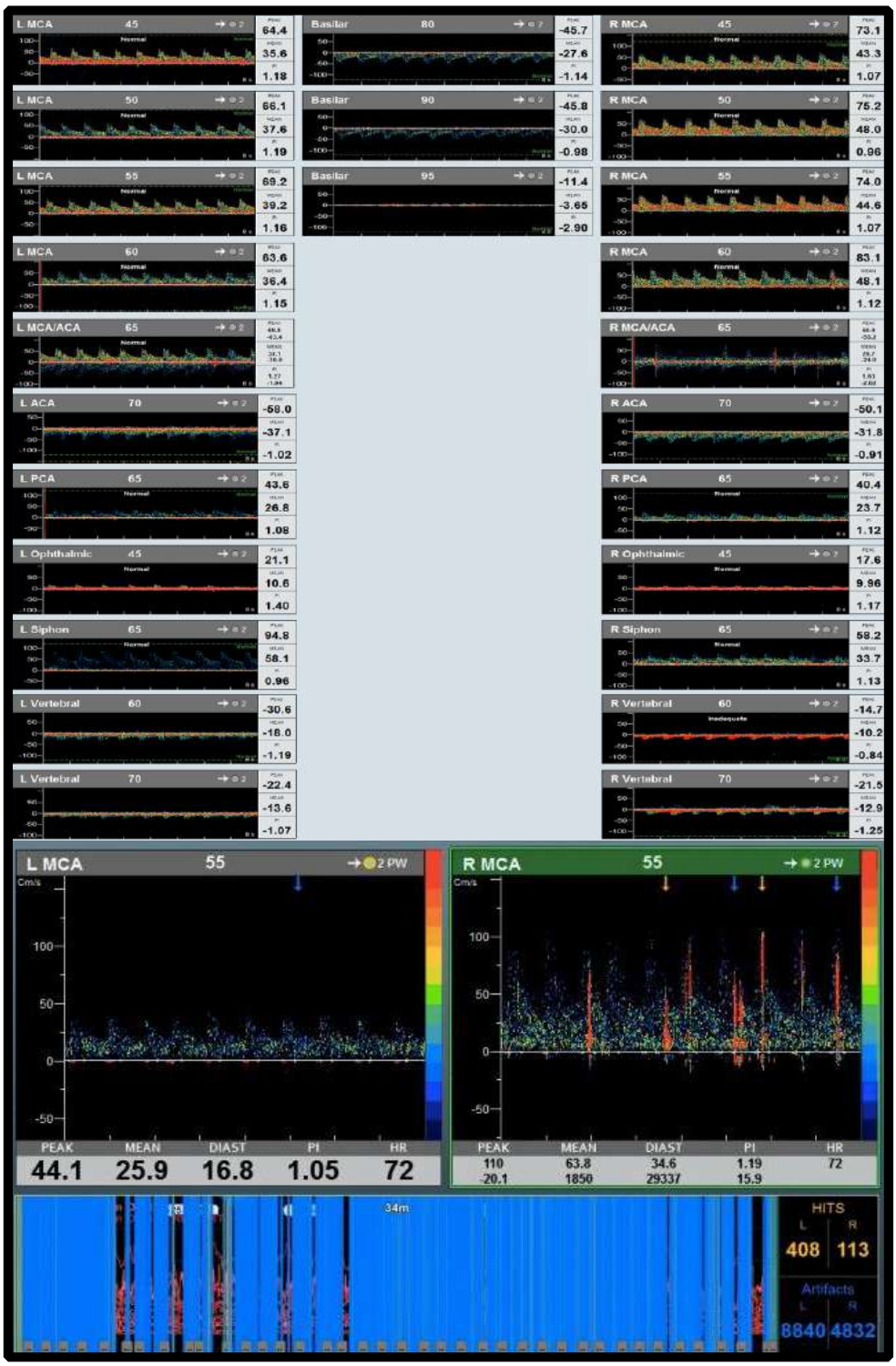

Figure 2: 48-year-old man with headache, left hemiparesis and numbness revealed acute cerebral infarction with hemorrhagic conversion in a background of PV confirmed on genetic testing. TCD showed multiple HITS (Spencer Grade V) on admission with blunted waveform (MFV 35-48 cm/s).

