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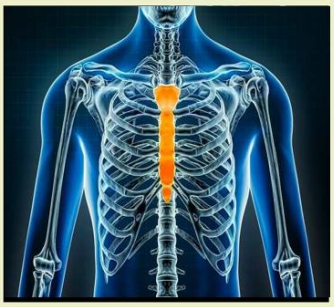

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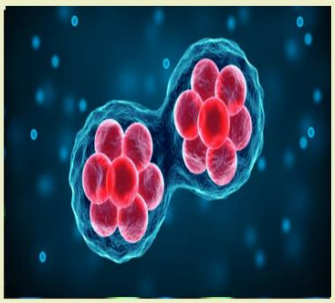

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CASE REPORTS

Meningioma with Hyperostosis: A Clinical Review up to Acrylic Cranioplasty Reconstruction in 3 Cases

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ABSTRACT

Meningioma is a type of tumor that commonly occurs in the central nervous system (CNS). Hyperostosis can occur in meningiomas. Hyperostosis is a condition in which the bone surrounding a meningioma thickens abnormally. Although hyperostosis is usually benign, leaving a small portion of bone that still has hyperostosis can increase the risk of recurrence. The case report was carried out by reviewing 3 medical records of meningioma sufferers with hyperostosis.

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Introduction

Meningiomas are tumors that arise from the meninges. The meninges are membranes that surround the brain, derived from pluripotent mesenchymal cells. The unique ability of these cells to differentiate into various cell types (such as fibrous, osseous, hematopoietic, and vascular) explains why many types of tissue can become meningiomas. Most cases show benign characteristics, with only one to nine percent being categorized as malignant or atypical.[1]

Meningiomas are a common form of tumor that occurs within the central nervous system (CNS). Meningiomas arise from arachnoid cells that are most commonly found near venous sinuses, parasagittal regions, sphenoid wings, middle cranial fossa, cerebellopontine angle, and olfactory sulcus.[2]

Meningiomas account for approximately 30% of all primary intracranial tumors in adults. The frequency of meningiomas is 83 cases per 100,000 individuals, with a greater predominance in women (with a gender ratio of 2-4:1 favoring women). With increasing age, the incidence of meningiomas is also increases, in the age group 0-19 years at 0.14/100,000, while in the age group 75-84 years at 37.75/100,000.[3]

In a significant portion (4.5% to 44%) of meningioma cases, the adjacent bone exhibits abnormal thickening, a phenomenon known as hyperostosis. This localized overgrowth is potentially linked to direct tumor cell infiltration into the bone matrix, facilitated by the hypervascular environment surrounding the meningioma.[4] Despite the often benign nature of hyperostosis associated with meningiomas, incomplete resection, even of a small residual area, can significantly elevate the risk of tumor recurrence. Therefore, achieving complete tumor and osseous resection remains paramount for optimizing long-term recurrence rates and patient quality of life.[5]

This case report was written because meningioma is the most common intracranial tumor in adults with a relatively high incidence of hyperostosis. By discussing this case, it is hoped that it can provide an overview of the clinical to therapeutic aspects of patients with meningioma with hyperostosis, thereby reducing the risk of recurrence and improving patient quality of life.

Cases

Case 1

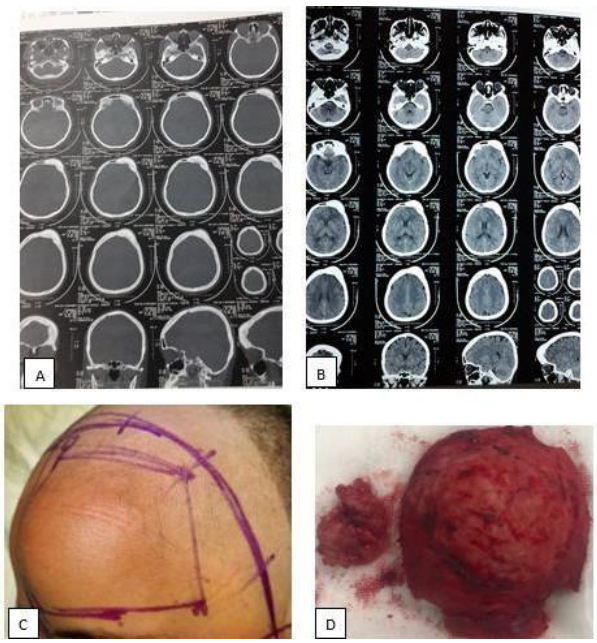

Figure 1. A. CT Scan with Bone Window, B. Non Contrast CT Scan, C. Mass Before Surgery, D. Mass After Surgery

Ms. S, age 39 years, a housewife, with a history of using injectable contraception every 3 months for 15 years, presented with symptom of a lump on her head (Figure 1C), since 5 years ago, followed by intermittent headaches since 1 year ago. The symptom gradually worsened, and seizures were denied. On examination, a mass was found in the left frontal region, one in number, measuring 6cmx4cm, with clear borders, not mobile, and the patient did not feel any tenderness. CT Scan examination (Figure 1A and B) showed a mass with bone thickening (hyperostosis) on the left frontal region. Tumor excision and removal of bone with hyperostosis were performed. Post-operatively, the mass was found to be a primary extracranial meningioma (Figure 1D), the patient's headache symptom improved, and cranioplasty using acrylic was performed 1 month later.

Case 2

Ms. R, age 47 years, a housewife with a history of using injectable contraception every 3 months for 18 years, presented with the main symptom of continuous headache, especially felt in the morning, since 6 months ago. The symptom gradually worsened, and seizures were denied.

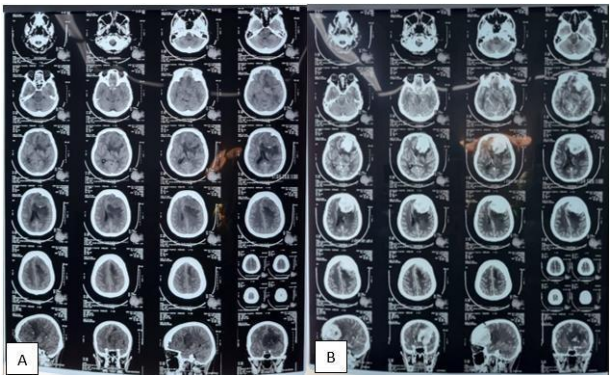

Figure 2. A. Non Contrast CT Scan, B. Contrast CT Scan

CT Scan with contrast showed (Figure 2B) a hyperdense mass image in the left frontal region, and the non-contrast CT Scan (Figure 2A) showed bone thickening (hyperostosis) in the left frontal region. Tumor excision and removal of bone with hyperostosis were performed. Postoperatively, the mass was found to be a meningioma, the patient's headache symptom improved, and cranioplasty using acrylic was performed 1 month later.

Case 3

Ms. P, age 53 years, a housewife with a history of using injectable contraception every 3 months for 20 years, presented with the symptom of recurrent seizures, since 1 year prior to presentation. The symptom was followed by intermittent headaches since 8 months prior to presentation.

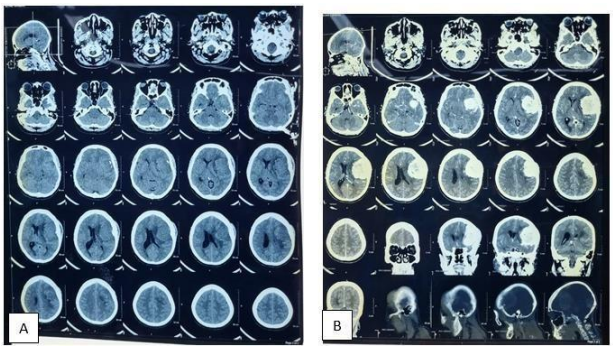

Figure 3. A. Non Contrast CT Scan, B. Contrast CT Scan

CT Scan with contrast (Figure 3B) showed a hyperdense mass image in the left temporoparietal region, and the non-contrast CT Scan (Figure 3A) showed bone thickening (hyperostosis) in the left temporoparietal region. Tumor excision and removal of bone with hyperostosis were performed. Postoperatively, the mass was found to be a meningioma, the patient's symptom improved, the seizure symptom had disappeared and the headache symptom had decreased, and cranioplasty using acrylic was performed 1 month later.

Acrylic Materials for Cranioplasty

All of our patients stayed in the hospital for 3-5 days, after which we began outpatient care.

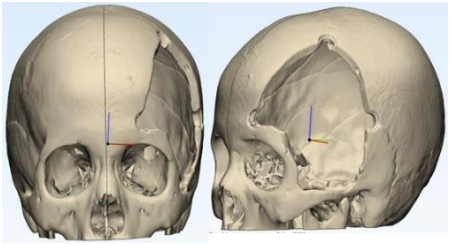

Figure 4. CT before Cranioplasty

The interval between craniectomy and cranioplasty was about one months. The material used was polymethyl methacrylate prostheses.

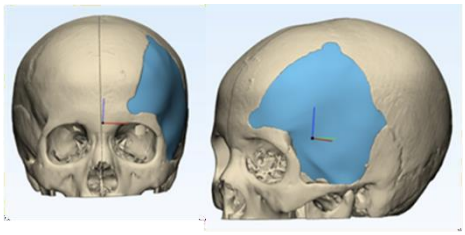

Figure 5. Reconstruction Skull Defect using CAD/CAM (computer-aided design and computer-aided manufacturing) technology

Figure 6. Formation of mold using prosthesis

Cranioplasty preparation started long before the actual surgery. It initiates with a pre-surgery CT scan (Fig. 4) to identify the size and location of the skull defect. Subsequently, we employ CAD/CAM (computer-aided design and computer-aided manufacturing) technology to reconstruct the defect, crafting a customized prosthesis for each patient (Fig. 5). This prosthesis is then fabricated using a 3D printer.

Figure 7. Cranioplasty using Acrylic

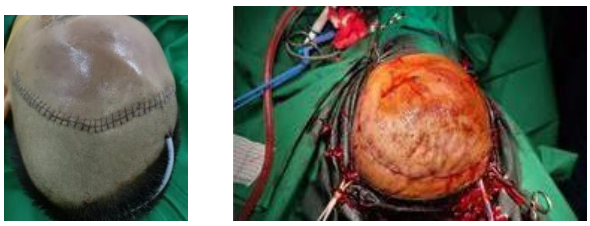

Figure 8. After undergoing cranioplasty surgery, the patient's skull shape returned to normal**.**

On the surgery day, all patients are administered perioperative antibiotics. The prosthesis is utilized to shape a mold, which undergoes sterilization (Fig. 6) and is employed during the surgery to create a patient-specific implant (Fig. 7). Following the cranioplasty procedure, the patient's skull shape was restored to its original state (Fig 8).

Discussion

This case report presents three female patients, all exceeding 39 years old and sharing the unique risk factor of long-term (over 15 years) injectable contraception use every 3 months. This finding aligns with existing research demonstrating a higher incidence of meningioma in women over 40 (18.69 per 100,000) compared to young women (0.16 per 100,000) and in women overall compared to men (2:1 ratio). This sex-based disparity may be linked to the known influence of sex hormones, thought to affect meningioma development since the late 1920s.[7] Growing evidence suggests that exogenous hormones, such as those used in hormonal contraception, can significantly increase the risk of meningioma development. Premenopausal women using these hormones face a potential 2.48-fold higher risk compared to postmenopausal women with a history of hormone use. This association appears to be driven by long-term exposure to exogenous progesterone, a common component of many contraceptives. The

mechanism behind this link may involve the progesterone receptor's interaction with coactivators and/or corepressor proteins, influencing gene expression patterns related to tumor development.[8]

Headache was the symptom reported by all patients in this case report. Patient 1 had headache for 1 year before admission to the hospital and also had a symptom of a mass in the left frontal region. Patient 2 had headache for 6 months before admission to the hospital, while patient 3 had headache for 8 months before admission to the hospital. Patient 3 was the only patient with a symptom of seizures in this study. These data are consistent with other studies that show that 60.5% (1,119 of 1,852 patients) of meningioma patients present with headache. Whereas, seizure can occur in 17.4% (323 of 1,852 patients). The time between the onset of headache in patients until the patient is diagnosed ranges from 6 to 24 months.[9] Brain tumor headaches often involve pressure and nerve irritation. These headaches disappear in most patients after surgery, especially for larger tumor. This improvement likely happens because removing a large tumor reduces pressure inside the skull, easing the headache.[10]

In the presented case report, the seizures experienced by patient 3 can be directly attributed to the unfortunate placement of the tumor within their temporoparietal region. This specific area of the brain, temporal lobes, harbors an elevated risk for triggering seizures in individuals with meningiomas.[11]

Primary extracranial meningioma is a rare form of meningioma. This occurred in patient 1 of the case report, where the patient had an extracranial meningioma with a mass appearance on the left frontal region. Extracranial meningioma is divided into primary and secondary. Primary indicates the absence of intracranial lesions, while secondary indicates the presence of intracranial meningioma lesions followed by extracranial lesions. The location of occurrence is often under the scalp. Extracranial meningioma is difficult to diagnose using only CT scan, because it will only appear as a hyperdense mass with occasional hyperostosis. MRI and angiography also do not show much difference with the surrounding tissues, so the definite confirmation is through anatomical pathology biopsy.[12] Extracranial meningioma can occur due to the descent of arachnoid cells in the protective layer of cranial nerves that migrate out of the intracranial during skull formation.[13]

All patients in this case report study had hyperostosis. Hyperostosis is a condition in which the bone surrounding the meningioma undergoes abnormal thickening.[4] Hyperostosis of the bone adjacent to meningioma, which can be observed on CT with bone window, has been well described, with many reports discussing the possible causes. A prominent theory is that bone invasion by tumor cells/tissue causes hyperostosis. This is supported by histopathological studies that have clearly shown tumor tissue invasion into adjacent bone in areas with hyperostosis, which is thought to be associated with strong somatostatin receptor subtype 2A (SSR2A) reactivity.[14] In cases of suspected meningioma with bone invasion, maximal resection of the adjacent bone will be the preferred option, thus requiring craniectomy.[15]

Craniectomy disrupts the brain's delicate balance, affecting pressure, CSF flow, and blood circulation following the Monro-Kellie hypothesis.

This can lead to potential complications like hydrocephalus and sunken flap syndrome.[16]

Cranioplasty is a surgical procedure that aims to repair acquired or congenital cranial defects.[17] Cranioplasty has a dual function, namely as a protector of cerebral structures and as a therapeutic intervention to manage changes in cerebrospinal fluid (CSF), blood circulation, and brain metabolic needs. In addition, it can offer aesthetic benefits by reconstructing cranial bone deformities.[18]

In this study, acrylic was chosen as a cranioplasty material because of its low cost and good biocompatibility, which is consistent with recent research.[19] Although acrylic cranioplasty is generally considered a safe method, its complication rates are comparable to, although not superior to, other synthetic cranioplasty techniques.[20-21] In fact, recent studies have shown that acrylic has a lower complication rate of infection than titanium mesh.[22]

The time interval between craniotomy and cranioplasty for patients in this study was one month, which was done to minimize the risk of infection and seizures after surgery. Studies have shown that infection is most commonly reported in the first 14 days after craniotomy, and the risk of seizure is observed to increase after 90 days.[23] Other studies have found that functional outcomes are better for cranioplasty performed at a time of less than 7 weeks or at 7-12 weeks compared to that performed at more than 12 weeks.[24]

Conclusion

Meningioma is a tumor that originates from the meninges. Meningioma is the most common intracranial tumor in adults. Common symptoms that patients often experience are headache and seizures. Meningioma can invade the surrounding bone, causing thickening of the bone called hyperostosis. Bone hyperostosis adjacent to meningioma can be observed on CT scan with bone window. In meningioma with hyperostosis, it is necessary to perform meningioma excision and remove all of invaded bone, thereby reducing the recurrence rate, and can improve the quality of life of patients.

Conflict of Interest

The author started there is no conflict of interest.

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REVIEW ARTICLE

Application of Enzymes in Drug Discovery Research: A Review

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ABSTRACT

Enzymes have effectively substituted many conventional chemical catalysts-reliant pharmaceutical drug manufacturing procedures. From this v-prospect, the use of enzymes in drug discovery research is quite encouraging. Numerous enzymes have been demonstrated to perform detoxification at the cellular level, for instance, the antioxidant enzymes, catalase, and superoxide dismutase (SOD). These enzymes work simultaneously to neutralize oxygen-free radical species. The enzyme-mediated pharmaceutical procedures include the synthesis of diverse semi-artificial antibiotics, dynamic enantiomers of medicines through kinetic determination, production of enantiomerically unadulterated types of amino acids, and others. Enzymes are being used to treat cancer and infectious disorders where antibiotics are no longer effective because of antibiotic resistance. Thus, the present article aims to review the diverse use of enzymes in the drug industries and discuss the features of enzymes that make them suitable drug candidates.