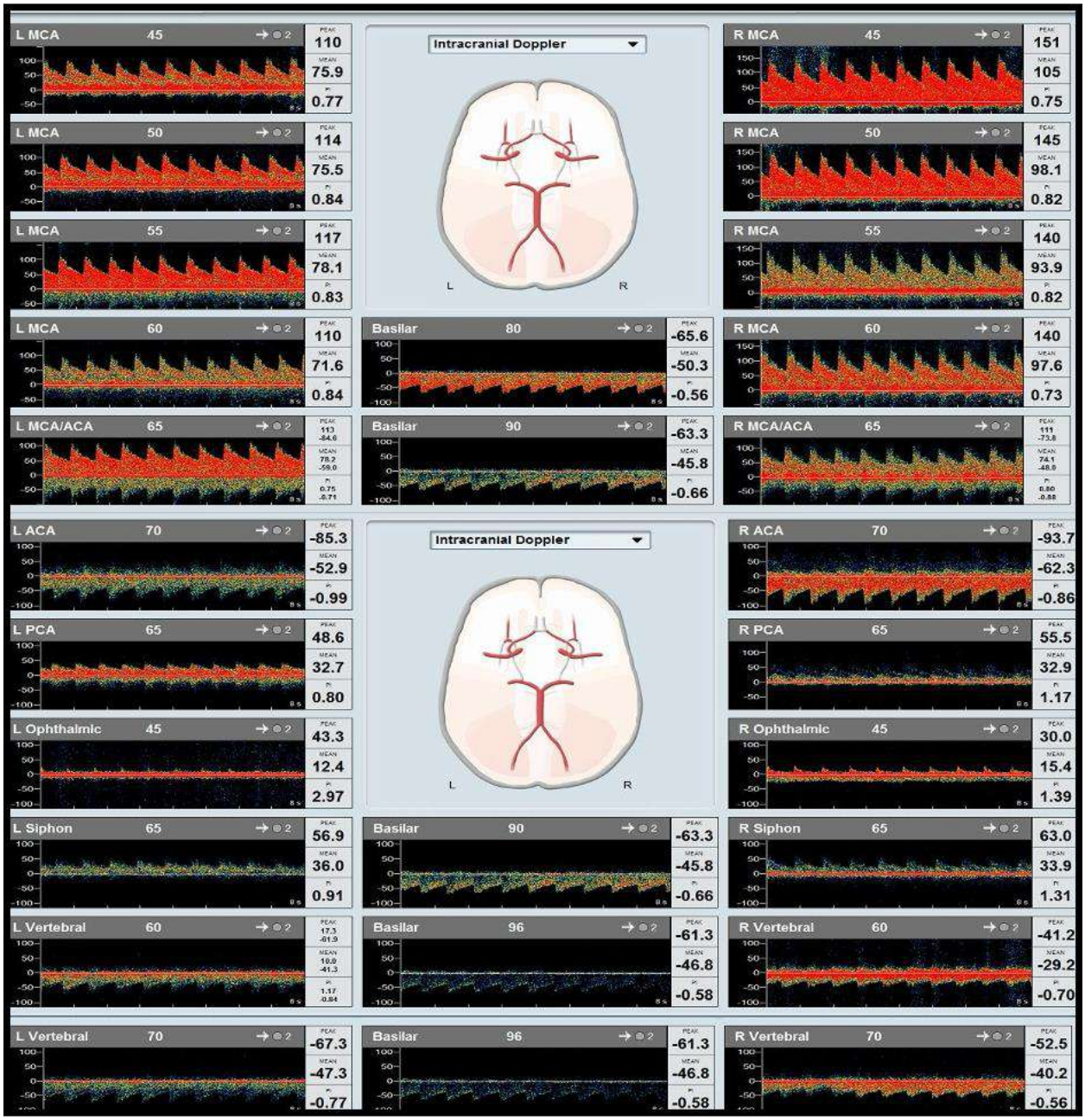

Figure 3: Follow up TCD after 3 months showing normalization of cerebral hemodynamics with MFV 71-105 cm/s. There were no noted HITS on MES monitoring and clinical improvement.

4. Discussion

This systematic review revealed that microembolic signals are common among patients with PV and ET consequent with increased hematocrit, hemoglobin, and platelets. Significant clinical improvement along with improved cerebral blood flow perfusion and absence of MES were observed after treatment initiation and normalization of blood panels. Intracranial stenosis, manifested as increased MFV, developed despite treatment.

The clinical utility of microemboli detection remains uncertain. However, MES has been detected in various potential embolic sources and found to predict stroke risk among patients with acute stroke, symptomatic carotid stenosis, and postoperatively after endarterectomy (King & Markus, 2009). In a meta-analysis, the prevalence of MES was 30% after an acute stroke or TIA, with higher risk of recurrence of cerebral ischemia. It was, however, not linked to poor functional outcomes or mortality (Sudheer et al, 2021). Our review found MES to be numerous

in patients with viscous blood panels that subsequently disappeared following treatment. In one study, MES reappeared after treatment interruption, but the resumption caused the absence of MES and clinical improvement (Blaser et al, 2001). The studies correlated MES detection to formation of microthrombi promoted by increased platelet and red blood cell aggregation, noting that there were no other potential sources of embolism. Thus, MES detection may serve as an indicator of an ongoing asymptomatic cerebral embolization and may be used to assess insufficient secondary stroke prevention.

Two studies of PV patients have documented intracranial stenosis in the background of a hyperviscous blood, as evidence by increased MFV on TCD (Del Sette et al., 1995; Segura et al., 2000). The development of intracranial stenosis among these patients were attributed to their prothrombotic state, causing clot formation, migration and subsequently, stenosis of vessels. An increase in hematocrit was also implicated causing endothelial dysfunction by reducing endothelial surface thickness, thereby modulating inflammation, permeability, and atherosclerosis formation (Richter et al., 2011).

Jak2VF mutation also contributes to thrombosis, as reported by Wang et al. where its expression in hematopoietic cells promotes the development of atherosclerosis at a faster rate, characterized by unstable plaques. This result is consistent with the higher incidence of atherothrombotic cardiovascular disease that has been observed in patients with clonal hematopoiesis or MPN associated with JAK2VF (Wang et al., 2018).

TCD may be used to monitor the effects of therapeutic interventions in PV and ET patients, as exhibited by this review. By tracking changes in cerebral blood flow dynamics and detection of MES, clinicians can gauge the cerebrovascular health of MPN (PV and ET) patients and make diagnostic and prognostic assessments based on these trends.

Limitations of the review include the lack of randomized trials and other observational studies with larger sample sizes to assess the practicability of TCD in monitoring PV and ET. Further, there are limited studies available that assess MPN with TCD using recent and more advanced technology, as the studies included in the review were dated two decades prior to the composition of this systematic review. For future studies, the authors recommend a standardized protocol for TCD examination, which includes monitoring at baseline, specific time frame post-treatment, and follow-up for uniform data reporting.

5. Conclusion

The review elucidates that while TCD is not a primary diagnostic tool for PV and ET, it can be practical and valuable in the context of monitoring cerebrovascular complications, assessing thrombotic risk, evaluating treatment responses, and conducting research related to these myeloproliferative diseases. Prognostically, it also enables clinicians to make informed predictions about the patient's future risk of cerebrovascular events and provides an opportunity for individualized risk assessments and treatment planning. However, TCD should be used as part of a comprehensive diagnostic and monitoring approach alongside other clinical and laboratory assessments. To enhance the validity of the present study, a larger study population among these patients are recommended in future research.

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: Not applicable.