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Introduction

Enzymes are biocompounds usually proteins, or nucleic acids (ribozymes), which lower the activation energy required to perform a chemical reaction. Nucleic acids accelerate only protein synthesis, while protein enzymes are for other bioprocesses. These biocatalysts regulate the progression of biochemical responses at rates appropriate for cellular functions, proliferation, and growth. [1-3] Even before their complete elucidation,

the enzyme and its applications were well known, and Wilhelm Friedrich K¨uhne was the first individual to offer a scientific vocabulary for this class of biomolecules.[4] Enzymatic processes have been demonstrated since the prehistoric Egyptian artifacts where microorganisms and their enzymes were utilized to preserve drinks and food. Lazzaro Spallanzani, a renowned Italian catholic priest, first discussed the relevance of this biomolecule in his work on biogenesis in 1783. He claimed that certain types of non-living materials had an inherent ability to start life, which enables live germs to produce them. [5] Gottlieb Sigismund Kirchhoff investigated the conversion of starch to glucose in 1812. He investigated and wrote a paper on the use of these biomolecules as catalysts in this procedure.[6] The first enzyme, diastase, was isolated and characterised by French scientist Anselme Payen in 1833 and [7] in 1960, NOVO started producing protease on an industrial scale using Bacillus lichnformis. After 1980, a lot of scientists began systematically using genetic engineering techniques to improve the efficiency of producing enzymes and change their properties. [8]

Naturally occurring enzymes have been applied extensively since primeval times and in leather, linen, and indigo manufacturing. All the procedures for creating these products rely on either the enzymes created by microbes or the enzymes found in other sources such as the papaya fruit or calves' rumen. [9] Because of their utility in the dairy and detergent industries, proteases continue as the primary type of enzyme under investigation from natural sources. [10] The second major group that underwent specific interventions are the carbohydrases, principally cellulases, and amylases due to their utility as detergents alongwith in the baking and textile industries. [11] The capability of enzymes maintain operational and carry out catalysis activities, even outside of their organism of origin [12], permits their application in several industrial procedures dependent upon chemical alterations of substrates to their identical products.[13]

The utility of enzymes far exceeds just their use within the human body; within the human surrounding can be seen in many of their approaches in several manufacturing applications. About 200 bacterial enzymes from 4000 known enzymes are used commercially. [14] Three companies create almost 75% of the overall enzymes: specifically, United States-based DuPont, Denmark-based Novozymes, and Switzerland-based Roche. [15] The remaining 25% are made by other companies, including Novus International Inc, El du Pont de Nemours and Company, ABF (Associated British Foods), a Dutch multinational corporation known as Koninklijke DSM NV, and AB Enzymes GmbH. Following the report presented by Mordor Intelligence named "Industrial Enzymes Market: Growth, Trends, and Forecast (2019–2024)", the international market of industrial enzymes is anticipated to rise at an approximate yearly development rate of 6.8% during the years 2019–2024. [16,17]

As a result of the relative importance of the enzyme industry and the potential effects of this growing industry on the world at large, an explanation associated with the previous market prediction of the most extensively utilized enzymes such as carbohydrases, proteases, and lipases and their market for the sectors of healthcare and pharmaceutical is presented for the reader's reference. Global Market Insights Industrial's Report [gm insights] predicted that the worldwide market for proteases is expected to increase to approximately 2 billion United States dollars by 2024. On the other hand, industrial wastes are expected to decrease through these enzymes as companies would rather pay to clean the mess than pay a fine. The use of enzymes in modern industry is discussed further in the following section.

Importance of Enzymes in Various Industries

Due to their many advantages, which range from their functioning in temperate response conditions to their remarkable product selectivity and their little physiological and atmospheric toxicity, enzymes are extremely effective biocatalysts researched for industrial-level catalysis. [18-20] These advantages of enzymes are in addition to cost-effectiveness when used as biocatalysts in chemical procedures. The enzymes have even 2000 times more TON (turnovers) and 1000 times higher lifetime than inorganic and nonbiological catalysts[21,22]. Due to their minimal energy needs, alleviation of waste generation, and primary routes of production, [23-24] enzymes have been partly appreciated in the beverage, pharmaceutical, and food industries [25-31]. The connection of the biocatalyst to a medium with additional electrical, physical, mechanical, or chemical properties has been the focus of research on the immobilisation of enzymes, and it has been shown that immobilising biocatalysts can improve their stability and activity across a wide range of working situations.[32-36]

Applications of Enzymes in Pharmaceutical Research

Recently, drug discovery is essential for the consistent application of different approaches. It enhances the effectiveness, executes novel technologies, and enhances the drug quality. Existing strategies observe detection in four steps: 'hit' selection, selection of lead, optimization of lead, and development selection.[37] Multiple research studies discovered the deprived properties that cause the deliberate destruction of development organizations. The candidate drugs select through experiments to ensure that the compounds with poor properties without progress.[38] In numerous cases, properties are determined to optimize pharmacokinetics, and the properties that influence human absorption and metabolism are applied. [39] If a compound has poor pharmacokinetic characteristics, it may not be therapeutic in vivo even while it is very dynamic in vitro. If a less effective substance's qualities allow for better exposure in vivo, it might produce a better healing effect. [40-41] One of the most critical obstacles

faced by pharmaceutical organizations is assigning their drug discovery reserves toward medicinally appropriate protein targets. Chemical explorations give a process to focus upon the efforts of preliminary novel target recognition towards proteins that are more effortlessly authenticated almost certainly to be efficient targets of a drug, thus generating a higher prospective for achievement. [43]

Principles of early drug discovery

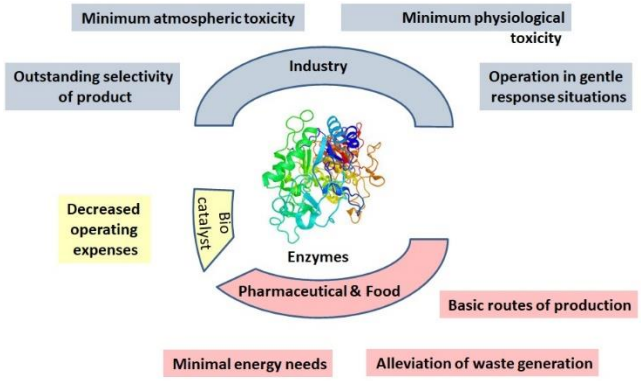

Figure 1. Working of release of new drug

When a disease or clinical condition exists for which there are no suitable pharmaceutical treatments available on the market, a drug development programme is initiated, and this unmet clinical need serves as the project's primary driving force. Drugs that fail in clinical trials typically do so for one of two reasons: either they are hazardous or useless. In order to strengthen confidence in the connection between the target and disease, target selection and validation is one of the key steps in the development of a novel drug.

Additional ways of identification include measuring mRNA/protein levels to ascertain the disease's expression and whether they are related to the disease's development or exacerbation. Another useful tactic is to look for genetic associations, such as whether a genetic variant is merely functional or is associated with the risk or progression of a disease. Phenotypic screening is an alternate method to find disease-relevant targets. Target identification and mechanism of action should be clarified very early in the drug discovery process due to the practical benefits that this knowledge provides.[44,45]

As more software systems for the prioritisation of pharmaceutical targets are created, they heavily rely on efficacy estimates based on ratings for the target-disease associations. Here, novel computational approaches are introduced that can be used to more precisely evaluate the efficacy and safety of potential treatment targets. The suggested efficacy scores enhance the inference of target-disease connections by utilizing tissue/disease-specific networks and existing gene expression data. [46]

Target proteins may be recognized via chemical explorations that can be potential drug targets.

Chemical probes can also be applied to validate research in cellular models or animals at both early periods of ailment model selection and throughout experiments of early target confirmation. [48] Additionally, specific chemical probe components and reactive clusters may serve as the cornerstone of a strategy for molecule inhibitors. Chemical investigations have already been used to identify

cysteine proteases involved in processes like apoptosis, [50] cataract formation, [47] and malaria infection. [48] Additionally, the number of reported chemical probes is increasing, and various mechanism-dependent affinity labelling inhibitors or reagents have been identified that could be used to create new categories of chemical probes. The protein phosphatases and protein kinases are two crucial families of enzymes that have been the focus of medical discovery efforts and are particularly amenable to chemical proteomics applications. These enzymes are important regulators of metabolism and cell signalling, and they are frequently thought of as potential therapeutic targets.[48, 49] A chemical proteomic method may be useful for the family of protein kinase enzymes. More than 500 members of this family provide various substrate and cellular functions.[50,51] Due to their involvement in numerous cell-signaling processes, protein phosphatases are becoming increasingly prominent as therapeutic targets.[52] Over 600 industrial goods are produced by enzymes, and there is a growing need for them in businesses looking for long-lasting solutions. [53]

Enzyme therapy

At the industrial level, catalysis by enzymes has been successfully used to produce compounds with pharmacological functionality. [54] The strong chemo-, regio-, and stereo-selectivity with which enzymes alter substrates to a resulting product is one of the most significant advantages of catalysis using enzymes over classical catalysis.[23,55] Due to the efficient product production processes and consistent improvement in the industry's economics, the high degree of product specificity is vastly preferred in these types of pharmaceutical operations.[56,57] On an industrial scale, the multidisciplinary strategy is appropriate for biocatalysts. It is highlighted by Merck's development of the enzyme-catalyzed sitagliptin, a medication used to treat type 2 diabetes mellitus. [58] Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) DPP-4 inhibitor that lowers diabetes-induced tight connection disassembly and avoids an increase in the blood-retinal barrier (BRB).[59] To produce sitagliptin traditionally, enamine is elevated-pressure hydrogenated using a catalyst supported by rhodium, followed by carbon management to remove trace amounts of rhodium and express sitagliptin in excess of 97% enantiomers.[60] A bicyclic proline intermediate, a significant precursor in the production of boceprevir, an NS3 protease inhibitor used for the management of persistent hepatitis C infections, has been desymmetrized using an MAO (monoamine oxidase)-catalyzed procedure that has been expanded in research by Merck and Codexis. [23, 61]

Use of enzymes as oral and inhalable drugs

An advanced marketable-level production technique for (S, S)-reboxetine succinate—a nor-epinephrine anti-depressant for the treatment of fibromyalgia—was reviewed by Hayes et al. in their study. Pfizer was in the last stages of developing this drug for the treatment of fibromyalgia. [62,63]

Pregabalin, a neuroactive drug with antiepileptic, analgesic, and anti-apprehension activity that is used to treat anxiety, epilepsy, and irrational social fear, was synthesised at an industrial level by Martinez et al. using a novel generation. [64, 65] Since de Duve proposed a therapeutic enzyme as part of alternative therapy for inherited inadequacies in the 1960s, the concept of the remedial enzyme has been around for at least forty years. [66] The FDA approved Alteplase (Activase; recombinant plasminogen activator for human tissue), the first recombinant enzyme preparation, in 1987. This 'coagulate-buster' enzyme, which was the second recombinant protein therapy to be promoted on the market (the first hereditarily created preparation was insulin in 1982), is used in the management of cardiac crises, which are caused by the occlusion of a coronary artery by a thick clot.[67,68] Numerous additional enzymes that are used as coagulant or anti-clotting medicines have received FDA approval. Peg Damage Bovine (Adagen), a type of bovine ADA treated with PEG, received approval in 1990 to treat individuals suffering from a form of SCID (severe combined immunodeficiency disease), which is caused by a persistent insufficiency of adenosine deaminase. It is significant to remember that the first healing enzyme recognised by the Food and Drug Administration under the Orphan Drug Act, or ODA, was pegadamase bovine (Adagen). The Orphan Drug Act was created in the USA in 1983 to encourage the pharmaceutical industry to create treatments for diseases affecting only a tiny population (not more than 200,000).

Proteolytic and glycolytic enzymes

The elevated levels of adenosine's toxicity to the immune system are lessened by the enzyme adenosine deaminase, which is present in the circulation of these patients. The change of adenosine deaminase with polyethylene glycol is crucial to the management's success.[69] Because the medication is derived from cattle, polyethylene glycol reduces the possibility of immunological reactions while increasing the enzyme's half-life (which is actually less than thirty minutes). Another enzyme used to treat CSID is sacrosidase, as patients with congenital sucrase-isomaltase deficiency are unable to absorb the disaccharide sucrose. [70] The amount of enzymes is used to manage the digestive issues that are triggered by a lot of sweets. The enzyme -galactosidase is taken as a digestive aid by people who have. The enzyme -galactosidase is taken as a digestive aid by people who have abdominal gas, bloating, and diarrhoea after consuming meals like beans, Brussels sprouts, broccoli, cabbage, and other members of the Brassica family of vegetables. [71] Lactase and -galactosidase are currently available as dietary supplements in some sets. When eating foods containing lactose, such as milk and milk products, those who have lactose intolerance experience gastrointestinal distress because they are unable to digest the sugar. [72] These folks have access to lactase supplements like lactase powder and lactase-enhanced milk. These supplements lessen lactose intolerance symptoms like gas, abdominal bloating, and diarrhoea by facilitating the dissociation of

lactose into its monomers, galactose and glucose. [73, 74] Following genetic modification, glycolytic enzymes should increase hydrogen production to an industrial-scale level, enabling them to replace current techniques for producing the element.[75]

Enzymes as anti-inflammatory drugs

When phenylalanine hydroxylase levels are low or nonexistent, phenylketonuria develops. This enzyme helps to maintain the body's normal levels of phenylalanine by converting it into tyrosine. [76] A plant's PAL (phenylalanine ammonia-lyase), which was obtained from recombinant yeast, was used to construct an oral treatment for the condition. This treatment is now on the market under the brand name Phenylase TM. Additionally, it has been demonstrated that the GIT's phenylalanine is hydrolyzed by phenylalanine ammonia-lyase. [77]

Based on the current knowledge of pancreatic secretions, a mixture of pancreatic enzymes, comprising lipases, proteases, and amylases, was developed as an all-purpose digestive support for the benefit of immunosuppressed patients. It has been demonstrated that the pancreatic enzyme mixture effectively lowers lipid malabsorption in HIV patients. [78,79] The management of pancreatic insufficiency, which occurs frequently in CF and chronic pancreatitis, is also aided by this cocktail of enzymes.[76] A mixture of pancreatic enzymes with the market name “TheraCLECTotalTM” is accessible commercially.

Conclusion

Enzymes find great applicability in drug development, and they are proven to be excellent drugs mainly owing to two of their properties. The first of these properties is that enzymes can bind specifically to their target site, and the second is that enzymes are catalytic, which aids the conversion of various target substrates to desired products. With these outstanding features, enzymes excel as a significant therapeutic component for a wide range of disorders that many other drug candidates can not achieve. Advent in biotechnology has had the pharmaceutical industries develop safe, cost-effective, high-specificity enzymes in the last decades. In line with scientific progress, drug laws have evolved, and drug administration bodies have taken initiatives to support the development of enzyme drugs. In the future, further interventions are expected to exploit more potential of the enzymes in the treatment of severe and rare diseases.

Conflict of Interest

The author started there is no conflict of interest.

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ORIGINAL ARTICLE

Level of Knowledge and Awareness Among Parents Regarding the Care of Children with Thalassaemia

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ABSTRACT

Background This study assessed parental knowledge and awareness of children with thalassemia. Thalassemia care among 65 parents at a Kota Kinabalu hospital focuses on parental knowledge and awareness of children with thalassemia. The objectives were to identify parents' level of knowledge of thalassemia care and assess their awareness of specific care needs.

Methods: This was a descriptive, cross-sectional study of the thalassemia families of patients at Likas Women and Children's Hospital, Kota Kinabalu, Sabah. Using random sampling. The study involved 65 respondents from Sabah Women and Children in Kota Kinabalu, Sabah. Data from questionnaires and tests were processed using SPSS version 24, with descriptive statistics analysing frequency and percentage, expressed as mean ± standard deviation.

Results Most respondents had a high level of knowledge about thalassemia, an inherited disease caused by insufficient red blood cell supply. They understood that untreated conditions could deteriorate thalassemia patients but could lead normal lives with proper therapy. They also knew that thalassemia could be detected through blood tests and that blood donation could be beneficial. However, they had moderate knowledge of the connection between thalassemia and anaemia, blood transfusions as the only treatment, and their ability to identify and avoid thalassemia during pregnancy.

Conclusion This study emphasises the need for education, community engagement, and healthcare involvement to enhance the understanding and support of individuals with thalassemia, suggesting that comprehensive strategies, including education programs and collaborations with local organisations, can be implemented.

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Introduction

Thalassemia is a genetic disease or inheritance that occurs worldwide. Thalassemia remains one of the diseases for which there is no cure or treatment. Therefore, the incidence of thalassemia shows a significant increase in this country because of marriage, especially among individuals categorised as minor carriers.[1] When both couples marry and have children, they can potentially have a child with thalassemia primary disease.[1,2] This situation will significantly impact couples and challenge the Malaysian Ministry of Health, particularly in providing exceptional care. Based on statistics from the Malaysian Ministry of Health, thalassemia cases in this country, especially in Sabah, have consistently increased yearly. This situation causes the annual incidence rate of thalassemia in the state of Sabah to increase.

Researchers have proposed and discussed various theories and assumptions regarding the significant increase from year to year. Although not explicitly discussed, what factors caused this increase, especially in Sabah? The possibility that this situation occurs because of knowledge of and exposure to thalassemia still needs to be discovered by the community in this state.[3] Based on a study[3,4] one of the factors that cause an increase in the number of thalassemia patients in this country is marriage between individuals who are both minor carriers.

The result of their marriage will give birth to a child who is prone to thalassemia. The interviews conducted by the researchers found that most of these couples did not know they would have a child at a high risk of giving birth to a child with thalassemia if both were carriers of thalassemia minor.

The most prevalent monogenic diseases worldwide are inherited haemoglobin abnormalities. In Malaysia and other tropical nations, thalassemia is one of the most prevalent autosomal recessive diseases, causing faulty haemoglobin formation. This was caused by a decrease in the production of one or more haemoglobin subunits composed of both globin chains.[5]

According to the World Health Organization (WHO)[6], thalassaemia is a major public health concern. Accurate data on the impact of the disease on health in nations with a high thalassemia prevalence is required. Although thalassemia is the most prevalent hereditary haemophilia in Malaysia, there still needs to be more information regarding the geographic distribution of patients, socioeconomic data, and clinical data, including treatment outcomes. 4.5 per cent of Malaysians were carriers. As various molecular abnormalities cause thalassemia, each ethnic group has a unique set of mutations. While uncommon among Malaysian Indians, thalassemia is more common in Malay and Kadazan-Dusun populations. Most cases of haemoglobin (Hb) Bart's hydrops fetalis have been recorded in Malaysian Chinese individuals.[7]

Methods

This was a descriptive cross-sectional study. The population of families of patients who came for treatment at Likas Women and Children's Hospital, Kota Kinabalu. Random sampling was used as the sampling method. Sample size calculation was performed using the Krejcie and Morgan 1970 table.

Respondents were 65 respondents. This study was conducted in Sabah Women and Children, Kota Kinabalu, Sabah. Data were collected from February to March 2023. Questionnaires were filled out for 15–20 minutes. The validity of the questionnaire was calculated using Cronbach's alpha to test the reliability and internal consistency of the responses obtained from the respondents.[8] Random sampling techniques were used in this pilot study. A questionnaire was created and pilot-tested using Cronbach's alpha reliability test, which yielded a value greater than 0.84.

The questionnaire was divided into two parts. The first part about the respondents' background included gender, age, marital status, living with someone and educational background. The second part was a question about respondents' awareness and knowledge of thalassemia. The questions were rated on a Likert-type scale. The questionnaire was administered with a brief description by the researcher regarding its purpose and stating. Respondents were given 20 min to respond.

Data collected through questionnaires and written tests were processed using the Social Science Statistics Package, namely SPSS version 24, to obtain results from the data obtained. Descriptive statistics were used to analyse the frequency and percentage of the data. Descriptive data are expressed as the mean ± standard deviation. An independent sample t-test was conducted to compare variables. Ethical Consideration: Permission to collect data from the hospital director was the approval to conduct the research from NMRR 124/2023.2

Results

Table 1 shows the representation of parents' demographic with 52.3% aged 31-40, 33.8% aged 31-40, and 13.8% aged 21-30. The study revealed a balanced sex distribution, with a slightly higher percentage of females (53.8%). Most participants (95.4%) were married and had a secondary or diploma education, with a smaller proportion (21.5%) having tertiary education. Most families (49.2%) had a family income below RM 2000, followed by those between RM 2000 and RM 4000 (30.8%). Most individuals (76.9%) resided with their families, while a smaller percentage (23.1%) resided with their parents and siblings.

Table 1 Demographic Data

Criteria	(N) Frequency	Percentage
Age		
21 – 30 Year	9	13.8
31 – 40 Year	34	52.3
> 41 Year	22	33.8
Gender		
Male	30	46.2
Female	35	53.8
Marital Status		
Married	62	95.4
Divorced	3	4.6
Education		
Secondary	23	35.4
Tertiary	14	21.5
Diploma	21	32.3
Degree and above	7	10.8
Family Income		
< RM 2000	32	49.2
RM 2000 - RM 4000	20	30.8

> RM 4000	13	20.0
Living With Who		
Own family	50	76.9
Parents & sibling	15	23.1

The findings of this study, referring to Table 2, that assessed parents' knowledge of how to care for children with thalassemia, revealed some significant findings. Most respondents indicated a high level of knowledge about numerous thalassemia-related topics. They constantly and firmly understood that thalassemia is an inherited disease (mean = 4.52, SD = 0.867) caused by insufficient red blood cells (mean = 4.63, SD = 0.574). Additionally, respondents demonstrated a clear understanding that thalassemia patients' conditions are likely to deteriorate if untreated (mean = 4.76, SD = 0.424) and that thalassemia patients can lead normal lives with the right therapy (mean = 4.64, SD = 0.570).

Additionally, many participants knew that thalassemia could be detected using a blood test (mean = 4.52, SD = 0.589) and that individuals with thalassemia could benefit significantly from blood donation (mean = 4.78, SD = 0.450). There were also differences in knowledge levels. The respondents' knowledge of the connection between thalassemia and anaemia was moderate (mean = 3.78, SD = 1.023), and they had a moderate comprehension that the sole available form of treatment was blood transfusions (mean = 3.35, SD = 1.351). Most respondents also showed high levels of knowledge about their capacity to identify thalassemia during pregnancy (mean = 4.12, SD = 0.760) and avoid it through genetic counselling and prenatal screening (mean = 4.44, SD = 0.750). The results showed that parents generally had a high level of knowledge of thalassemia, with only a few areas requiring additional education or awareness to improve their understanding.[9]

Table 2 Knowledge of parents regarding the care of children with Thalassemia

Item	N	Mean	Std Deviation	Interpretation
Thalassemia is due to not having enough Red Blood Cells	65	4.63	.574	High
Thalassemia is an Inherited Disease	65	4.52	.867	High
If thalassemia is left untreated, the person will get worse	65	4.76	.424	High
Individuals who have Thalassemia can lead normal lives with appropriate treatment	65	4.64	.570	High
Individuals who have Thalassemia are anaemic	65	3.78	1.023	Medium
A blood test can identify thalassemia	65	4.52	.589	High
Blood donation can help Thalassemia patients	65	4.78	.450	High
Blood transfusion is the only treatment for Thalassemia patient	65	3.35	1.351	Medium
Thalassemia can be detected during pregnancy	65	4.12	.760	High
Thalassemia can be prevented by genetic counselling, pre-marital and prenatal screening	65	4.44	.750	High

Bast on Table 3 Findings of Parents' Awareness regarding the care of children with Thalassemia. Parents showed various levels of Awareness of several thalassemia and related topics. With a mean score of 4.40 and a standard deviation of 0.932, they generally understood that thalassemia can occasionally be recovered with blood transfusions, showing a " high " level of awareness. With mean scores of 3.78 and 3.27, with various standard deviations, knowledge regarding the use of drugs and surgery as treatment options for thalassemia was moderate, reflecting a "Medium" degree of awareness.

However, there were some areas in which Awareness needed to be improved. With a mean score of 2.83 and a higher average deviation of 1.364, parents showed only a " low " degree of awareness regarding the genetic risk for thalassemia when one parent was a carrier. The average score was 4.72 out of a possible 5.00, with a relatively small standard deviation of 0.599, indicating a "High" degree of awareness regarding the hereditary risk when both parents are carriers. Additionally, parents had a "High" level of awareness, as shown by a mean score of 4.33 and a standard deviation of 0.776, regarding preventing Thalassemia by avoiding marriage with carriers or sufferers. With a mean score of 4.44 and a small standard deviation of 0.613, they also demonstrated a high awareness of the availability of screening tests for thalassemia gene detection before marriage, again demonstrating a "High" level of awareness.

In addition, there was moderate awareness that even if neither parent was a carrier, they could still have a child with thalassemia disease, with a mean score of 3.09 and a high standard deviation of 1.800, indicating a "Medium" level of understanding. Finally, with a mean score of 4.58 and a small standard deviation of 0.658, indicating a "High" level of awareness, parents demonstrated a high comprehension that thalassaemia can be treated via bone marrow transplant. Unfortunately, they had a "Low" level of awareness, with a mean score of 2.93 and a larger standard deviation of 1.356, about the requirement for frequent blood transfusions in Thalassemia carriers.

Table 3 Awareness of parents regarding the care of children with Thalassemia

Item	N	Mean	Std Deviation	Interpretation
Thalassemia can sometimes be treated with blood Transfusion	65	4.40	.932	High
Thalassemia can sometimes be treated with medications	65	3.78	1.256	Medium
Thalassemia can sometimes be treated with surgery	65	3.27	.875	Medium
If one parent has the Thalassemia carrier, the couple has a chance of having a child with Thalassemia disease	65	2.83	1.364	Low
If both parents have the Thalassemia carrier, there is a chance of having a child with Thalassemia disease	65	4.72	.599	High
Thalassemia can be prevented by not marrying a Thalassemia carrier or	65	4.33	.776	High

Thalassemia patients				
Screening tests for Thalassemia gene detection can be done before marriage	65	4.44	.613	High
If neither parent has the thalassemia carrier, they can have a child with thalassemia disease	65	3.09	1.800	Medium
Thalassemia can be treated by bone marrow transplant	65	4.58	.658	High
A person with thalassemia carrier requires frequent blood transfusion	65	2.93	1.356	Low

Discussion

The majority of respondents showed a good understanding. For example, a sizeable proportion strongly concurred that thalassemia is inherited. It showed that the participants understood thalassemia's genetic basis and possible effects.

The participants also demonstrated a high awareness of the requirement for routine blood transfusions in thalassemia patients. Most respondents strongly agreed that patients with thalassemia need frequent blood transfusions, consistent with the fact that transfusions are a frequent and important treatment option for thalassemia management.[1]

Findings indicate that the participants thoroughly understood the therapeutic approaches required for thalassemia patients. The importance of genetic counselling and premarital screening tests was well understood by participants in terms of preventive measures.[10] Many firmly believe that premarital screening and genetic counselling effectively prevent thalassemia.

Determines the significance of identifying carrier status and the role of informed decision-making in family planning to prevent thalassemia transmission to future generations.

However, there were also aspects where participants showed a small quantity of uncertainty or knowledge gaps. For instance, many individuals questioned had misunderstandings or divergent opinions about their ability to spot thalassemia in pregnant women.[11v]This finding suggests the need for further education and awareness regarding prenatal testing and its role in identifying thalassemia in unborn children. Furthermore, some participants disagreed about treating thalassemia with medication, surgery, or bone marrow transplant. Indicates a potential knowledge gap regarding available treatment options for thalassemia.[12] Therefore, it is important to publish accurate information about various therapeutic approaches and their applicability in various thalassemia cases.[13]

Most respondents recognised that thalassemia is an inherited disease, emphasising the importance of genetic factors in its development. This understanding is crucial for providing appropriate care for children with thalassemia, as it enables healthcare providers to identify and support at-risk families, provide genetic counselling, and offer early interventions.[14]

Furthermore, participants' awareness of the need for frequent blood transfusions in patients with thalassemia is vital for caring for affected children.

Regular blood transfusions are essential for managing thalassemia symptoms and preventing complications. The participants' recognition of this aspect indicates a level of knowledge that aligns with the established medical guidelines for thalassemia treatment.[15]

However, there were areas where participants demonstrated uncertainty or a lack of knowledge. For example, some participants expressed uncertainty regarding detecting thalassemia during pregnancy. This knowledge gap can have significant implications for the care of children with thalassemia, as early detection during pregnancy allows for timely interventions, including specialised prenatal care, genetic counselling, and informed decision-making regarding the child's future.[16]

Moreover, the participants' varying levels of knowledge regarding the treatment options for thalassemia can impact the care provided to affected children. While the majority agreed or strongly agreed that thalassemia can be treated with interventions, such as medications, surgery, or bone marrow transplantation, a notable number expressed uncertainty or disagreement. Highlights the importance of ensuring accurate information dissemination to healthcare providers and families to facilitate informed decisions regarding the most appropriate treatment modalities for individual cases.[17]

It is crucial to address these knowledge gaps to improve the care of children with thalassemia. Education and awareness programs can be pivotal in providing accurate information about thalassemia, its management, and available treatment options. These programs should target healthcare professionals, parents, and the general public, foster a comprehensive understanding of thalassemia, and promote best practices in care.[18]

Additionally, healthcare providers should prioritise genetic counselling services and facilitate access to premarital and prenatal screening programs. Increasing awareness and promoting these preventive measures can minimise the risk of thalassemia transmission, and parents can make informed decisions regarding family planning.

Data analysis also sheds light on parents' awareness regarding caring for children with thalassemia. The participants' responses provided insights into their awareness and understanding of the specific needs, challenges, and considerations involved in caring for children with thalassemia. One aspect of parental awareness is their understanding of the need for regular blood transfusions in children with thalassemia.[19]

Most participants agreed or strongly agreed with the statement that individuals with thalassemia require frequent blood transfusions. Indicates heightened awareness among parents about the critical role of blood transfusions in managing thalassemia and ensuring the well-being of the affected children.

Also, the fact that most people who took part agreed or strongly agreed that people with thalassemia can live normal lives with the right treatment shows that they are optimistic about the chance for children with thalassemia to have fulfilling and important lives. This awareness is crucial in empowering parents to provide their children with the necessary support, care, and opportunities, promoting their overall well-being and quality of life.[20]

However, it is important to note that there were areas where participants expressed uncertainty or disagreement, indicating potential gaps in their awareness and understanding. For instance, some participants were unsure or had mixed opinions regarding their ability to detect thalassemia during pregnancy. It suggests a need for further education and awareness regarding prenatal testing and the importance of early diagnosis and intervention in improving outcomes in children with thalassemia.[21]

People in the study had varying knowledge and agreement about treatment options such as drugs, surgery, or bone marrow transplantation. This could mean they did not know about or did not understand the different ways to treat thalassemia.[22] The importance of providing comprehensive information and support to parents, ensuring that they are well informed about the different treatment modalities and their potential benefits for their children.

Targeted educational initiatives are essential for enhancing parents' awareness of caring for children with thalassemia. Healthcare providers and organisations should provide comprehensive information to parents, address common misconceptions, and highlight the importance of early diagnosis, regular medical follow-up, and adherence to treatment plans.

Empower parents to actively participate in their child's care actively, promoting better health outcomes and overall well-being. Furthermore, support groups and counselling services can play a vital role in raising awareness and providing emotional support to the parents of children with thalassemia. These resources can facilitate sharing experiences, exchanging information, and developing coping strategies, empowering parents to navigate the challenges and complexities in caring for children with thalassemia.[23]

The study examining how parents care about kids with thalassemia found that most parents knew much about it. Parents knew that their kids would need regular blood transfusions and that, with the right care, they could live normal lives. However, there are areas where awareness and understanding can be improved, such as prenatal testing, treatment options, and holistic care for children with thalassemia.[24] By implementing targeted educational programmes, providing comprehensive information, and fostering support networks, we can enhance parental awareness and empower parents to provide the best care for their children with thalassemia.

Parental awareness is crucial in ensuring that children with thalassemia receive appropriate and timely medical intervention. With an understanding of the need for regular blood transfusions, parents can actively collaborate with healthcare providers to ensure their child receives the necessary transfusions at the recommended intervals. This awareness can contribute to better management of thalassemia-related symptoms and complications, ultimately improving children's overall health and quality of life.[25]

Moreover, awareness of treatment options such as medications, surgery, or bone marrow transplantation allows parents to have meaningful discussions with healthcare professionals. They can weigh different interventions' potential benefits and risks and make informed decisions regarding their children's most suitable treatment course. This level of awareness empowers parents to advocate for

their children's health, ensuring they receive the best available care and treatment options.[26]

Parental awareness extends beyond medical intervention. It encompasses a holistic understanding of the daily challenges and unique needs of children with thalassemia. Includes awareness of the importance of regular monitoring, adherence to medication schedules, dietary considerations, and children's emotional well-being. By recognising and addressing these aspects, parents can provide comprehensive care that supports their children's overall development and quality of life.[27]

Additionally, parental awareness influences the support network available to children with thalassemia. When well-informed, parents can seek resources, connect with support groups, and access educational materials that provide guidance and assistance.[28] This network offers valuable emotional support, practical advice, and opportunities to share experiences with other families who face similar challenges. Parental awareness creates a strong foundation for building a supportive community around the child, fostering a sense of belonging, and reducing the feelings of isolation that sometimes accompany thalassemia.[29]

Collaboration among healthcare providers, advocacy groups, and educational institutions is crucial to enhance parents' awareness regarding the care of children with thalassemia.[30] These stakeholders can collaborate to develop and implement educational programmes addressing parents' needs and concerns. Such initiatives should provide accurate information, practical guidance, and opportunities for support and engagement. [31] Furthermore, healthcare providers should prioritise open and effective communication with parents, ensuring that information is compassionate and culturally sensitive.[32] This approach can build trust and empower parents to participate actively in decision-making processes related to their child's care.