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 106-113
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.311

Surgery for Complications and Sequelae of Pulmonary Tuberculosis

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Abstract
Tuberculosis, colloquially recognized as the "malady of indigence," stands as an ancient affliction that has pervaded human history. Its contagious nature was meticulously chronicled by medical luminaries such as Hippocrates and Galen, with archeological evidence revealing its existence in Egyptian mummies from a bygone era, extending over five millennia. The 1980s marked a resurgence of tuberculosis on a global scale, disproportionately impacting low-income nations. The resurgent relevance of surgery in the therapeutic armamentarium against pleuropulmonary tuberculosis and its sequelae has once again become a pertinent subject. The primary aim of our study is to elucidate the management of sequelar and/or complicated pleuropulmonary tuberculosis. Methods: This constituted a descriptive cross-sectional study conducted from January 2012 to August 31, 2023. The study encompassed the collection of data from 157 patients, all of whom had experienced at least one episode of tuberculosis and undergone surgical intervention. Results: The average age of our patients was 36.83 (±13.18) years, ranging from 19 to 60 years. Males predominated, constituting 36.69% of the cohort. Major symptoms included hemoptysis in 56.05% and bronchorrhea in 33.76% of cases. The primary surgical indications were predominantly bronchiectasis (31.84%), aspergilloma (26.75%), and encapsulated pleuritis (15.29%). Postoperative outcomes were uneventful in 82.80% of cases. The average duration of hospitalization was 13.8 days (±2.2). Conclusion: Despite the technical challenges associated with the surgical management of complications and sequelae arising from pleuropulmonary tuberculosis, the outcomes remain promising.

Keywords: Tuberculosis, Sequelae, Surgery, Complications

1. Introduction

Pleuropulmonary tuberculosis is a condition for which the cornerstone of treatment is anti-tuberculous chemotherapy (Rosenblatt MB, 1973). Since its discovery in the mid-1940s, this therapeutic approach has revolutionized the prognosis of a disease that was predominantly fatal at that time. With the preliminary success of this therapeutic modality, there was a collective belief that tuberculosis would swiftly be eradicated and relegated to the annals of history (Murray, 2004). However, this optimistic outlook failed to account for the enduring factors of poverty, demographic challenges, limited access to healthcare, substance abuse, the

emergence of multi-drug-resistant strains, human immunodeficiency virus, and more recently, extensively drug-resistant tuberculosis (XDR-TB) (Hargreaves, 2008). Tuberculosis, characterized as the "disease of poverty," initially seemed easily "controllable" through anti-tuberculous chemotherapy but continues to be a significant cause of global morbidity and mortality.

Despite adequate medical treatment, tuberculosis often leaves behind numerous sequelae, and surgery plays a pivotal role in the comprehensive management of these sequelae. This study aims to elucidate the specific role and types of surgery within the therapeutic arsenal for the sequelae of pleuropulmonary tuberculosis.

2. Patients and Methods

This study is a descriptive cross-sectional investigation, complemented by a prospective follow-up of patients with a history of successfully treated pulmonary tuberculosis and presenting suspected sequelae based on clinical, biological, and/or radiological signs, subsequently undergoing surgery in our department.

Prior to admission, all patients underwent a comprehensive clinical examination, standard chest X-ray, CT scan, and cardiorespiratory assessments (ECG, echocardiography, pulmonary function tests). Additionally, medical preparation and preoperative physiotherapy were deemed necessary.

For recent sequelae (tuberculous pneumothorax or encapsulated pleuritis), surgery was scheduled after the 5th month of anti-tuberculous treatment to address anatomical lesions sterilized by medical intervention.

The procedure was conducted under general anesthesia. The anesthetist employed a dual-lumen selective intubation tube, allowing modulation of lung ventilation during the operation for enhanced surgical comfort and prevention of septic contamination of the contralateral lung. Thoracotomy was the chosen surgical approach for all patients.

Following surgery, patients spent 24 to 48 hours in the intensive care unit before transitioning to the regular hospitalization unit. During this period, vigilance was maintained for the occurrence of postoperative complications. The assessment of results was based on clinical, radiological, and biological criteria.

3. Results

The study population comprised 157 patients of both genders meeting inclusion criteria and admitted to the Thoracic Surgery Department between January 1, 2012, and August 31, 2023.

The average age of the patients was 36.83 (±13.18) years, ranging from 19 to 60 years. Males constituted the majority at 63.69%. Patients either had a history of treated and declared cured tuberculosis in 139 cases (88.54%), of which 19 patients received second-line anti-bacillary chemotherapy, or presented with histological evidence of tuberculosis during treatment in 18 cases (21.46%).

The major symptom observed was hemoptysis in more than half of the cases (56.05%), with bronchorrhea also being a frequent symptom in 33.76%. Other symptoms included dyspnea (28.66%), thoracic pain (7.64%), and chronic cough (5.10%).

Lesions were predominantly unilateral in 98.73% of cases, with 54.84% affecting the right side. The distribution of patients based on surgical indications revealed a predominance of parenchymal lesions in 64.97% of cases, while pleural involvement was observed in 35.03%.

Among the surgical indications, parenchymal involvement took precedence. This was primarily represented by bronchial dilations (31.85%) and aspergilloma (26.75%). Notably, there were 9 cases of completely destroyed lungs and a singular case of paracicatricial emphysema. Pleural involvement was mainly characterized by encapsulated pleuritis (15.29%), pneumothorax (11.46%), and empyema (6.37%).

Table 1: Detailed Description of Surgical Indications

Surgical indication	Number	Percentage
Parenchymal involvement	102	64.97%
- Parenchymal involvement	50	31.84%
- Aspergilloma	42	26.75%
- Destroyed lung	9	5.37%
- Paracicatricial emphysema	1	0.67%
Pleural Involvment	55	35.03%
- Encysted pleurisy	24	15.29%
- Pnomothorax	18	11.64%
- Empyema	10	6.37%
- Hydropneumothorax	3	1.91%
Total	157	100%

The parenchymal excision procedures included lobectomies (50.32%), pneumonectomies (5.10%), and segmentectomies (3.18%). The extent of parenchymal involvement necessitated a bi-lobectomy in 3.82%. A combined excision with pleurectomy was performed in 3.18% of cases.