Conclusion

This study stresses the importance of education, community, and healthcare involvement to understand and help people with thalassemia. It suggests that broad strategies, such as education programmes and working with local groups, can be implemented.

Conflict of Interest

The authors declare no potential conflicts of interest or competing interests. The authors received no financial assistance or grants from public, private, or non-profit funding agencies.

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ORIGINAL ARTICLE

Maternal and Infant Mortality Rates's Contributing Factors Description and Its Prevention in Kencong Healthcare Center, Jember Regency : A Descriptive Study

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ABSTRACT

Background: Maternal Mortality Rates (MMR) and Infant Mortality Rates (IMR) are two of the indicators on the success of health programs in Indonesia. Jember has become the district with the highest rate of maternal and infant deaths throughout 2020-2021.

Methods: This research assessed the contributing factors of MMR and IMR in Puskesmas Kencong, Jember Regency. This study uses a qualitative descriptive research design. Data in this study were taken by conducting interviews to fill out questionnaires to mothers who had given birth at least once and the Coordinating Midwife and Head Midwife of PONED (Basic Emergency Neonatal Obstetrics Services) at the Puskesmas Kencong. Then the data from the questionnaires and interviews will be processed and then explained in the narrative.

Results:. Based on data from questionnaires filled out by 37 respondents, as well as questions posed to the midwife, Puskesmas Kencong has fulfilled the requirements needed as a PONED Health Center according to PONED Guidelines.

Conclusion: The PONED Health Center at Kencong Health Center has a low prevalence of MMR and IMR.

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Introduction

Maternal Mortality Rates (MMR) is one of the indicators on the success of health programs in Indonesia. MMR can be defined as all deaths during pregnancy, childbirth, and puerperium. Maternal mortality rates in Indonesia tends to decrease every year, but the number is still insignificant and hasn't met the target of Sustainable Development Goals (SDGs). MMR, which was initially progressively decreasing throughout the year, had increased again in 2020 and reached its peak in 2021. MMR in 2021 was mainly caused by COVID-29 infection followed by post-partum bleeding and hypertension in pregnancy [1]. Infant Mortality Rate (IMR) is all infant deaths in the age of 0-59 months. This mortality rate along with MMR is also one of SDGs targets of 2021. The number of infant deaths in 2021 was 27.566, which had decreased from 2020, which was 28.158 deaths. Even though we can see the decrease in numbers, this decrease is still not significant and has not met the SDGs target of 25 deaths per 1.000 births [1].

The Maternal Mortality Rate in Jember Regency in 2021 had increased to 115 cases from 61 cases in 2020. This figure had brought Jember Regency to become the district with the highest Maternal Mortality Rate in East Java Province in 2021. This was due to the lack of complete pregnancy checks so that high risk pregnancies were left undetected. There were 9 cases of maternal mortality in Jember Regency in 2021 caused by bleeding, 15 cases of hypertension during pregnancy, 1 case of infection, and 90 other cases. Jember Regency also became the highest Infant Mortality Rate (IMR) in East Java Province with 300 cases in 2021. The most cases of infant mortality in Jember Regency were caused by low birth weight as many as 88 cases. [23]

Puskesmas Kencong is one of the health centers in the Jember Regency with a working area covering Kencong and Wonorejo Villages. Kencong District has an area of 5865.3 ha / 65.92 km2 with a total of 71,430 inhabitants. Kencong sub-district has 46 posyandu, two supporting health centers (*puskesmas pembantu*), and one village polyclinic (*poliklinik desa*) spread throughout the Kencong sub-district. The complications of pregnancy and childbirth that are most often encountered and referred to at the *Puskesmas Kencong* are premature rupture of membranes, severe preeclampsia, prolonged 1st stage of birth, premature parturition, and hepatitis B positive patients. Meanwhile, most neonatal referral cases are caused by giant babies, low birth weight babies, and severe asphyxia. In 2021, there were three cases of maternal death and one case of infant death at *Puskesmas Kencong* [23].

MMR can be caused by the 3T (*3 Terlambat*) or 3 Delays factors, namely Delay in Making Decisions, Delay in Referring, and Delay in Obtaining Services [4]. Delay in decision making is possible due to being late in realizing a complication or late in early detection of a complication, fear of the hospital, or lack of funds. Delays in reaching referral sites may be due to difficulties in transportation facilities, while delays in obtaining services may occur due to a lack of medical equipment facilities, limited operating rooms, and limited blood supplies. The delay in service in this case refers to services at referral hospitals, and this factor has the greatest impact on maternal mortality, because not all facilities provide emergency obstetric services, so that it becomes a separate problem for the health care system [5]. In addition, internal factors or 4T include too young in maternal age (< 20 years), too old in maternal age (> 35 years), too close in pregnancies

interval (< 2 years), and too many children (more than four) can affect MMR [67]. IMR is closely related to factors that affect MMR because the baby is directly related to the mother in terms of nutrition, immunity, and so on [8].

The high MMR and IMR are the main focus of this research. The risk factors that influence the occurrence of AKI and IMR, especially in Jember, which is the highest contributor to MMR and IMR in East Java, need to be studied and found out so that prevention and mitigation efforts can be made.

Methods

This study uses a qualitative descriptive research design and has been approved by the Ethical Committee of Medical Faculty of Jember University. Data to determine the late decision factor in this study were taken by conducting interviews to fill out questionnaires on November 2022 to mothers who had given birth at least once from 2020-2022. Data to find out the late referral factor was carried out by conducting interviews with the Coordinating Midwife and Head Midwife of *PONED* (Basic Emergency Neonatal Obstetrics Services) at the *Puskesmas Kencong*. Then the data from the questionnaires and interviews will be assessed according to PONED Guidelines and then explained in the narrative.

Results

The questionnaire given to the respondents was divided into several sections according to the question criteria. Respondent characteristics including place of residence, age, mother's educational background, ethnicity, and religion are shown in Table 1.

Table 1. Respondents Characteristics

	n	**%**
Address		
Cakru	1	2,7
Gumuk Mas	1	2,7
Gumuk Banji	12	32,4
Kencong	4	12,8
Krajan	11	29,7
Pondok Waluh	1	2,7
Ponjen	3	8,1
Wonorejo	4	10,8
Age		
<20 year old	1	2,7
20 - 35 year old	33	89,2
>35 year old	3	8,1
Mother's Educational Background		
Has not completed primary school	1	2,7
Primary School Graduate	4	10,8
Junior High School Graduate	10	27
Senior High School Graduate	15	40,5
College Graduate	7	18,9
Ethnic		
Javanesse	27	73
Javanesse - Maduranesse	5	13,5
Maduranesse	2	5,4
Others	3	8,1
Belief		
Islam	37	100

The characteristics of the respondents presented in Table 1 shows that the majority of respondents we met at the Kencong Health Center lived in Gumuk Banji (32.4%), followed by Krajan (29.7%) and Kencong (12.8%). Most of the respondents were mothers aged 20-35 years (89.2%), then more than 35 years (8.1%), and less than 20 years (2.7%). The majority of respondents were senior high school graduates (40.5%) followed by junior high school graduates (27%). The respondents we met were Javanese (73%), Maduranese (8.1%), and Javanese-Maduranese (5.4%), and all of them were Muslim.

We examined the characteristics of the respondents to determine the socio-cultural background of the

respondents and their influence on habits that could increase MMR and IMR.

Mother's basic information can be seen in Table 2, where we included it in the questionnaire to analyze the effect of basic information such as occupation, gravida, parity, etc. on the MMR and IMR figures.

Table 2. Mother's Basic Information

	n	%
Occupation		
Housewife	31	83,8
Farmer	1	2,7
Civil Worker	1	2,7
Nurse	2	5,4
Tailor	1	2,7
Midwife	1	2,7
Gravida		
First	10	27
Second	19	51,4
Third	5	13,5
Fourth	2	5,4
Fifth	1	2,7
Parity		
0	3	8,1
1	20	54,1
2	12	32,4
3	2	5,4
Mother's age at birth of first child		
Abortion	3	8,1
<20 year old	4	10.8
20 -35 year old	30	86,5
>35 year old	0	0
Mother's age at birth of last child		
Abortion	3	8,1
<20 year old	3	8,1
20 -35 year old	30	86,5
>35 year old	1	2,7
Pregnancies Interval		
First pregnancy	12	32,4
<2 years	1	2,7
2 - 10 years	18	48,6
>10 years	5	13,5
Maternal medical history before pregnancy		
None	34	91,9
With medical history		
Typhoid fever	1	2,7
Hypertension	1	2,7
Vulvar Tumor	1	2,7
History of complications during last pregnancy		
None	32	86,5
With complications		
Abortion	4	10,8
Late due date	1	2,7
History of complications during last delivery		
None	35	94,6
With complications		
Prolonged first phase	1	2,7
Post Date	1	2,7
History of complications during last delivery		
None	35	94,6
Referral if there are complications during the last delivery		
Not referred	1	14,3
Referred	7	85,7
Referral destination		
Puskesmas	1	12,5
Clinic	2	25
Regional Public Hospital	3	37,5
Private Hospital	2	25

Based on the questionnaire data in Table 2, the majority of respondents (83.8%) were housewives who did not work. Most of the respondents had been pregnant twice (51.4%), and following in second place were respondents with their first pregnancy (27%). Most of the respondents had given birth once (54.1%). The age of the mother at the time of giving birth to her last child was mostly in the age range of 20-35 years (86.5%) with the interval between pregnancies being the majority in the range of 2-10 years (48.6%). The majority of respondents did not experience any complications during pregnancy (91.9%), while one respondent had experienced hypertension during pregnancy, one respondent had experienced a vulvar tumor, and one respondent had had typhoid fever. 10.8% of respondents had experienced an abortion in a previous pregnancy. The majority of respondents did not experience complications during childbirth, but respondents were found with prolonged first phase (2.7%) and late due date (2.7%). Seven of the respondents who experienced complications were

referred (85.7%) with the most referral destinations being regional public hospitals (37.5%), clinics (25%), and private hospitals (25%).

Infant's basic information is presented in Table 3 as an overview of the baby's birth history as things that can affect IMR

Table 3. Infant's Basic Information

	n	%
Current age of last child		
<1 year old	7	18,9
1-3 year old	11	29,7
3-5 year old	6	16,2
>5 year old	10	27
Gender of last child		
Female	23	67,6
Male	11	32,4
Mother's gestational age at last delivery (weeks)		
Preterm (<37 weeks)	17	40.5
Aterm	12	32.4
Postterm	5	13.5

The majority of respondents' babies are currently in the range of 1-3 years (29.7%). The sex distribution of the respondent's babies was 67.6% female and 32.4% male. The majority of respondents gave birth at term (40.5%), but the percentage of preterm births was still large, namely 32.4%.

Antenatal visits are presented in Table 4 to describe the pregnancy examination status of the respondents.

Table 4. Antenatal Visits

	n	%
ANC visit		
Ever	37	100
Never	0	0
Gestational Age at first visit (K1)		
1 month	21	56,8
2 months	8	21,6
3 months	5	13,5
4 months	2	5,4
5 months	1	2,7
Comprehensiveness of ANC		
Complete (standard 1:1:2)	32	86,5
Uncomplete	5	13,5
ANC Treatments and Care		
Maternal Weight Check		
Yes	37	100
No	0	0
Maternal Blood Pressure Check		
Yes	37	100
No	0	0
Uterine fundal height measurement		
Yes	35	94,6
No	2	5,4
Administration of TT Immunization		
Yes	26	70,3
No	11	29,7
Administration of Blood Supplement Tablets		
Yes	35	94,6
No	2	5,4
Urine test for STD detection		
Yes	24	64,9
No	13	35,1
Counseling		
Yes	35	94,6
No	2	5,4
Antenatal Care Examiner	**n**	**%**
Midwife	32	86,5
Obstetricians	4	10,8
Quack	1	2,7
Antenatal Care Place	**n**	**%**
Midwife's private practice	17	45,9
Posyandu	9	24,3
Puskesmas/ Pustu	6	16,2
Clinic	3	8,1
Polindes	1	2,7
Other people's resident	1	2,7
Source of recommendations for antenatal care/ANC		
Own desire	32	86,5
Health Cadre	2	5,4
Neighbour	2	5,4
Husband	1	2,7
Mother's assistance during antenatal care/ANC		
Alone	12	35,1

Husband	22	59,5
Parents	2	5,4
Parent in laws	1	2,7
Family members	1	2,7
Health workers who conducts the antenatal care / ANC		
Midwife	33	89,2
Obstetricians	4	10,8

All of the respondents had done antenatal care with most of the first visits being made at one month's gestation (56.8%). The completeness status of respondents' ANC visits according to the standard reached (86.5%). Most of the standard checks on ANC have been carried out except for urine tests and immunizations which are carried out according to the indications and immunization status of the respondents. ANC is mostly done by midwives (86.5%) and most is done in midwife's private practice (45.9%). The majority of respondents came for prenatal checks of their own free will (86.5%) and came accompanied by their husbands (59.5%). However, not a few also came to health facilities (35.1%) to do ANC. Basic childbirth information is presented in Table 5 as an overview of how childbirth in the area was done.

Table 5. Basic Childbirth Information

	n	**%**
Helper for the last birth		
Midwife	26	70,3
Obstetricians	10	27
Reasons for choosing the birth helper		
Think it's safer	13	35,1
Near mother's residency	7	18,9
The only health workers available are midwives	2	5,4
Close relationship with the healthworker	5	13,5
There were complications so they were referred to birth attendants	7	18,9
Others	3	8,1
Place of last delivery		
Puskesmas	9	24,3
Hospital	8	21,6
Midwife's private practice	7	18,9
Private clinic	5	13,5
Other people's residence	5	13,5
Maternity Hospital	2	5,4
The source of recommendations for choosing the place of delivery during the last delivery		
Own desire	27	73
Husband	5	13,5
Parents	2	5,4
Health cadre	3	8,1
Healthworker's referral	2	5,4
Doctor	1	2,7
Mother's companion during the last birth		
Alone	1	2,7
Husband	31	83,8
Parents	12	32,4
Parent in laws	6	16,2
Family members	2	5,4

The majority of respondents chose to have their birth assisted by a midwife (70.3%) unless they experienced complications that had to be referred, on the grounds that they felt it was safer to have it done by a midwife (35.1%). Respondents mostly chose the place of delivery at the Puskesmas (24.3%), hospital (21.6%), and midwife's private practice (18.9%). The decision on where to give birth was mostly due to the respondents' personal wishes (73%), and 83.8% of respondents gave birth accompanied by their husbands. Basic health information is presented in Table 6 to describe the health support facilities for respondents outside the availability of health workers.

Table 6. Basic Health Information

	n	**%**
Health Insurance Ownership		
None	18	48,6
Own a health insurance		
BPJS	13	35,1
KIS	4	10,8

Jamkesmas	1	2,7
Mediciline	1	2,7
Distance from Home to Health Facility		
<1 km	20	54
1-5 km	16	43,2
>5km	1	2,7
Total family income in one month		
< Rp. 1.000.000	5	13,5
Rp 1.000.000 - Rp 1.499.000	9	24,3
Rp 1.500.000 - Rp 1.999.000	9	24,3
≥ Rp 2.000.000	14	37,8

Most of the respondents did not own any health insurance (48,6%). BPJS was owned by most respondents (35,1%) who claimed to have health insurance. The average distance of health facilities from the respondents residency was less than 1 kilometer (54%), or in the range from 1 to 5 kilometres (43,2%).

We also conducted interviews with the Coordinating Midwife and Head Midwife of *PONED* to assess the fulfillment of the criteria for the *Puskesmas* Kencong as *PONED* (Basic Emergency Neonatal Obstetrics Services). The data from the questionnaire states that the *Puskesmas* Kencong has 4 ready-to-use ambulances with the availability of health workers consisting of 19 midwives, 2 general practitioners, 25 nurses, and a dentist who works on a 24-hour shift system. Drugs and equipment used in obstetrics emergencies and fetal distress are available and can function properly. The most obstetric referral cases from 2020 were premature rupture of membranes, and the most referred neonatal cases were giant babies. The main referral goals for the *Puskesmas* Kencong include dr. Soebandi Public Regional Hospital, Balung Public Regional Hospital, and dr. Haryoto Public Regional Hospital Lumajang.

Discussion

The Maternal Mortality Rate (MMR) is an indicator of the success of health programs in Indonesia. MMR can be defined as all deaths during pregnancy, childbirth and the puerperium. The maternal mortality rate tends to decrease every year but the decrease that occurs is insignificant and still does not meet the target of the Sustainable Development Goals (SDGs). AKI in Indonesia will increase again in 2020 and reach its peak in 2021. AKI in 2021 is mainly caused by COVID-19 infection followed by postpartum hemorrhage and hypertension in pregnancy [1].

The Maternal Mortality Rate in Jember Regency in 2021 has increased to 115 cases from 61 cases in 2020. This figure has brought Jember Regency to become the district with the highest Maternal Mortality Rate in East Java Province in 2021. This is due to restrictions on visits for pregnancy checks so that the screening of high-risk pregnant women becomes less than optimal. There are 9 cases of maternal death in Jember Regency in 2021 caused by bleeding, 15 cases of preeclampsia, 1 case of infection and 90 other cases. There will be no cases of maternal death in *Puskesmas* Kencong in 2021 [23].

The Infant Mortality Rate (IMR) is all infant deaths aged 0-59 months. This figure is also one of the SDGs targets. The number of infant deaths in 2021 was 27,566 which decreased from 2020, which was 28,158. This reduction, which is still not significant, still does not meet the SDGs target of 25 deaths per 1,000 births [1]. Jember Regency in 2021 has the highest Infant Mortality Rate (IMR) in East Java Province with 300 cases. The most cases of infant mortality in Jember Regency were caused by LBW as many as 88

cases. At *Puskesmas* Kencong there were 3 cases of infant death in 2021 [23].

This high maternal and infant mortality rate can be caused by the 3T factor, namely Delay in Making Decisions, Delay in Referring, and Delay in Obtaining Services [4]. In addition, internal factors or 4Ts, including Too Old, Too Young, Too Close Distance of Pregnancy, and Experiencing Too Many Pregnancies also affect MMR [6]. IMR is also closely related to factors that affect MMR because the baby is directly related to the mother in terms of nutrition, immunity, and so on [8]. Other factors that can influence are the mother's age, multigravida, parity status, ANC visits that are incomplete and not according to the 10T standard, family support, and decisions about where to give birth which are not determined by the pregnant women themselves [9].

Maternal age has a significant influence on maternal mortality because age is a factor that needs to be considered to maintain the stability of the mother's condition during pregnancy [1011]. At the age of <20 years and> 35 years will increase the risk of maternal death. This is because at the age of <20 years the mother's reproductive organs are still not mature enough and when the mother is >35 years old a degenerative process occurs [1213]. This study shows that 33 out of 37 respondents are in the age of 20-35 years old. At this age, it is said that the age is not at risk, so it does not increase cases of maternal and infant mortality.

Gravida is the total number of maternal pregnancies, including normal and abnormal intrauterine pregnancies, abortions, ectopic pregnancies and hydatidiform moles. Gravida has no significant effect on maternal mortality, but increases the risk factors for pregnancy complications. This is consistent with the theory that explains the relationship between gravida and the incidence of complications of pregnancy and childbirth. Primigravida and gravida ≥ 4 are one of the factors causing problems in pregnancy and childbirth. Mothers with gestational primigravida are more susceptible to blood pressure problems, namely preeclampsia, bleeding, miscarriage, preterm (premature) labor, congenital disorders and abnormalities, impaired fetal growth in the womb [14]. In this study, it was found that 20 out of 37 respondents were primigravidas, 12 out of 37 respondents had been pregnant twice.

Parity is the number of babies born alive by the mother [15]. Parity is said to have no relationship to maternal mortality but the higher the parity can have a negative impact on the mother. Women with high parity can increase welfare and quality of life problems [16]. High parity will increase the mother's risk of developing cardiovascular disease and type 2 diabetes mellitus [17]. The results of this study found that 20 out of 37 respondents had given birth to a live birth once and 12 out of 37 respondents had given birth to a live birth twice.
Pregnant women are required to make antenatal care (ANC) visits at least four times during pregnancy. This visit is carried out at least once in the first trimester (K1), at least once in the second trimester (K2), and at least twice in the third trimester (K3 and K4). Examinations that must be carried out during ANC visits are known as 10T [18]. Antenatal Care (ANC) must be carried out from the beginning of pregnancy so as to be able to detect early risk factors for pregnancy and childbirth so that proper prevention and management can be carried out [19]. Pregnant women are required to make ANC visits at least four times during their pregnancy because it can reduce maternal mortality through screening and early treatment [20].

In this study it was found that all respondents carried out ANC examinations with a

distribution of 34 respondents doing K1 in the first trimester, and 3 respondents doing K1 in the second trimester. There were 32 out of 37 respondents who had made standard ANC visits, namely at least once in the first trimester (K1), at least once in the second trimester (K2), and at least twice in the third trimester (K3 and K4). Meanwhile, 5 out of 37 respondents did not make ANC visits at the appointed time. Examinations carried out by all pregnant women at ANC are weighing and measuring blood pressure. There were 11 pregnant women who did not get TT immunization because these pregnant women already fulfilled the TT vaccination status. There were 2 mothers who did not get iron tablets, 13 respondents did not do urine tests, and 2 respondents did not do counseling with health workers.

One effective solution in reducing the Maternal Mortality Rate (MMR) and Infant Mortality Rate (IMR) is by increasing delivery assistance provided by trained medical personnel provided by health care facilities. In addition, it requires the participation and awareness of mothers on the importance of prenatal check-ups at health care facilities by health workers. The Ministry of Health of the Republic of Indonesia requires pregnant women to carry out pregnancy checks by professional health workers and at health service facilities. This is intended so that pregnant women receive quality and comprehensive services [18]. The results of this study found that 32 out of 37 chose to have a pregnancy check-up at the Independent Practicing Midwife, 26 out of 37 respondents gave birth with the help of a midwife, 11 out of 37 respondents gave birth at a Gynecologist. Respondents have also conducted ANC pregnancy checks and deliveries at health care facilities. Respondents said that carrying out examinations and deliveries at health facilities was safer so as to reduce maternal and infant mortality. In addition, the respondents made ANC visits and deliveries at health facilities as a result of good education by midwives in classes for pregnant women.

Forms of family support can be in the form of positive appreciation of individuals, encouragement, approval of individual opinions, as well as support and attention [21]. Family support that plays a very important role is support from the husband who is the closest person to pregnant women [22]. Family support plays an important role in influencing the motivation and psychology of mothers in carrying out health behaviors. From this research it can be seen that the respondents get support from the family. This can be seen from the assistance of respondents when carrying out ANC examinations and childbirth. During the ANC examination, 22 out of 37 respondents were accompanied by their husbands. During the delivery process, 36 out of 37 respondents were accompanied by their husbands and/or family. In addition, this family support can be seen from the majority of the husbands and/or families of the respondents who gave authority to the respondents to determine the place for ANC examinations and their own deliveries.

The number of maternal deaths in Indonesia in 2021 has increased compared to 2020. This shows the low quality of maternal health services. WHO states that one of the important aspects of maternal and child health services is the existence of a close relationship with the health services that are above it. This close relationship is reflected through an effective referral system [9]. An effective health service referral system is one of the efforts to improve the quality of health services

which can have an impact on reducing the Maternal Mortality Rate (MMR) and Infant Mortality Rate (IMR) [23]. The results of this study indicate that the referral system at the *Puskesmas* Kencong has been running well so there is no delay in referring. This is proven by the available infrastructure according to the PONED Capable Health Center guidelines, midwives provide education before being referred, midwives contact destination hospitals to prepare for patient acceptance, transport using ambulances, midwives bring tools and medicines needed during the trip, and fill out referral letters online completely.

Conclusion

Based on data from questionnaires filled out by 37 respondents, as well as questions posed to the midwife, *Puskesmas Kencong* has fulfilled the requirements needed as a PONED Health Center according to PONED Guidelines. However, the promotion strategies to enrich mothers' knowledge about pregnancies and infants care should be enhanced.

Conflict of Interest

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ORIGINAL ARTICLE

Association of Endothelial Nitric Oxyde Synthase (eNOS) Levels and Modifiable Risk Factors for Acute Myocardial Infarction with ST-Segment Elevation (AMI-STE)

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ABSTRACT

Background: The pathological process underlying myocardial infarction is atherosclerotic thrombosis that causes endothelial dysfunction. In the AMI-STE process, eNOS has functions as the body's defense mechanism to prevent more severe damage to the endothelium. Decreased eNOS levels were found in modifiable AMI risk factors. This study aimed to determine the association of eNOS levels based on modifiable risk factors for AMI-STE patients.
Methods: This study was an analytical observational study with a historical cohort design. The samples were patients with AMI-STE diagnosis who had undergone PPCI at M. Djamil Hospital Padang from March to June 2022. The eNOS levels were taken from the blood samples. Modifiable AMI risk factors were taken from patient's medical record. The T test was carried out to determine statistical analysis.
Results: The average age of the 38 subjects was 62.53 ± 8.2 years, and 92.1% among them were male, and 52.6% subjects were diagnosed with anterior AMI-STE. The average eNOS level in subjects was 47.47 ± 23.88 (normal level is 48.16 pg/mL). More than half (73.5%) of the subjects in low eNOS group had diabetes mellitus as risk factor (P<0.0001) and most subjects (78.9%) in group with low eNOS had hypertension (p=0.022). Other risk factors, namely dyslipidemia and smoking, were also more common in group with low eNOS. However, statistical tests showed that there was no statistically association between eNOS levels with dyslipidemia and smoking.
Conclusion: There was statistically significant association between eNOS levels with diabetes mellitus and hypertension as modifiable risk factors for AMI-STE.

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Introduction

Coronary heart disease (CHD) is one of main problems among all heart diseases. CHD that occurs acutely is known as Acute Myocardial Infarction (AMI) and is one of the main causes of death. Based on the World Health Organization (WHO) report in 2017, around 17.8 million people died due to cardiovascular disease. In the United States, every 40 seconds, a citizen suffers from AMI, of which there were 785,000 new cases and 470,000 cases of recurrent AMI in 2017.[1–2] In Indonesia, based on Basic Health Research (RISKESDAS) in 2018, the prevalence of heart disease was 1.5% of the total Indonesian population, in West Sumatra alone the prevalence of heart disease is higher than the national prevalence figure, namely 1.6%, in 2018 based on Riskesdas.[3] Exact data on the incidence, morbidity and mortality rates of myocardial infarction in Indonesia are still very limited. Acute Myocardial Infarction with ST-Segment Elevation (AMI-STE), a form of AMI, is a disease that occurs when there is total blockage of the coronary arteries.[4] Based on the Jakarta Acute Coronary Syndrome Registry from October 2014 – July 2015, there were 1024 patients with AMI-STE of which 81% underwent primary percutaneous coronary intervention (PPCI).[5] Based on the COMPLETE Trial study conducted on AMI-STE patients who underwent PCI in 2019, it was found that the death rate from cardiovascular disease, recurrent AMI, ischemia requiring revascularization, heart failure and unstable angina pectoris accounted for 34.5% of the total 4041 patients.[6]

The pathological process underlying myocardial infarction is atherosclerotic thrombosis, which is an interaction between susceptible plaque and thrombosis. In myocardial infarction, the inflammatory response plays an important role in the initiation of atherosclerotic plaque and the development of the plaque into a vulnerable plaque, characterized by thin fibrous vesicles, an extensive lipid core, and a large accumulation of inflammatory cells, especially macrophages that are highly susceptible to rupture and form thrombus.[7]

The cause of all this is a problem with the endothelium, known as endothelial dysfunction. Endothelial dysfunction is a decrease in the ability of the endothelium to carry out the functions of blood vessel homeostasis. This decrease in function causes disturbances in blood vessel tone, as well as a condition known as endothelial activation, namely pro-inflammatory, proliferative and pro-coagulation.[8] Decreased endothelial function is reflected in reduced levels of Nitric Oxyde (NO), where NO itself is produced by NO synthase. Currently, 3 isoforms of NO synthase are known and one of them is the largest contributor to NO formation, namely endothelial Nitric Oxide Synthase (eNOS). In the AMI-STE process, eNOS function decreases, where eNOS has functions as the body's defense mechanism to prevent more severe damage to the endothelium.[9] In 2016, Abdel Hamid et al conducted research on AMI-STE patients showing that there were circulating endothelial cells and endothelial cell dysfunction which could predict major cardiovascular events such as death, recurrent myocardial infarction and heart failure in patients with AMI-STE.[10] So that the occurrence Endothelial dysfunction correlates with reduced eNOS levels.

Decreased eNOS levels were also found in various CHD risk factors. eNOS expression was found to be decreased in metabolic syndrome[11]. Normal insulin signaling will increase eENOS enzymatic activity. On the other hand, conditions

of insulin resistance will disrupt the P13K-Akt pathway which will cause reduced eNOS activity, reduced NO formation and consequently vasoconstriction[12]. Likewise with other CHD risk factors, such as hypertension and dyslipidemia, eNOS levels have also been found to be reduced in various studies. In dyslipidemia, oxidative and non-oxidative LDL will interfere with immunity and regeneration of cells experiencing inflammation. In addition, oxidative LDL inactivates the eNOS/NO pathway[13]. Mean endothelial eNOS levels were significantly lower in the group of smokers compared to non-smokers.[14] Genetics may also influence eNOS expression because clinical studies in humans have shown that polymorphisms in the eNOS gene predispose to hypertension, insulin resistance, and type 2 diabetes, the three main clinical features of metabolic syndrome. which is a risk factor for CHD events. The literature shows that among people with CHD risk factors, the likelihood of developing severe CHD such as AMI-STE increases if they have low eNOS levels.[13]

Based on the background that has been explained, the aim of this study was to determine the association of Endothelial Nitric Oxide Synthase (eNOS) Levels based on Modifiable Risk Factors for Coronary Heart Disease in Acute Myocardial Infarction Patients with ST Segment Elevation.

Methods

This research was an analytical observational study with a historical cohort research design conducted during patient care. The study population was AMI-STE patients who had undergone PPCI at the Integrated Heart Care Installation at Dr. M. Djamil Hospital Padang in March 2022 to June 2022. The minimum sample size in this study obtained based on the sample formula was 38 people.

The inclusion criteria for this study were patients with a diagnosis of AMI-STE and who had undergone PPCI with TIMI Flow 3 MBG 3 and received standard medical therapy for the treatment of acute myocardial infarction at the Integrated Heart Services Installation of Dr. M. Djamil Hospital Padang. The exclusion criteria in this study were patients who were diagnosed with AMI-STE but had sepsis, had previous heart surgery, had a history of previous AMI, had burns, had a history of multiple trauma and had stage III as well as stage IV of chronic kidney disease.

The sampling technique for this research was simple random sampling, taking samples from the population randomly without paying attention to the strata in the population and each member of the population has the same opportunity to be sampled and meets the research inclusion criteria and selection to be included in the research until the required subjects are met[15]. The independent variable in this study was eNOS levels, while the dependent variable was modifiable CHD risk factors. The subjects who met the inclusion criteria were then divided into two groups, namely group I with low eNOS level and group 2 with normal eNOS level. Between both groups, the eNOS levels were then compared according to risk factor variables, such as diabetes mellitus, hypertension, dyslipidemia and smoking

The research procedures began from subjects who met the research criteria had their eNOS levels checked. The steps taken in this research were blood samples taken during treatment at Dr. M. Djamil Hospital Padang within

24 hours from the onset of acute myocardial infarction symptoms. A 3 ml blood sample was taken from a peripheral vein, placed in an EDTA tube. Each specimen that had been centrifuged was then placed into a 1.5 ml micro cup which had been given a name, research number and medical record number then stored at -80oC in the Biomedical Laboratory of the Faculty of Medicine, Andalas University. Examination of eNOS levels was carried out by the Biomedical Laboratory of the Faculty of Medicine, Andalas University. CHD risk factors that can be changed include hypertension, hyperlipidemia, diabetes mellitus, obesity, smoking informations were obtained from patients medical records.

Statistical analysis was carried out by univariate and bivariate. Univariate analysis was carried out by analyzing each research variable. For categorical research variables which included major cardiovascular events, gender, hypertension, dyslipidemia, smoking and family history of disease, analysis was carried out by looking at the frequency distribution which was presented in the form of frequencies and percentages. Meanwhile, continuous data, namely age and eNOS levels, are expressed in mean values and standard deviations. At the beginning of the bivariate analysis, a data normality test was carried out using the Shapiro Wilk test. Because the data were normally distributed then the T test was used to determine the association of eNOS levels with CHD risk factors in AMI-STE patients treated at Dr M Djamil Hospital. Data analysis was carried out with a confidence level of 95% and $\alpha = 0.05$. If the p value <0.05 means there is an association between the research variables studied. All analyzes were carried out with the SPSS for Windows computer program. This research has passed ethical review from the Research Ethics Committee, Medical faculty of Andalas University, with letter numbers 602/UN.16.2/KEP-FK/2023.