Decortication was performed in 23.57% of patients, with 36 patients undergoing simple decortication. This was associated with the closure of a cutaneous fistula in a single patient.

Pleural symphysis through pleurectomy was carried out in 10.19% of cases, specifically in cases of post-tuberculous pneumothorax resistant to drainage. This pleurectomy was combined with emphysematous bulla resection in three patients.

A solitary thoracoplasty was performed, addressing a case of pulmonary aspergilloma where the respiratory function did not permit excision.

Table 2: Description of Surgical Procedures Based On Operative Indication

	Surgical indication									
Surgical Procedure	Bronchectasis	Aspergilloma	Destroyed lung	Emphyema paracicatricial	Pleurésie enkystée	Pneumothorax	Empyema	Hydro-pneumothorax	Total	Pourcentage
Lobectomy	40	39	-	-	-	-	-	-	79	50.32%
Pneumonectomy	1	-	7	-	-	-	-	-	8	5.10%
Segmentectomy	4	1	-	-	-	-	-	-	5	3.18%
Bi-lobectomy	5	1	-	-	-	-	-	-	6	3.82%
Pleuro-lobectomy	-	-	-	1	-	2	-	-	3	1.91%
Pleuro-pneumonectomy	-	-	2	-	-	-	-	-	2	1.27%
Decortication	-	-	-	-	24	-	10	3	37	23.57%
Pleurectomy	-	-	-	-	-	16	-	-	16	10.19%
Thoracoplasty	-	1	-	-	-	-	-	-	1	0.64%
Total	50	42	9	1	24	18	10	3	157	100%

Among the entire study population, postoperative complications occurred in 17.20% of patients.

The most common postoperative complication was pulmonary re-expansion deficit, observed in 7% of patients, followed by hemothorax at 3.82% and infectious complications also at 3.82%, including one case of right post-pneumonectomy bronchial fistula. Residual pleural effusion was noted in 1.91% of patients, and a solitary case of acute respiratory distress syndrome (ARDS) was documented.

Table 3: Description of Surgical Complications

Complication	Number	Percentage %
- Deficient Lung Expansion	11	7.00%
- Haemothorax	6	3.82%
- Infectious complications	6	3.82%
- Residual Pleural Effusion	3	1.91%
- ARDS	1	0.64%
Total	27	17.20%

Among the patients who experienced postoperative complications, accounting for 17.20% of cases, a favorable outcome was observed in 77.78% of patients following medical treatment combined with active physiotherapy or thoracic drainage. However, 22.22% of patients required a surgical intervention, including decortication in two patients, thoracoplasty in two patients, debridement in one patient, and pneumonectomy in another.

Across all operated patients, none experienced postoperative tuberculosis relapse during an average follow-up period of 14 months.

Operative mortality encompasses all deaths occurring within 30 days following surgical intervention. The overall operative mortality rate is 1.27% of cases, involving one case of bronchial fistula following pneumonectomy and one case of acute respiratory distress syndrome (ARDS) after thoracoplasty.

Hospital stay is calculated from the day of surgical intervention until the day the patient leaves the hospital to continue recovery at home. The average postoperative hospital stay is 13.8 ± 1.9 days.

4. Discussion

Our study focuses on a population of 157 patients admitted and operated for complications or sequelae of pleuropulmonary tuberculosis. Pulmonary tuberculosis sequelae predominantly affect adults, likely due to the aging of the patient population.

In our study, the average age is younger at 36.8 years compared to international publications, where the average age is 46 years for (Souilamas, 2001), 40.2 years for (Connery, 2003), and 52 years for (Gueza, 2018). This age difference can be attributed to the relatively younger population composition in our country.

The observed male predominance with a sex ratio of 1.75 aligns with international literature: 2.38 for (Gueza, 2018) and 3.76 for (Robert, 2020). However, the specific cause for this male predominance remains unexplained, apart from the known association between male gender and a higher prevalence of smoking. Smoking induces bronchial inflammation, contributing to the progression of tuberculosis and the development of sequelae.

Symptomatically, sequelae of pulmonary tuberculosis can manifest with various clinical signs. In our series, hemoptysis (56.05%) and bronchorrhea (33.76%) were prominent. The frequency of these symptoms is linked to the etiologies of tuberculous sequelae in our series, dominated by bronchiectasis and aspergilloma.

Despite well-conducted initial treatment, tuberculosis can evolve towards the formation of fibrotic lesions resulting in pleuro-parenchymal and bronchial mutilation, presenting various sequelae. Bronchiectasis is the

primary sequelae in our series, representing 31.84% of observed sequelae. This rate appears higher compared to the literature, such as 5% for (Mouroux ,1996), 12% for (Gursoy, 2010), and 18% in the (Prieto, 2001) series.

The presence of aspergilloma is explained by the epithelialization of a cavity after evacuation of caseous necrosis. Communication with the respiratory tree allows colonization by aspergillus spores. Local conditions, marked by spore arrival and cavity aeration, foster fungal material proliferation, forming an "aspergillar truffle." In our series, aspergilloma was found in 26.75% of cases, aligning with Kim's study (Kim, 2005) (27.9%) and Souilamas' report (Souilamas, 2001) (45%). However, other publications report no cases of pulmonary aspergilloma.

Destroyed lung is an extensive form of post-infectious tuberculosis sequelae. It occurs after a prolonged course of untreated or inadequately treated pulmonary tuberculosis. Destroyed lung can also complicate stenosis of a sequelar main bronchus from tuberculous bronchitis. In our series, parenchymal destruction was present in 5.37% of cases. Literature analysis shows higher rates, such as 14.1% for (Zaidane, 2018) and 22.6% for (Kone, 2020). This difference may be attributed to our younger population being managed at an earlier stage before lesion extension.