Results

Baseline Characteristics of AMI–STE Patients Undergoing Primary Percutaneous Coronary Intervention

Table 1 explains the basic characteristics of research subjects. Based on table 1, the average age of the research subjects was 62.53 ± 8.2 years. Almost all patients (92.1%) were male and only a small number (7.9%) of patients were female. Cardiovascular risk factors in research subjects were smoking, diabetes mellitus, hypertension and dyslipidemia, respectively. Only 1 patient with family history of CHD as one of unmodifiable risk factors was found in this study. More than half (52.6%) of the study subjects were diagnosed with anterior AMI-STE. Most of the research subjects (65%) were patients with Killip class I.

Table 1. Characteristics of Research Subjects

Variables	**n = 38, f (%)**	**mean ± SD**
Age (years), mean ± SD		62.53 ± 8.2
Gender, n (%)		
Male	35 (92.1)	
Female	3 (7.9)	
Blood Pressure (mmHg)		
Systolic		124 ± 22.032
Diastolic		70 (50 – 97)
MAP		89 ± 13

AMI-STE Diagnosis, n(%)		
Anterior	20 (52.6)	
Inferior	18 (47.40)	
Risk Factors, n (%)		
Diabetes Melitus	17 (44.7)	
Smoking	30 (78.9)	
Dyslipidemia	10 (26.3)	
Hypertension	23 (60.5)	
Family History of CHD	1 (2.6)	
Onset		6.82 ± 2.903
Killip Class (n=20)		
I	13 (65)	
II	7 (35)	

Average eNOS levels of AMI–STE patients undergoing primary percutaneous coronary intervention

For 38 research subjects, eNOS levels were measured at admission. Based on table 2, the average eNOS level in research subjects was 47.47 ± 23.88. Median eNOS level was 37,050. The eNOS levels of the subjects in this study ranged from 17,000 – 121,956. Based on the literature, eNOS levels in healthy subjects are 48.16 pg/mL[13]. This means that the eNOS levels of AMI-STE patients in this study were lower than the normal eNOS level.

Table 2. eNOS levels in AMI-STE patients

Measurement Results	**Value**
Mean ± SD (pg/mL)	47,47 ± 23,88
Median (Minimum – Maksimum)	37,050 (17,000 – 121,956)

Association of eNOS Levels with Modifiable Risk Factors in AMI-STE Patients

As seen on table 3, the research subjects were divided into two groups, 19 people on group I with low eNOS levels and 19 subjects were group 2 with normal eNOS levels. Group I had average eNOS level of 34,69 ± 7,007 pg/mL, while the group II with Normal eNOS level of 54.74 ± 26,13 pg/mL.

Table 3. Groups of subjects based on eNOS levels

Groups	**eNOS Level (Mean ± SD in pg/mL)**
Group I (Low eNOS)	34,69 ± 7,007
Group II (Normal eNOS)	54.74 ± 26,13

Based on table 4, it can be seen that overall risk factors were found to have low eNOS levels compared to normal ones. More than half (73.5%) of the subjects in group I (low eNOS) had diabetes mellitus as the risk factor and only a small portion (15.8%) of subjects in group II (normal eNOS) had risk factors in the form of diabetes mellitus. eNOS levels had a statistically significant association with diabetes mellitus as a risk factor for AMI-STE ($p<0.001$). Subjects with risk factors for hypertension also had similar findings. More than half of the subjects (78.9%) in group I had hypertension as the risk factor. However, in group

II almost half (42.1%) had hypertension. eNOS levels had a statistically significant association with hypertension as a risk factor for AMI-STE (p=0.022). Other risk factors, namely dyslipidemia and smoking, were also more common in group I. However, statistical tests showed that there was no statistically significant association between eNOS levels and dyslipidemia (p=0.135) and smoking (p=0.346) as risk factors for AMI-STE.

Table 4. Association of eNOS Levels with Modifiable CHD Risk Factors in Research Subjects

Variables	Group I (Low eNOS levels), N (%)	Group II (Normal eNOS) N (%)	P value
Diabetes Melitus	14 (73.5)	3 (15.8)	<0.001
Hypertension	15 (78.9)	8 (42.1)	0.022
Dyslipidemia	7 (36.8)	3 (15.8)	0.135
Smoking	16 (84.2)	14 (73.7)	0.346

Discussion

This research was carried out at the Integrated Heart Center Installation of Dr. M. Djamil Hospital Padang from March 2023 to December 2023. A total of 38 patients with AMI-STE had met the inclusion criteria. The subjects were then divided into groups with low eNOS levels and normal eNOS levels. This study showed that the average age of the research subjects was 62.53 ± 8.2 years. This is in line with Bloos et al's research on 576 AMI-STE patients, it was found that the majority (83%) of AMI-STE patients were over 50 years old and only a small portion (17%) of patients were under 50 years old**.**[16] However, based on various previous studies, there are also slight differences in terms of age. The average age at first onset of ACS in the United States is 65 years for men and 72 years for women. About two-thirds of myocardial infarctions occur in patients over 65 years of age and one-third in patients over 75 years of age. In addition, 60% of hospitalizations due to ACS occur in patients over 65 years of age[16,17]. Age in AMI-STE patients is not only a risk factor, but also has prognostic significance. Age is known to be an independent risk factor for predicting the clinical outcomes of AMI-STE patients after the procedure. In addition, older age is associated with more comorbidities and risk factors.[17]

Characteristics of research subjects based on gender in this study showed that almost all (92.1%) of the subjects were male. This result was in accordance with various other studies. Research conducted by Duraes et al and N'Guetta et al, found that more than 50% of STEMI patients were mostly men.[18] There are various theories that can explain this finding. The American Heart Association (AHA) states that men have a higher risk of heart attack than women. The low incidence of AMI-STE in women is due to the protective effect of estrogen which slows the progression of atherosclerosis by influencing plaque stability and protecting it from plaque rupture. When entering menopause, women have almost the same risk of heart disease as men. Apart from that, another factor that play a role is the lifestyle of the younger generation which is characterized by work stress, overwork, smoking, drinking alcohol and overeating, which can cause disturbances in the internal organs such as coronary atherosclerosis, increasing the number of heart attacks. Alexander et al.'s study found gender differences in younger

patients, such that smoking was more common in younger men than in women.[19]

Based on infarct location, more than half (52.6%) of the study subjects were diagnosed with anterior AMI-STE. Research conducted by Obeidat et al showed that the anterior region (67%) was the most common location in myocardial infarction patients.[20] It is known that the anterior wall is the most common location with significant morbidity and mortality. The anterior wall of the heart receives blood supply through the Left Anterior Descending (LAD) Coronary artery, which supplies blood to the anterior wall of the left ventricle, the anterior part of the interventricular septum, and the anterior wall of the right ventricle. When rupture occurs in an existing atherosclerotic lesion, it leads to thrombus formation and tissue ischemia. If ischemia continues, the blood supply to the myocardium will be acutely reduced, causing myocardial necrosis. This study showed that the most common risk factors for AMI-STE sequentially were smoking in 30 people (78.9%), hypertension in 23 people (60.5%), diabetes in 17 people (44.7%), and dyslipidemia in 10 people (26.3%). In this study, only one patient had a family history of coronary heart disease.[20]

There are various explanations for these findings. Research by Aminuddin et al in 2023 showed that atherosclerosis is related to the innate immune response and is characterized by a chronic inflammatory process in the walls of blood vessels. Various studies show that in AMI-STE patients, smoking is the most common risk factor found. Smoking is known to increase vascular disease by causing blood vessel inflammation and oxidative stress. Exposure to cigarette smoke can cause excessive matrix metalloproteinase (MMP) activity and inflammation. Increased MMP activity is responsible for activated and unstable plaques in Acute Myocardial Infarction.[21] This theory is in line with this research, it was found that the most common risk factor was smoking with 30 people (78.9%).

As shown in table 2, the mean eNOS level in this study was 47.47 ± 23.88. Median eNOS level was 37,050. Based on the literature, eNOS levels in normal subjects was 48.16 pg/mL[15]. So it was found that the average eNOS level in AMI-STE patients in this study was lower than the eNOS value in healthy people.

Biomarkers of the NO pathway play an important regulatory role in preventing further cardiac damage in AMI-STE patients. eNOS has a major effect on coronary arteries during a heart attack. When there is a blockage in the coronary arteries, blood flow to certain parts of the heart stops. This condition triggers eNOS to produce nitric oxide (NO) which functions as a vasodilator, resulting in widening of the coronary arteries to increase blood flow and oxygen to the heart tissue affected by ischemia. Therefore, eNOS works as protective agent to reduce heart damage caused by a lack of oxygen supply during a heart attack. However, at the same time eNOS can also play a role in producing oxygen free radicals and reactive nitrogen. These substances can trigger oxidative stress conditions and ultimately damage heart cells. Therefore, the role of eNOS in AMI-STE may have a dual impact, both protective and destructive. [22]

Additionally, potential mechanisms through low eNOS levels in cardiovascular risk factors were suspected to cause endothelial dysfunction. Oxidative stress and endothelial dysfunction in the coronary and peripheral

circulation have important prognostic value for the occurrence of AMI. There has not been much research on eNOS levels in AMI-STE patients, but NO levels and oxidative stress are closely related. The research results of Parenica et al showed that NO pathways, such as nitrite/nitrate – (NOx), ADMA, neopterin, and oxidative stress were increased in patients with AMI-STE. Research by Yang and colleagues showed that eNOS levels in AMI-STE patients were significantly reduced compared with normal people, (6.35 ± 0.22 U/ml vs 7.86 ± 0.19 U/ml). Research by Tasolar et al. have findings that support the findings of Yang et al, namely that eNOS levels were reduced in patients with slow coronary flow (SCF) compared to normal subjects, specifically reaching 32.58 ± 21.36 pg/ml in SCF and 48.16 ± 24.35 pg/ ml in normal people.[21,22]

The results of this study showed that overall risk factors were mostly found with low eNOS levels compared with normal ones. eNOS levels had a statistically significant association with diabetes mellitus ($p<0.001$) and hypertension ($p=0.022$) as risk factors for AMI-STE. However, statistical tests showed that there was no statistically significant association between eNOS levels and dyslipidemia ($p=0.135$) and smoking ($p=0.346$) as risk factors for CHD.

In the AMI-STE process, there is a decrease in eNOS function, where eNOS functions as the body's defense mechanism to prevent more severe endothelial damage.[11] In addition, endothelial dysfunction correlates with a decrease in eNOS levels.. This can explain why overall risk factors were found more common in low eNOS levels group compared to normal eNOS group. eNOS expression was found to be decreased in metabolic syndrome.[14] In diabetes mellitus, normal insulin signals will increase eENOS enzymatic activity. On the other hand, conditions of insulin resistance will disrupt the P13K-Akt pathway which will cause reduced eNOS activity, reduced NO formation and consequently cause vasoconstriction in AMI-STE.[15,16]

Activation of eNOS occurs due to phosphorylation of serine 1177 by the protein kinase Akt/PKB. Hyperglycemia-induced mitochondrial superoxide overproduction increases O-linked conversion of N-acetylglucosamine and reduces O-linked phosphorylation of the transcription factor Sp1. In bovine aortic endothelial cells, hyperglycemia inhibited eNOS activity by 67%. Inhibition of hyperglycemia-associated eNOS was accompanied by a twofold increase in eNOS modification by O-linked N-acetylglucosamine and a decrease in O-linked serine phosphorylation at residue 1117. Inhibition of eNOS and changes in post-translational modifications were reversed by inhibition of antisense glutamine:fructose-6-phosphate amidotransferase, the rate-limiting enzyme of the hexosamine pathway, or by blocking mitochondrial superoxide overproduction by releasing protein-1 (UCP-1) or manganese superoxide dismutase (MnSOD). Chronic changes in eNOS activity through this mechanism may explain some of the accelerated atherosclerosis in diabetes.[22]

Likewise with other CHD risk factors, such as hypertension and dyslipidemia, eNOS levels have also been found to be reduced in various studies.[17] Decreased levels of nitric oxide (NO) produced by catalyzed endothelial nitric oxide synthase (eNOS) are associated with higher blood pressure. As is known, eNOS produces the compound nitric oxide (NO) which functions as a vasodilator. A decrease in eNOS levels causes a decrease in NO, so that vasodilation will be

hampered, resulting in an increase in blood pressure.[22] In dyslipidemia, oxidative and non-oxidative LDL will interfere with immunity and regeneration of cells experiencing inflammation. In addition, oxidative LDL inactivates the eNOS/NO pathway.[18,19] Based on latest study, mean endothelial eNOS levels were significantly lower in the group of smokers compared to those who did not.[20] However, in this study no statistically significant differences were found.

Conclusion

The characteristics of the subjects in this study were that the majority of subjects were male by the average age of 62.53 ± 8.2 years. Among the subjects, most of them had anterior AMI-STE, and smoking as the risk factor. There was a statistically significant association between eNOS levels and diabetes mellitus, as well as hypertension as modifiable risk factors for CHD. However, there was no association between eNOS levels with dyslipidemia and smoking as the risk factors for CHD.

Conflict of Interest

The authors declare no potential conflicts of interest or competing interests. The authors received no financial assistance or grants from public, private, or nonprofit funding agencies.

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REVIEW ARTICLE

Health Care Access And Equity Among Migrants: A Literature Review

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ABSTRACT

Background: Health inequality often occurs among disadvantaged population groups, including migrants. Currently, the migrant population does not always receive adequate health services. In addition, the health care system is not optimized for migrants, especially in terms of language, access, genomic data and the expertise of medical personnel. The health condition of these migrants is a global problem that needs attention if countries want to meet the Sustainable Development Goals (SDGs) targets by 2030. This study to map the latest existing research on the topic of migrant health, both qualitative and quantitative.

Methods: Narrative literature review and literature search were carried out using an electronic database with the automatic selection feature used in the electronic database according to the specified inclusion criteria.

Results: Obtained an overview of inequality in [1] access to health services for migrants in general, [2] utilization of health services and health-seeking behavior, [3] health literacy, [4] health services related to the COVID-19 pandemic, and [5] maternal and child health services. All authors agree on this division of groups.

Conclusion: Migrants who do not have documents or are illegal, skin color (black migrants) who migrate to western countries, languages that are not the same, and do not understand their own health conditions due to lack of health education due to language barriers, these factors are obstacles for migrants to achieve equality in countries where migrants have migrated.

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Introduction

Health inequality often occurs in disadvantaged population groups, including migrants. Migrants, especially illegal ones, experience significant health injustice in the form of discrimination, lack of access to healthcare services, nutritious food, and decent housing.[1,2] With the increasing mobility of people around the world, it is expected that the number of the migrant population will continue to increase. According to the latest available estimates, there were 280.6 million global migrants in 2020. In the past decade alone, nearly 60 million more people have become international migrants. This increase is mainly driven by labor or family migration. The proportion of international migrants in the world's population is also increasing, reaching 3.6% in 2020, up from 3.2% a decade ago, and 2.6% in 1960.[3]

Currently, the migrant population does not always receive adequate healthcare services. In addition, the healthcare system is not optimized for migrants, especially in terms of language, access, genomic data, and medical expertise. In addition to infectious disease issues, non-communicable diseases and mental health issues also require special attention. The migrant population is vulnerable to various non-communicable diseases and mental health issues, including psychological trauma, low vaccination rates, or lack of access to antenatal care for pregnant women. The problem is exacerbated by the often-low socioeconomic conditions, which means they have poor sanitation facilities and low health literacy among migrants.[4,5]

The health condition of these migrants is a global issue that needs attention if countries want to meet the Sustainable Development Goals (SDGs) targets by 2030, particularly Goal 10 which is 'reducing inequalities', and Goal 3 which is 'good health and well-being'.[1,6,7] Improving healthcare services is the main way to achieve health equality, as set out in the SDG target 3.8, which aims to 'achieve universal health coverage (UHC), including financial risk protection, access to quality essential healthcare services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all.[1,7]

Given the importance of providing optimal healthcare services for migrants, it is necessary to obtain an overview of migrant access to healthcare services in various countries.[8] The purpose of this article is to review various recent research articles (both quantitative and qualitative research) on the health conditions of migrants around the world, with a primary focus on access to healthcare services and equality in accessing healthcare services. The importance of mapping existing research is to gain a comprehensive understanding of what is known and the gaps in research. This article is expected to provide input to policy makers at the local, national, regional, and global levels to recognize health problems in the migrant population so that appropriate policies can be made.