The development of emphysème paracicatriciel post-tuberculeux can result from the distension of a residual tuberculous cavity, typically located within parenchymal consolidation or within a bulging area due to irregular adjacent fibrous bands or airflow obstruction caused by pachypleuritis. It may be situated peripherally in subpleural regions at this stage. Alternatively, it can result from the compression of the bronchus upstream by tuberculous hilar lymphadenopathy. This compression leads to air trapping in the parenchymal territory with progressive distension, eventually forming a large bulla encompassing an entire segment, lobe, or even an entire lung.

In our study, cases of paracicatricial emphysema were rare (0.67%), in contrast to the study by (El Mghari, 2017), where they represented 13.19% of cases.

Regarding pleural sequelae, our study demonstrated the frequency of encapsulated pleuritis. Tuberculous pleuritis is often paucibacillary; repeated aspirations or untimely thoracic drainage can lead to compartmentalization, resulting in the formation of encapsulated pleuritis or pleural pockets. These pockets are characterized by their thickness and significant fibrosis associated with hyper-vascularization.

The deposition of fibrinous material on the pleural surface and colonization by fibroblasts lead to their transformation into collagen, which can calcify in certain circumstances, transforming these encapsulated pleural pockets into true "cuttlefish bone."

Tuberculous pneumothorax constitutes a rare and particularly severe form of tuberculosis. It often complicates cavitary tuberculosis, but certain forms can be observed in miliary tuberculosis or on late fibrous sequelae. It may result from the rupture of a tuberculous cavity, causing a bronchopleural fistula, or the eruption of caseum into the pleural cavity, causing local fibrosis and a parenchymal expansion defect. Another theory involves the development of bronchiolar lesions, where localized trapping promotes the formation of blebs, the rupture of which leads to the release of air into the pleural cavity.

Empyema necessitatis, or perforating empyema, is a rare complication where the inflammatory mass of an empyema spontaneously forms a tract from the pleural cavity to the soft tissues of the thoracic wall, resulting in the formation of a subcutaneous abscess that may sometimes open to the skin. This complication often represents a reactivation of pleural tuberculosis in malnourished or poorly managed patients from the outset.

Hydropneumothorax results from the acute rupture in the pleura of a tuberculous cortical focus in the lung with bronchopleural fistula, which entails the maintenance of pleural infection, hindrance to the re-expansion of the ipsilateral lung, and the risk of inhalation of pus contained in the pleura with seeding of both lungs (Taeib, 1980).

In our series, the rate of pleural sequelae is approximately 35.03%. We documented 15.29% encysted pleuritis, 11.64% tuberculous pneumothorax, 6.37% empyema, and 1.91% pneumothorax. (Simerabet, 2008), in a study involving 145 patients undergoing surgery for pleuropulmonary tuberculosis and its sequelae, of which 112 patients were treated for tuberculosis sequelae, recorded a pleural involvement rate of 69.64%, dominated by encysted pleuritis (26.78%) and empyema (19.64%).

From a curative standpoint, most authors (Stevens, 2000), (Rakotoson, 2011) recommend a combination of medical treatment and surgical intervention for therapeutic strategies. The key issue lies in the initiation date of postoperative treatment. This is scheduled and administered to patients from the first, or at the latest, the second postoperative day after conducting a hepatic assessment.

Surgical treatment combined with pre- and postoperative anti-tuberculous chemotherapy appears to yield favorable outcomes, according to (Sung, 1999). However, determining the postoperative therapeutic regimen and its duration remains to be established. Postoperative chemotherapy is recommended to last 22 to 24 months by some authors and 18 months by others (Mert, 2003) to reduce the potential risk of disease reactivation due to postoperative immunosuppression.

In our patients undergoing surgery for sequelae of pleuropulmonary tuberculosis, surgical procedures were performed after five to six months of anti-tuberculous treatment to achieve sterilization of the tuberculous focus (Rosenblatt, 1973), with a correct nutritional status, stable biological parameters, and after correction of any potential comorbidity risk factor. We consider that the sterilization of pleuropulmonary tissues by preoperative anti-tuberculous chemotherapy helps reduce the severity of inflammatory processes typically encountered in this type of surgery, making the operative technique less challenging and less prone to hemorrhage. Postoperatively, patients were promptly and systematically placed on specific therapeutic treatment for a duration of two months, following consensus and in agreement with our pulmonology colleagues due to the risk of disease reactivation.

Concerning the surgical procedures, parenchymal resection was performed in 65.60%, with lobectomies being the most common at 50.32%, occasionally associated with pleurectomy in 1.91%. Ten patients underwent pneumonectomy; however, it is noteworthy that pneumonectomy for benign inflammatory pathologies like tuberculosis is a highly risky procedure, associated with significant hemorrhagic morbidity and elevated mortality, leading many authors to recommend its avoidance (Rahibi, 2009), (Belcher, 1960).

In our series, bronchoplastic lobectomy was not undertaken due to the absence of endobronchial tuberculosis (Kawamura,1999), (Hsu 1997). Apical pleurectomy with or without bullectomy was conducted in 10.19% of cases, primarily for recurrent or chronically resistant pneumothorax requiring definitive surgical intervention. In one patient, lobectomy was performed for a giant paracicatricial bulla sequela of pulmonary tuberculosis.

Pleuropulmonary decortication, indicated in the pachypleuritis stage, accounted for 23.57%, with one case combined with the management of a cutaneous fistula. Typically performed after infection control and in the sequelae stage of tuberculous lesions, some authors suggest intra-pleural administration of antituberculous drugs in addition to oral treatment due to the low intra-pleural concentration of antituberculous drugs in cases of empyema caused by its thick and poorly vascularized capsule (Gupta, 2015).

Thoracoplasty has limited indications in the surgery of sequelae of pleuropulmonary tuberculosis. In our study, only one primary thoracoplasty was performed for a patient with pulmonary aspergilloma, where pulmonary resection was not feasible due to compromised respiratory function. Nevertheless, this technique still has its place in the surgery of tuberculosis sequelae, particularly in the presence of postoperative complications following parenchymal resection or inadequate lung expansion (Kim, 2005), (Gupta, 2015), (Daly, 1986), (Al-Zeerah, 1998).

In the short-term postoperative course, 82.80% of cases showed uncomplicated recovery, while 17.80% experienced postoperative complications, including hemorrhage, pleural empyema, parietal suppuration, air

leaks, and acute respiratory failure, consistent with findings reported in various literature (Kim, 2005), (Csekeo, 1997), (Akbari, 2005).

Two deaths were recorded in our study (1.27%), one due to bronchial fistula post-pneumonectomy in a cachectic patient and another from acute respiratory distress syndrome (ARDS) following thoracoplasty. Mortality is contingent on preoperative factors (functional respiratory and laboratory assessments), anesthesia, and effective postoperative care. However, specific procedure-related factors also contribute. Presently, overall mortality ranges from 0 to 10%, as reported by several authors.

5. Conclusion

In a nutshell, tuberculosis persists as a pervasive dilemma within regions constrained by limited resources. Notwithstanding diligent medical interventions, its enduring legacy of substantial sequelae necessitates surgical intervention. Despite the intricate challenges posed by inflammatory processes, surgery emerges as an imperative and irreplaceable modality in addressing these lingering repercussions, characterized by rates of morbidity and mortality deemed within acceptable rates.

Ethical statement: All procedures performed in this case study involving human participants, were in accordance with the ethical standards of the Faculty of Medicine of Algiers and with the 1964 Helsinki declaration and its later amendments. Written and informed consent for publication was obtained from the patient.

Funding: We attest that we have not received any financial support or grants from any institution during the realization of this report.

Conflict of interest: The authors have no conflict of interests to declare.

Authors' contributions: Conception, data collection, and writing of the original draft (KG); literature review (KG and MK, AH); methodology (KG, AH, AD, MK, MB); resources (KG, LH).

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The Asian Institute of Research
Journal of Health and Medical Sciences
Vol.7, No.1, 2024: 114-120
ISSN 2622-7258

DOI: 10.31014/aior.1994.07.01.312

Advancing Biosimilars in Latin America: A Comprehensive Analysis of Regulatory Frameworks, Market Trends, and Future Perspectives

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Abstract
Introduction: With the struggle to find cost-effective therapeutic options, there has been increased market interest for biosimilars in the Latin American region. This paper presents an in-depth exploration of the biosimilar landscape in Latin America. Methods: Key recommendations from the "Recommendations for the regulation of biosimilars and their implementation in Latin America," as published in the Generics and Biosimilars Initiative Journal in 2014, were synthesized and integrated into insights from various reputable sources. Results: A nuanced perspective on the regulatory landscapes, market dynamics, and the challenges and opportunities that define the biosimilar ecosystem in Latin America. Discussion: There are persistent challenges in the Latin America, including physician and patient acceptance, pharmacovigilance, and the need for continuous education. However, there are several potential opportunities for growth and development within the region. Conclusion: Latin American countries would benefit from banding together to form an organization that allows all to contribute and benefit from relationships formed naturally by common geography, language, and goals

Keywords: Biosimilars, Latin America, Regulatory

1. Introduction

Latin America is a region characterized by great geographical, political, and social diversity, particularly with regards to with extreme differences in income and access to quality healthcare, a daunting problem throughout the region. In 2015, the average median price of drugs to fight cancer was north of $120,000 per year, vastly more than the per capita income of any country in Latin America (The World Bank, 2024). With the struggle to find cost-effective therapeutic options, there has been increased market interest for biosimilars in the region.

In 2022, Julie Reed, Executive Director at The Biosimilars Forum, said that "biosimilars are a ready-made solution that can address current healthcare pressures and provide equitable healthcare for patients" (Pfizer, 2019). The biggest advantage that biosimilars provide is cost reduction on the back end that is passed on to providers

and end-customers on the front end. When patents expire on an original pharmaceutical, there is a window of opportunity for biosimilars to rise. Rapidly ascending technologies like Artificial Intelligence (AI) not only cut costs during the research and development (R&D) phase of creating biosimilars but also lower the lead time to market arrival and make the process more efficient. Speed and cost are the two most vital keys in getting patients who have suboptimal resources the access they need to quality medicine.

2. Methods

This article synthesizes key recommendations from the "Recommendations for the regulation of biosimilars and their implementation in Latin America," as published in the Generics and Biosimilars Initiative Journal in 2014, and integrates insights from various reputable sources.

3. Results

3.1. Regulatory Frameworks for Biosimilars

The landmark 2014 GaBI (Generics and Biosimilars Initiative) journal article, "Recommendations for the regulation of biosimilars and their implementation in Latin America" (Alvarez et al., 2014) was released at the forefront of the biosimilar wave, with countries all over the world breaking into new territory while Latin America struggled to make significant progress. The article made several recommendations for how to not only get biosimilars into the region but also how to make sure they were being dispensed properly, giving citizens the highest chance for success of using them effectively. These recommendations include:

- Training regulatory authorities on the process of evaluating biosimilars.
- Establishing a Latin America-wide group of regulatory authorities who are experts in biosimilars and who can share their experiences in regulating biosimilars.
- Establishing a native working group for each Latin American nation with the purpose of providing guidance to regulatory authorities as they begin to develop and subsequently introduce biosimilars in their countries.
- Utilizing the PRAIS website to encourage and explore healthy dialogue on biosimilars, including industry news, technological advances, problems in the industry, and so on, in order to provide transparency.
- Dedication by individual countries to promote pharmacovigilance by way of more training, more public and professional awareness, and better data analysis. A traceability system should also be put in place to ensure any negative events can be traced to the root and eliminated.
- Evaluate existing biological drugs classified as 'intended copies' to measure if they are truly biosimilars or if they are some other product that requires extra scrutiny. Intended copies are not true biosimilars and thus an unknown and potentially dangerous group of products.