Methods

This article is a narrative literature review, given the broad and diverse scope of the topic and literature used, a systematic review could not be conducted. The purpose of this review is to map out the latest research on migrant health, both qualitative and quantitative. The definition of migrant used in this study refers to individuals or a

group of people who choose to move not because of direct threats of persecution or death, but primarily to improve their lives by seeking employment, or in some cases for education, family reunification, or other reasons (whether legal or illegal/undocumented). This definition should be distinguished from that of refugees. Unlike refugees who cannot safely return home, migrants do not face such barriers to return. If they choose to return, they will continue to receive protection from their government.[9]

Literature searches were conducted using electronic databases, namely: Pubmed, ScienceDirect, ProQuest, Springer Link, and JSTOR. The search terms used were: (migrant* or immigran*) and (health or healthcare or access or equity), except for ScienceDirect where the symbol '*' was not used because it is not compatible.

Automatic selection features were used in the electronic databases, including: journal articles published in 2017 or later, written in English, and consisted of both qualitative and quantitative research articles. Selection of relevant articles was based on the research question: "How is access to healthcare services and health equity for migrant populations?". Exclusion criteria include: [1] non-research articles, such as literature reviews, letters to the editor, and correspondence, [2] not studying migrant populations, [3] complete articles were not found.

Results

After conducting the search and selecting articles that met the criteria, the authors agreed on 22 relevant articles. Of the 22 articles that met the criteria, 11 (50%) used qualitative research methods (10-20), 8 (36%) used quantitative research methods[5,21-27], and the remaining 2 used mixed methods [28] and intervention methods.[29] The countries studied were distributed worldwide, with European countries (N=9) and Asia (N=7) being the most dominant. The migrants' countries of origin were mostly from Asian and African countries.

A summary of the results of each study was grouped into five categories (according to their respective themes) and summarized in Table 1. The categorization includes: [1] access to healthcare services for migrants in general, [2] utilization of healthcare services and health-seeking behaviors, [3] health literacy, [4] healthcare services related to the COVID-19 pandemic, and [5] maternal and child healthcare services. All authors agreed on this categorization.

Discussion

1. Access to Health Services

All migrants, regardless of their status, are entitled to receive healthcare that is equal to that of the citizens within it. Carrasco-Sans et al. (2018) revealed that migrant health is worse than non-migrant health in Europe, with 90% of the causes being the lack of access to healthcare services. Access to healthcare services is hindered by the lack of clear documentation regarding migrant identity in Europe.[27] Furthermore, Nepalese migrants in Japan also have poor access to healthcare services due to insurance and communication barriers.[30]

African migrants face difficulties in accessing healthcare services, including finding suitable doctors or healthcare services for their illnesses, as well as communication barriers. Healthcare services cannot be accessed equally by all inhabitants of Norway. This ultimately leads to Norwegian citizens avoiding healthcare services if they have health problems. The lack of seeking healthcare services by immigrants may have long-term implications for the health problems they experience.[12] Perez's research in 2019 also revealed that factors causing African women to have limited access to healthcare services include fear of healthcare services being unfriendly to African immigrants (with dark skin), communication barriers, and African women perceiving racism against black people.[13]

2. Utilization of Health Services and Health-Seeking Behavior

Twelve European countries have limited rights to healthcare for asylum-seeking children, including Germany, which stands out as the country with the strictest healthcare policy for migrant children. The healthcare needs of undocumented migrants from other European Union countries are often overlooked in European healthcare policies.[16] More than 300,000 asylum-seeking children were registered in Europe alone during 2015. The right to healthcare for migrant children in Europe and Australia is based on the framework of the United Nations Convention on the Rights of the Child.[29]

Verified information on global healthcare service utilization by undocumented migrants is essential in understanding how immigrants use healthcare services based on their needs. We compared healthcare service utilization between undocumented migrants, documented migrants, and Spanish citizens in the autonomous community of Spain.[23]

Although there is a broad consensus that access barriers exist for immigrants in the United States, European evidence exploring this issue provides a diverse picture, with studies from various European jurisdictions presenting different conclusions. In this context, Ireland, a European country with substantial private involvement in healthcare provision and a large young immigrant population, provides an opportunity to investigate healthcare service utilization by immigrants compared to the native population in a European country with a mixed private-public healthcare provision.[24]

In addition to Europe, healthcare service utilization in the Americas and Asia provides information on the use of healthcare by migrants but does not distinguish between usage by nationality of the migrants. It provides information on the use of various emergency services by Nicaraguan and Costa Rican migrants. The focus is on emergency services because if the presence of migrants is high, it must be noted anywhere, in this case from the services. All individuals in Costa Rica are entitled to immediate access to emergency services, even if bills are presented after the ward (and may not be paid). On the other hand, non-emergency care, such as admission to general hospitals, may be less available to uninsured foreigners because, on the one hand, CCSS may refuse services, and on the other hand, uninsured

migrants may also tend to seek medical attention in non-emergency situations.[21]

In Asia, the health issues of irregular and vulnerable migrant populations remain largely unexplored. Specifically, while mainland China has become a new and popular destination for domestic workers, health status remains largely invisible as a public and academic issue. For some health problems, they tend to use self-treatment and food healing.[17]

Health-seeking behavior in Europe is on countries like France, Italy, Norway, Portugal, and Spain, where all categories of migrant children regardless of their legal status are given equal rights and are included in the same healthcare system as national children. Sweden and Belgium offer the same rights to asylum-seeking children and children from third-country migrants who are irregular, but the rights of children from irregular EU citizens are not clear. Greece is a special case, where regulations that give rights to asylum-seekers and non-EU migrant children for the same healthcare are severely limited in practice by economic constraints.[16]

The behavior of seeking healthcare information did not show any effect on the hypothetical immigrant's healthcare seeking behavior, while it specifically showed a positive effect on the healthcare seeking behavior of all groups using lower healthcare services in the following year compared to the year in which the study was conducted, except for stable remaining dental care usage. Information about the healthcare system embedded in language school programs potentially facilitates immigrant access to healthcare services. However, the results underscore the need for further improvement and development of educational interventions, as well as ensuring adequate utilization of healthcare services in other ways.[29]

Furthermore, the irregular use of healthcare services by migrants is much lower than that of Spanish citizens (as well as documented migrants), regardless of their region of origin and length of stay in Spain. This lower utilization of healthcare services is likely related to the social consequences of their irregular legal status (such as job insecurity, economic hardship, discrimination, and fear of deportation), although the methodology used in our study does not allow us to identify specific underlying determinants. These findings are highly relevant given the current political, socio-economic, and healthcare challenges posed by the increasing number of international migrants and may help facilitate evidence-based decision-making by policymakers, both in Spain and around the world, seeking to create a system that offers truly universal healthcare coverage that includes undocumented migrants.[24]

On the American continent, healthcare seeking behavior in Costa Rica provides information on total consultations and hospitalizations between 2000 and 2011 that may be associated with migrants. This administrative data comes from national health services and is based on total consultations and hospitalizations in all public healthcare facilities. The migrant portion of total hospitalizations was 5.84 percent in 2000 and increased to 6.7 percent in 2011. The portion of outpatient consultations that may be associated

with migrants ranged between 4 and 5 percent per year. In both cases, the utilization of healthcare services for either inpatient care or outpatient visits is far below the stock of migrants in the country.[21]

Healthcare seeking behavior in China to build a more inclusive healthcare service system that supports foreign PLRTs in mainland China, health policymakers must first eliminate or at least reduce institutional barriers for foreigners. By doing so, the Chinese government can develop more inclusive health policies that enable workers to better access local healthcare services. For example, additional measures such as offering information and knowledge related to the Chinese healthcare system, as well as offering relevant language support to foreign PLRTs, can facilitate their willingness and ability to visit general hospitals, thereby reducing the likelihood of treatment delays. These steps can help non-permanent migrant workers in mainland China gain better access to healthcare services to improve their health conditions.[17]

3. Health Literacy

Health literacy is an important factor in determining individual health status, particularly for migrants who may face difficulties in accessing and understanding available health information. A study conducted by Wångdahl et al. (2018) in Sweden aimed to explore the distribution of comprehensive health literacy (CHL), general health, psychological well-being, and reasons why refugees refrain from seeking healthcare in Sweden, as well as to examine the relationship between CHL and these factors. CHL was measured using the European Health Literacy Questionnaire (HLS-EU-Q16) and it was found that a majority of refugees in Sweden had limited CHL, poor health, and disrupted well-being, and refrained from seeking healthcare. Furthermore, low CHL was associated with poor health, disrupted psychological well-being, and refraining from seeking healthcare.[5]

This study was followed up by Bergman et al. (2021) who explored CHL and electronic health literacy (EHL) among Arabic-speaking migrants in Sweden. EHL was measured using the eHealth Literacy Scale (eHEALS), and all questionnaires were distributed in both Swedish and Arabic. The study found that Arabic speakers had significantly lower mean scores on EHL (28.1) and lower proportions of CHL compared to Swedish speakers. The relationship between limited CHL and EHL was found to be related to underutilization of the internet and a lack of recognition of its importance. In addition, longer periods of time spent in Sweden were associated with higher levels of CHL among Arabic speakers. The study suggests that the internet could be an appropriate channel for disseminating health information to Arabic-speaking migrants.[26]

4. Access to Healthcare Services and Migrant Issues during the Covid-19 Pandemic

During the coronavirus (Covid-19) 2019 pandemic, migrants who have moved to another country are at high risk of contracting Covid-19. For instance, immigrants from Chile who face complex forms of poverty and social vulnerability. The health and well-being of migrants are influenced by several factors, including poverty, social isolation, hazardous working environments,

and living conditions below standard. In the context of a global pandemic and efforts to achieve universal health coverage, this situation is very concerning. The social vulnerability experienced by international migrants can be seen from two main aspects as a migrant and the lack of social support and networks, vulnerabilities and needs can be assumed such as economic difficulties, loss of income and employment, marginalization, and lack of institutional support.[19]

Migrants in Chile experience structural racism and xenophobia, which can increase social vulnerability and affect their ability to obtain necessary care. Health concerns of participants center on a lack of knowledge about where to seek help if they become ill and a desire for direct advice on how to proceed in pandemic situations.[19]

Immigrant patients who will access inpatient care services are also hampered by incomplete documents held by immigrants. Various policies and interventions are needed to ensure that undocumented migrants and other underserved groups have access to health services.[25] Especially if there is a potential health crisis that could exacerbate existing health disparities. The social and economic consequences of the COVID-19 pandemic quickly exacerbate pre-existing vulnerabilities of underserved groups, and concerns have been raised that health policies may be blind to the needs of marginalized groups. Migrants also face difficulties in accessing Covid-19 vaccinations, and they continue to face urgent situations that pose greater risks to their health and safety. The public health benefits of managing the pandemic by considering the unique characteristics of the world's migrant population will be maximized if governments are proactive and open-minded.[18]

As the number of COVID-19 cases in the UK began to increase rapidly, the government implemented a healthcare policy that prioritized COVID-19 patients, temporarily suspending the practice of providing the same level of care to all patients. The reality of the pandemic prevents the system from distributing its resources to maintain accessibility for all. This means that some previously scheduled care for patients without COVID has been postponed, and people who are not infected with the virus are not given equal access to healthcare. These measures have the greatest impact on patients with chronic diseases such as diabetes mellitus or cancer whose treatment is postponed or even canceled. After the initial wave of infections subsides, severe stockpiling in the system makes the effects of these emergency measures more enduring.[25]

Even in times of severe resource tension, health inequality can be reduced if fairness is prioritized in the implementation of health policies. Therefore, it may be important in preventing the spread of COVID-19 in the community to address the main barriers to caring for underserved groups through individual policies and practices.[25] Despite improvements in laws and protections, migrant worker populations in Singapore and elsewhere continue to face long-standing issues such as unequal access to healthcare, information, and resources targeted towards the local populations of host countries, and even exclusion from national crisis response plans, especially pandemic

preparedness plans. To bridge this gap, NGOs play a crucial role as service providers, intermediaries between businesses and funding sources, and advocates for disadvantaged groups by voicing their concerns in cross-sector partnerships. Due to language and cultural barriers, it is difficult for general healthcare services to incorporate mental healthcare for this population. The high stigma of mental illness in the home country of migrant workers adds a heavy burden to the unmet need for specialized mental healthcare. The COVID-19 pandemic in Singapore has exacerbated these service shortages in the NGO sector, as widespread quarantines and isolation of migrant worker accommodations have drastically reduced NGO access to these services.[31]

5. Maternal and Child Health

Health issues among mothers and children are crucial among migrants, as they belong to a high-risk group. A study conducted by Carrasco-Sanz et al. (2018) assessed the perception of European pediatricians as primary healthcare providers for migrant children, examining their impressions of health issues and needs of migrant children, and barriers faced by migrant children and families in accessing healthcare. From the survey conducted on 482 pediatricians from 10 European countries, it was found that 63% of respondents reported that the general health of migrant children was worse than non-migrants (chronic diseases being the most common health problem), and 66% of pediatricians reported that migrant children have different health needs compared to non-migrant children. Cultural/language factors serve as barriers to accessing healthcare services, but only 37% of providers have access to professional interpreters and cultural mediators. 52% and 32% did not know whether one or more family members were undocumented and whether they were refugees/asylum seekers. Recent guidelines for the care of migrant children were only available to 35% of respondents, and 80% of them have not received specialized training on the care of migrant children.[27]

In line with health issues among mothers and children of migrants, Siddaiah et al. (2018) conducted a study on the utilization of maternal healthcare among female migrant workers working in the brick kilns of Northern Haryana, India. The study involved 500 women of reproductive age, with a history of one childbirth and able to understand and speak Hindi. Based on the study findings, one-third of the women had received cash benefits under the Janani Suraksha Yojana (JSY) (a government of India national health mission) or had used free ambulance services. Related factors such as gaps in knowledge about the local healthcare system, substandard private healthcare services provided at the brick kilns, prevent migrant workers from accessing basic community healthcare services. Misunderstandings and lack of trust in the community healthcare system affect the utilization of maternal healthcare services by migrant women working in brick kilns, making them a vulnerable subgroup of the population in terms of maternal healthcare utilization.[28]

Another related study was conducted by Vesely et al. (2021), which delved deeper into the experiences and perspectives of Central American immigrant mothers on Early Care and Education

(ECE). This qualitative research involved 55 undocumented immigrant mothers from El Salvador, Guatemala, and Honduras. Based on the study findings, barriers to accessing quality ECE for their children were influenced by income insecurity and undocumented status. Accessing and maintaining quality ECE for them is an ongoing struggle throughout the early years of childhood. This study provides a greater understanding of how immigrant families adapt to the challenges of early childhood education and wider social inequalities and discusses implications for the delivery of ECE services that relate to the diversity of mixed-status Central American immigrant families.[20]

Conclusion

Equality in migrant communities in various countries remains an ongoing issue, particularly in terms of access to healthcare services for migrants in general, utilization of healthcare services and health-seeking behaviors, health literacy, healthcare services related to the COVID-19 pandemic, and maternal and child healthcare. Migrants who do not have proper documentation or are illegal, have black skin (black migrants) migrating to western countries, speak a different language, and lack understanding of their own health conditions due to a lack of health education caused by language barriers, are some of the factors that hinder migrants from achieving equality in the country where migrant communities are residing.

Conflict of Interest

The authors declare no potential conflicts of interest or competing interests. The authors

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ORIGINAL ARTICLE

Comparison Between Hypnoanesthesia and Local Anesthesia in Minor Surgery

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ABSTRACT

Background: Hypnoanesthesia is a state of anesthesia achieved through hypnosis techniques. Meanwhile, local anesthesia is anesthesia carried out by injecting local anesthetic drugs in or around the surgical site which causes temporary obstruction to the conduction of afferent impulses. Objective: This research was conducted to prove that there is no difference between hypnoanesthesia and local anesthesia in minor surgical procedures, with the indication of pain relief.
Methods: The research subjects were patients with benign soft tissue tumors consisting of 40 people who were divided into 2 groups, namely treatment and control. Minor surgical procedures with hypnoanesthesia were performed in the treatment group, while in the control group, minor surgical procedures were performed with local anesthesia using 2% lidocaine. Pain is measured with FPS (Face Pain Scale) and monitored with a vital sign monitor. The intervention process was recorded with camcorder video. Changes in serum levels of excitatory neurotransmitters (Glutamic Acid and Substance P) and inhibitory (Beta Endorphin, Enkephalin, and Serotonin) before and after intervention were analyzed using ELISA (Enzym-Link Immunosorbent Assay) in both groups.
Results: In the treatment group, it was discovered that patients did not feel pain after undergoing hypnoanesthesia intervention by providing suggestions for the relief of pain in the area where surgery would be performed. In the control group, patients also did not feel pain after local anesthetic intervention in the area to be operated on. However, the results of research and statistical tests showed that there was no significant difference in changes in Beta Endorphins, Enkephalin, and Serotonin as inhibitory neurotransmitters ($p > 0.05$) or Glutamic Acid and Substance P as excitatory neurotransmitters ($p > 0.05$) before and after the intervention in both groups of research subjects.
Conclusion: the results of this study show that there is no significant difference between the treatment and control groups, they have equality in the final result, namely the relief of pain.