More specific recommendations from the study include:

Preclinical and Clinical Requirements

- Quality, efficacy, and safety studies are all mandatory prerequisites for any company seeking to manufacture biosimilars.
- Examining the specific preclinical and clinical criteria recommended for biosimilar approval.
- Analyzing how these criteria contribute to ensuring the safety and efficacy of biosimilars.

Extrapolation of Indications

- Investigating the concept of extrapolation and its role in expanding the indications of biosimilars beyond those studied in clinical trials. Extrapolation is not a welcome addition when undergoing any sort of research, as it speculates without having hard evidence to back up its claims. Evaluating the regulatory considerations surrounding extrapolation and its impact on market access

Post-marketing Surveillance

- Assessing the post-marketing surveillance strategies recommended to monitor the long-term safety and

efficacy of biosimilars
- Exploring how robust pharmacovigilance contributes to building confidence in biosimilars among healthcare professionals and patients

3.2. Market Dynamics of Biosimilars in Latin America

In late August 2020, GaBi published "The biosimilars market in Latin America: a summary", an article covering the previous decade's movements in biosimilar research. In this section, we will explore the trends and challenges.

3.2.1. Market Trends

As of late 2020, Mexico, Brazil, and Argentina topped the list for the largest numbers of approved similar biotherapeutic products (SBPs) in Latin America. Mexico is also the largest exporter of pharmaceutical products in the region, followed by Brazil.

The Andean countries, including Peru, Ecuador, Colombia, and Bolivia, combine for just 14 SBPs. Meanwhile, the MERCOSUR trade bloc countries of Venezuela, Uruguay, Paraguay, and Chile have a total of 17, however, Uruguay significantly lags the rest with only one. This information is also flawed by the fact that some countries struggle to report accurately. The market for SBPs in Latin America, much like most economic conditions there, is quite fragmented, with only the largest countries being attractive homes to suppliers of biosimilars from outside their territories.

The factors driving the growth of the biosimilar market include increasing healthcare costs and the expiration of biologic patents. Discussing the evolving trends in physician and patient acceptance of biosimilars.

Mexico is the leading investor in biosimilars from 2010-2015, spending as much as $11.43 billion. Argentina ranks second at $6.1 billion, followed closely by Brazil at $4.9 billion (Ortiz-Prado et al., 2020). On the flip side, there are countries like Costa Rica investing just $24 million, Peru at $35 million, and no record of spending at all from Uruguay and Venezuela. Uruguay has the economic capability to produce biologics and only imports FDA and EMA-approved products. Venezuela keeps most of its activities clandestine from world forums. These numbers and traditional economic trends indicate the Latin America marketplace is divided into three groups.

The first group includes countries that are continuously growing and have few to no barriers when it comes to marketing and commercializing biosimilars. In addition to the Big Three mentioned above, this group also includes Chile, Colombia, Uruguay, and Peru. The second group, including Bolivia, Ecuador, Paraguay, and Uruguay, have smaller economies with less attractive investment opportunities for pharmaceutical companies, which reduces their ability to access biosimilars. These countries are largely consumers and importers of biological products on a much smaller scale. The final group is those whose information cannot be verified. The chief two entries in this category are Venezuela and Cuba.

3.2.2. Market Challenges

Market challenges are numerous and frustrating for the countries of Latin America, even beyond Venezuela's political turmoil. In 1952, French demographer Alfred Sauvy first coined the term "First World" countries, which has grown to mean "developed countries" that have advanced technology, high standards of living, are stable, have innovation taking place, have little-to-no risk of any form of insurgency, and have specific influence, both politically and culturally, around the rest of the world. Economic factors such as gross domestic product (GDP) and gross national product (GNP) both play a huge role in making this determination (World Population Review, 2024). As of 2022, the only Latin American countries to qualify to register First World status are:
- Argentina
- Chile
- Costa Rica
- Uruguay

This is a frightfully low number out of a region with 33 countries, coming in at barely 12%. The simple truth is that countries that don't fall under the First World designation typically are not focused on high-concept scientific advancements like biosimilars when they can't maintain a proper infrastructure and are swimming in debt. The market structure in countries that don't have First World advantages is based more on innovative drugs, and their small biotech companies cannot hope to compete with the large pharmaceutical companies that have multinational reach. The long reach of corruption may also rear its ugly head here.

Similarly, patients in Latin America will only switch from one form of treatment to another if there is a notably lower price point involved. In economies where wages are widely varied, and health care insurance ranges from top-end companies that cover costs to millions of people with no health insurance who have to rely on local physicians and homemade remedies to ward off injuries and illnesses, the idea of suddenly paying huge amounts of money for cutting edge technology in the form of bio-engineered drugs just isn't possible for an overwhelming majority of the citizen population.

3.2.3. Similar Biotherapeutic Products Approved and Marketed in Latin America

As of July 2019, there are 23 biosimilars that have gained a foothold in Latin America and have been made available to the general population (Generics and Biosimilars Initiative (GABI), 2013). The following chart lists their product names, areas of therapy, countries approved/marketed in, and Latin American partners, if applicable.

Table 1: Biosimilars in Latin America

Product Name	Therapeutic Area	Countries approved/marketed	Latin American partner
Bevax	Cancer treatment	Argentina	N/A
Blastoferon	MS	Argentina	N/A
Bioferon	Hepatitis C	Argentina	N/A
Novex	Rheumatoid arthritis & Leukemia	Argentina	Laboratorio Elea
Osteofortil	Osteoporosis	Argentina	N/A
Reditux/Tiedcron	Rheumatoid arthritis & Leukemia	Bolivia, Chile, Ecuador, Paraguay, Peru	CF Reclacine, Western Pharmaceutical, Farmindustrya, FAPASA
Remsima	Crohn's disease, Psoriasis, Arthritis, Colitis	Brazil, Colombia, Venezuela	Amarey Nova Medical
Usmal	Rheumatoid arthritis & Leukemia	Bolivia, Honduras	N/A
Zedora	Breast cancer & gastric cancer	Brazil	N/A

Escleroferon	MS	Argentina	N/A
Etanar	Psoriasis	Colombia	La Sante
Etart	Psoriasis	Mexico	N/A
Fiprima	Neutropenia	Brazil	N/A
Granulosum	Neutropenia	Argentina	N/A
Hemax	Anemia & kidney failure	Argentina	N/A
HHT	Prader-Willi syndrome, Turner Syndrome	Argentina	N/A
Hypercrit	Anemia & kidney failure	Argentina	N/A
Infinitam	Psoriasis	Mexico	N/A
Inter 2A	Hepatitis C	Argentina	N/A
Kikuzubam	Arthritis & Leukemia	Mexico	N/A
Lenoboio	Kostman's syndrome	Argentina	N/A
Lumiere	Diabetic Retinopathy	Argentina	N/A
Neutromax	Neutropenia	Argentina	N/A
Novex	Rheumatoid arthritis & Leukemia	Argentina	Laboratorio Elea
Osteofortil	Osteoporosis	Argentina	N/A
Reditux/Tiedcron	Rheumatoid arthritis & Leukemia	Bolivia, Chile, Ecuador, Paraguay, Peru	CF Reclacine, Western Pharmaceutical, Farmindustrya, FAPASA
Remsima	Crohn's disease, Psoriasis, Arthritis, Colitis	Brazil, Colombia, Venezuela	Amarey Nova Medical
Usmal	Rheumatoid arthritis & Leukemia	Bolivia, Honduras	N/A
Zedora	Breast cancer & gastric cancer	Brazil	N/A

The simplest takeaway from this chart is that Argentina is far and away the leader in biosimilars in Latin America, home to 13 of the 23 that have been released, amounting to approximately 57%. A second item to note is that very few of the biosimilars that have been released by larger companies are doing so with a Latin America partner, suggesting there is little to no movement in the region's market for biotechnology companies outside of Biosidus, Argentina's pioneer in the industry. Founded in 1983, Biosidus is the manufacturer of nearly one-half (11) of the biosimilars in the above chart. Just four of the 23 products, about 17%, have a Latin American partner as part of the equation.

4. Discussion

4.1. Challenges and Future Perspectives

An analysis of the challenges faced by biosimilars in Latin America is crucial for understanding the road ahead. This section explores persistent challenges, including physician and patient acceptance, pharmacovigilance, and the need for continuous education. Additionally, it discusses future perspectives, highlighting potential opportunities for growth and development.

Unfortunately, problems have plagued Latin America at the beginning of the biosimilar era, including instability of economies, government regimes, and the like. A 2015 report, "Payer and physician evidence and discount requirements for biosimilars in three Latin American countries" published by the GaBI Journal showed that budgets are huge detractants from biosimilar adoption, representing one of the biggest barriers facing residents of Argentina, Brazil, and Mexico. The comfort level that payers have for using biosimilars, usually with little to no knowledge of what the drugs are or what they do, leads to a lack of interest in paying for them, even at a discounted rate (Sandorff et al., 2015).

Physician Key Opinion Leaders (KOLs) indicate that most patients wouldn't consider biosimilars unless they were priced at a discount rate greater than 20 to 25% of the price of the referenced biologic medications. The survey in this study across Argentina, Brazil, and Mexico finds that total budget size is the number one worry for patients when it comes to utilizing biosimilars, particularly in Brazil. Other top concerns include how widespread the approved medications are, knowledge of information regarding how the treatment is used and how it assists their overall recovery, and how the treatments are ranked by their physicians and clinics of choice. For the physicians themselves, the value that offering biosimilars brings to their practices and clinics is the number one concern in all three countries, followed by the lack of information about clarity of treatment pathway, budget size to obtain the biosimilars, the complexity of the diseases they treat, and the value of acute versus chronic treatment duration offered by each.

In October 2023, both Brazil and Mexico's regulatory authorities voiced their desire to reduce the complexity of getting drugs approved, which would reduce their reliance on importing biologic agents at high costs and move into production faster (RAPS, 2023). Earlier in 2023, Brazil's National Health Surveillance Agency (ANVISA) commented publicly about a proposed rule change that would make an easier path for biologics and biosimilar drugs to receive marketing authorization. Mexico's Federal Commission for the Protection against Health Risks announced similar objectives a day later.

5. Conclusion

The only way forward for Latin America in the biosimilar industry is together. As in many things, the region could greatly benefit by emulating Europe's European Union (EU) structure in which countries form a naturally beneficial organization that allows all to contribute and benefit from relationships formed naturally by common geography, language, and goals. Each country in the region is focused on its own agenda, with no thoughts on assisting neighbors and finding mutually beneficial ways to thrive. Because of this, the cycle of struggling to afford, promote, and market biosimilars as an alternative to both painfully expensive traditional medications and the out-of-control market for illegal and fake pharmaceuticals will only continue. The region is in desperate need of a traceable, collaborative vision of pharmacovigilance that offers strength in numbers and security in the

supply chain to follow medicine from its point of origin to the end customer's hands, ensuring safety, health, and proper usage. The region desperately needs strong advisory forces to band together to form a framework that will start making this type of treatment available and recognizable to end consumers who often struggle with trusting new treatment plans, particularly those that challenge their economic needs. Strides must also be made to give more companies in more countries the opportunity to play a larger role in the production and distribution of biosimilars and their agents. Otherwise, the high price of exporting them will continue to be detrimental to the level of the economy.

Author Contributions: All authors contributed to this research.

Funding: Not applicable.

Conflict of Interest: The authors declare no conflict of interest.

Informed Consent Statement/Ethics Approval: Not applicable.

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