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Introduction

Pain relief can occur with hypnoanesthesia for minor surgical procedures. This phenomenon has been known empirically in the medical field since the 18th century. Every surgical procedure, both minor and major, requires anesthesia to relieve pain during the surgical procedure. In minor surgical procedures, local anesthesia using 2% lidocaine is standardly used. The state of anesthesia achieved through hypnosis techniques is called hypnoanesthesia. Hypnoanesthesia was first used in the medical field by James Esdaille, a Scottish surgeon, for surgical procedures, both minor and major. The hypnoanesthesia process does not require anesthetic drugs so the negative impact of anesthetic drugs can be eliminated.[1,2] The mechanism for the anesthesia process in the area undergoing surgical procedures in hypnoanesthesia is due to the obstruction of nociceptive pain impulses which are transmitted to the brain, however, the scientific explanation of the mechanism of obstruction of the transmission of nociceptive pain impulses is still unclear and requires further research.[2–7]

In 1957, hypnoanesthesia was used for the first time in obstetrics and gynecology during section and hysterectomy procedures at Chicago Lying-in Hospital.[3] In the same year in the field of Dentistry, the Michigan State Board of Dentistry recognized the use of hypnosis in dental practice as legal.[8] In the period between April 1994 and June 1999, the United States National Institute of Health reported 197 thyroidectomy surgical procedures and 21 cervical exploration procedures for hyperparathyroidism using hypnoanesthesia.[9] This study examines the differences between hypnoanesthesia and local anesthesia, regarding neurotransmitters that play a role in pain mechanisms comprehensively, both excitatory neurotransmitters, Glutamic Acid and Substance P, and inhibitory ones, Beta Endorphins, Enkephalin, and Serotonin.

Hypnoanesthesia is preceded by changes in pain perception. Suggestions given in the form of visual, sound, and/or tactile stimuli, penetrate the Reticular Activating System in the Reticular Formation in the Brain Stem and are received by the Dorsolateral Prefrontal Cortex as a stimulus which then undergoes a process of selection, interpretation until it becomes a new perception from the perception of pain to the perception of pain relief.[10] The Reticular Activating System in a state of relaxation becomes inactive so that the suggestions given are not criticized or analyzed.[3,11] This new perception is stored in the Ventromedial Prefrontal Cortex as short-term memory and can be marked using an “anchor” as a “password” to be used again when needed.[12,13]

In local anesthesia, local anesthetic drugs work by blocking sodium channels, thereby preventing the entry of sodium into nerve cells. The inhibition of sodium causes no depolarization to occur so that no action potential can be initiated or continued. Depolarization barriers cause the flow of impulses through these nerves to stop, so that all kinds of stimuli or sensations do not reach the central nervous system. The above process shows that local anesthesia will inhibit excitatory neurotransmitters, both glutamate and Substation P so that the pain relief.[14]

Methods

This research is a Quasi-Experimental study with a Randomized Control Group pre-test and post-test design. The research was conducted at Dr. Mohamad Soewandhie Regional General Hospital, Surabaya, Indonesia. The population in this study were patients who were clinically diagnosed with benign soft tissue tumors and patients who required an incision biopsy without inflammation who came for treatment at the surgical clinic. The number of research subjects for each group was 20 people, consisting of a treatment group and a control group, so there was a total of 40 people. This research has received a Letter of Clinical Research Ethics Eligibility No.001/KE/KEPK/2020 dated 27 October 2020.

Inclusion criteria are male or female patients (16-18 years), able to communicate in Indonesian (not deaf-mute), and cooperative with a minimum education level of Elementary School. Surgical action (excision) is carried out on clinically benign soft tissue tumors without any signs of inflammation (calor, dolor, rubor, functional laesa) and the location of the tumor is in the ventral part of the patient's body and surgery can be performed in the supine position with a benign tumor size of no more than 5 cm. Patients who do not achieve optimal levels of anesthesia when hypnoanesthesia is performed and/or patients who experience abreaction are included in the exclusion criteria.

Patients signed an informed consent form to participate in the research process. The pain scale and vital signs were measured and recorded on the research form. The pain scale (Face Pain Scale) is determined by clamping using tweezers on the area where the surgery will be performed and its surroundings. Next, blood samples are taken from peripheral blood intravenously, to check Beta Endorphins, Enkephalins, Glutamic Acid, Substance P, and Serotonin by the nurse. Local anesthesia was performed in the control group with 2% lidocaine in the area to be operated on until the level of anesthesia was achieved. Meanwhile, the treatment group underwent hypnoanesthesia in the area where surgery would be performed. The indicator of achieving the level of hypnoanesthesia is clamping using tweezers on the area where the surgical procedure will be carried out and its surroundings to determine whether the pain has been relieved and looking at the patient's face pain scale (Face Pain Scale) until it reaches a scale value of 0. The research process in both groups was monitored using a vital sign monitor and recorded using a camcorder.

The surgical procedure is carried out by the operator while maintaining the level of anesthesia until the surgical procedure is completed. Then the pain scale, vital signs, and a second blood sample were taken 10 minutes after the incision was made. Data from the results of the first and second blood draws were analyzed using ELISA examination at the Laboratory of Dr. Soetomo General Academic Hospital. The data collected was processed manually using SPSS 17 software. The level of significance of the statistical test used in this research was 0.05.

Results

Table 1. Characteristics of Research Subjects

Characteristics	Control (n = 20)	Treatment (n = 20)
Age		
Mean ± SD	30,4 ± 13,220	28,15±2,076
Sex [n(%)]		
Male	12 (60%)	5 (25%)
Female	8 (40%)	15 (75%)
Last Education [n(%)]		
Elementary	2 (10%)	2 (10%)
Junior high school	1 (5%)	3 (15%)
Senior high school	14 (70%)	14 (70%)
Bachelor	3 (15%)	1 (5%)
Pain scale		
Before	10	10
After	0	0
Sistole Blood Pressure		
Before	137,45±27,810	133,60±9,672
After	132,70±23,622	130,75±20,047
Diastole Blood Pressure		
Before	77,80±15,419	71,80 ± 13,320
After	76,55±14,376	69,90 ± 9,597
Heart rate (x/minute)		
Before	92,15±20,399	84,85 ± 16,813
After	82,9 ± 18,894	81,30 ± 15,755
Respiratory rate (x/minute)		
Before	23,35 ± 2,084	21,05 ± 3,103
After	20,60 ± 1,465	20,00 ± 1,864
Awareness (before/after)		
Compos mentis	20 (100%)	20 (100%)

All research subjects in the control group and treatment group during the research were in composmentis conditions.

Table 2. Differences in Changes in Beta Endorphins, Enkephalins, Serotonin, Glutamic Acid and Substance P Between Groups

Variable	**Groups**	**n**	**Mean ± SD** **Median (min-max)**	**P value**
Beta Endorphins	Control	20	-1,50 ± 24,121	0,758
	Treatment	20	0,86 ± 23,944	
Enkephalins	Control	20	-0,30 ± 0,858	0,220
	Treatment	20	0,11 ± 1,173	
Serotonin	Control	20	4,06 ± 14,990	0,799
	Treatment	20	2,48 ± 23,136	
Glutamic Acid	Control	20	0,04 ± 0,160	0,937
	Treatment	20	0,035 ± 0,230	
Substance P	Control	20	-8,7 (-56,3 – 113,9)	0,507

Treatment	20	0,05 (-135 – 156)

The results of the 2 independent sample t-tests showed that there were no significant differences in Beta-Endorphins, Enkephalin, Serotonin, and Glutamic Acid between groups ($p > 0.05$), while the results of the Mann-Whitney test showed that Substance P between groups was not significantly different ($p > 0.05$).

Treatment Group Analysis (Hypnoanaesthesia)

Based on Table 3, the Pearson correlation shows that variable Y1 is not correlated with Y2 because the p-value is > 0.05 (r = 0.082). Variable Y1 is very strongly correlated with Y3 with a correlation value of 0.992 ($p = 0.000<0.01$). Variable Y1 is very strongly correlated with Y4 (Glutamic acid) with a value of 0.990 ($p = 0.000<0.01$). Variable Y1 has a very strong correlation with Y5 (Substance P) with a correlation coefficient = 0.992 ($p<0.01$). Variable Y2 is not correlated with Y3 because $p = 0.748>0.05$. Variable Y2 is not significantly correlated with Y4 because $p = 0.679>0.05$. Variable Y2 is not correlated with Y5 because $p = 0.761>0.05$. Variable Y3 has a very strong correlation with Y4 with a correlation coefficient of 0.985 ($p<0.01$). Variable Y3 is very strongly correlated with Y5 (r = 0.985) with $p<0.01$. Variables Y4 and Y5 have a very strong correlation with a correlation coefficient of 0.994 ($p<0.01$).

Table 3. Correlation Between X1, Y1, Y2, Y4, Y5 and Y6

		Correlation						
		X1	Y1	Y2	Y3	Y4	Y5	Y6
X1	Pearson Correlation	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
	Sig. (2-tailed)	0	0	0	0	0	0	0
	N	20	20	20	20	20	20	20
Y1	Pearson Correlation	.[a]	1	.082	.992**	.990**	.992**	.[a]
	Sig. (2-tailed)	.	.	.731	.000	.000	.000	.
	N	20	20	20	20	20	20	20
Y2	Pearson Correlation	.[a]	.082	1	.077	.099	.072	.[a]
	Sig. (2-tailed)	.	.073		.748	.679	.761	.
	N	20	20	20	20	20	20	20
Y3	Pearson Correlation	.[a]	.992**	.077	1	.985**	.985**	.[a]
	Sig. (2-tailed)	.	.000	.748		.000	.000	.
	N	20	20	20	20	20	20	20
Y4	Pearson Correlation	.[a]	.990**	.099	.985**	1	.994**	.[a]
	Sig. (2-tailed)	.	.000	.679	.000		.000	.
	N	20	20	20	20	20	20	20
Y5	Pearson Correlation	.[a]	.992**	.072	.985	.994	1	.[a]
	Sig. (2-tailed)	.	.000	.761	.000	.000		.
	N	20	20	20	20	20	20	20
Y6	Pearson Correlation	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
	Sig. (2-tailed)	.	.	.	.	.	.	
	N	20	20	20	20	20	20	20

**. Correlation is significant at the 0.01 level (2-tailed)

a. Cannot be calculated because at least one of the variables is constant

Notes:

X 1: Hypnoanesthesia

Y 1: Beta-endorphin

Y 2: Enkephalin

Y 3: Serotonin

Y 4: Glutamic acid

Y 5: Substance P

Y 6: Pain relief

Path Analysis between Y1, Y2, Y3 and Y4

In the Summary Model of the path regression test Y1, Y2, and Y3 against Y4, it was found that the R square was 0.982, thus the path coefficient ε (variable outside the model) was 0.134.

$$\rho_{Y5\varepsilon} = \sqrt{(1 - 0{,}982)} = \sqrt{0{,}018} = 0.134$$

Meanwhile, in the coefficients in the Anova test, it was found that the path coefficients Y1, Y2, and Y3 were 0.800, 0.019, and 0.190. And the only significant correlation is Y1 (0.009 < 0.05). This shows that only Beta-endorphin has a significant correlation with Glutamic acid of 0.800.

Path Analysis between Y1, Y2, Y3 and Y5

In the Summary Model of the path regression test Y1, Y2, and Y3 against Y5, the R square is 0.984, so the path coefficient ε (variable outside the model) is 0.126. Meanwhile, in Figure 1 below, it can be seen that the path coefficients Y1, Y2, and Y3 are 0.912, -0.009, and 0.081. And the only significant correlation is Y1 (0.002 < 0.05). The correlation from Y1, Y2, and Y3 to Y4 is shown in red correlation numbers with magnitudes of 0.800, 0.019, and 0.190 respectively. Meanwhile, the correlation of Y1, Y2, and Y3 with Y5 is shown in the blue correlation figures with respectively 0.912, -0.009, and 0.081 (Figure 1).

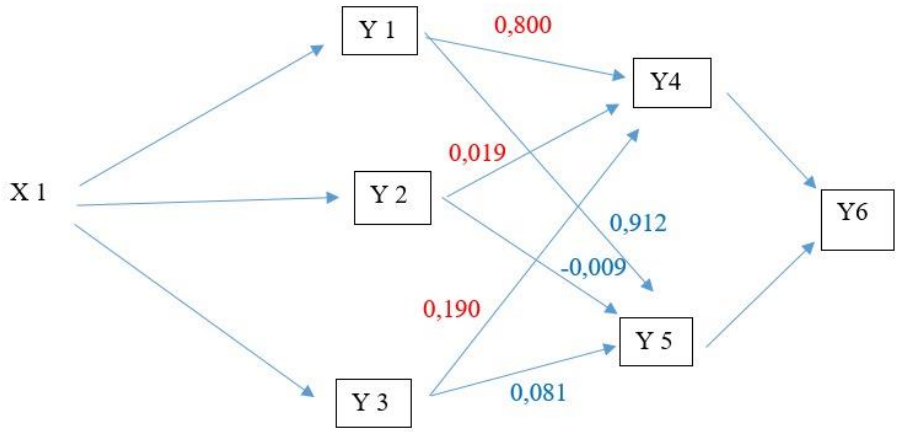

Figure 1. Treatment Group Path Analysis Model

In Figure 1, X1 will suppress Y4 and Y5 which are excitatory neurotransmitters so that painful stimuli are not transmitted to the brain or do not feel pain (Y6). If Y4 and Y5 are suppressed, Y1, Y2, and Y3 as inhibitory neurotransmitters are also suppressed or not released in the brain's nervous system. Y1, Y2, and Y3, when stimulated, will inhibit pain so that the pain relief.

Control Group Analysis Results

The control group in this study had their data analyzed to see differences in the results of each variable after administering local anesthetic drugs to the research subjects.

Table 4: Correlation of X1, Y1, Y2, Y3, Y4, Y5, and Y6

		Correlation						
		X1	Y1	Y2	Y3	Y4	Y5	Y6
X1	Pearson Correlation	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
	Sig. (2-tailed)		.	.	.	.	.	.
	N	20	20	20	20	20	20	20
Y1	Pearson Correlation	.[a]	1	-.316	.803**	.879**	.762**	.[a]
	Sig. (2-tailed)	.	.	.175	.000	.000	.000	.
	N	20	20	20	20	20	20	20
Y2	Pearson Correlation	.[a]	-.316	1	-.189	-.076	-.017	.[a]
	Sig. (2-tailed)	.	.175		.424	.749	.944	.
	N	20	20	20	20	20	20	20
Y3	Pearson Correlation	.[a]	.803**	-.189	1	.800**	.842**	.[a]
	Sig. (2-tailed)	.	.000	.424		.000	.000	.
	N	20	20	20	20	20	20	20
Y4	Pearson Correlation	.[a]	.879**	-.076	.800**	1	.810**	.[a]
	Sig. (2-tailed)	.	.000	.749	.000		.000	.
	N	20	20	20	20	20	20	20
Y5	Pearson Correlation	.[a]	.762**	-.017	.842	.810	1	.[a]
	Sig. (2-tailed)	.	.000	.944	.000	.000		.
	N	20	20	20	20	20	20	20
Y6	Pearson Correlation	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]	.[a]
	Sig. (2-tailed)	.	.	.	.	.	.	
	N	20	20	20	20	20	20	20

**. Correlation is significant at the 0.01 level (2-tailed)
a. Cannot be calculated because at least one of the variables is constant

Variable Y1 (Beta-endorphin) has a strong correlation with Y3 (Serotonin) of 0.803, Y4 (Glutamic Acid) of 0.879, and Y5 (Substance P) of 0.762. Meanwhile, Y1 is not strongly correlated with Y2 (Enkephalin), with a negative correlation direction. This negative correlation direction also occurs between Y2 and Y3, Y4 and Y5; If Enkephalin increases, Serotonin, Glutamic Acid and Substance P will decrease, and vice versa. Variable Y3 (Serotonin) has a strong correlation with Y4 (Glutamic Acid) and Y5 (Substance P), respectively 0.800 and 0.842.

Path Analysis between Y4 and Y5 towards Y1

It can be seen from the results of the coefficients in the Anova test for paths Y4 and Y5 that they are 0.763 and 0.143. The only significant correlation is Y4 (0.001 < 0.05), whereas in the Model Summary table, it can be seen that the R square is 0.754, so the path coefficient ε (variable outside the model) is 0.495.

$$\rho_{Y5\varepsilon} = \sqrt{(1 - 0.754)} = \sqrt{0.246} = 0.495$$

This means that the proposed hypothesis is not completely accepted because based on testing, only the path coefficient from Y4 to Y1 is statistically significant. This shows that the only influence on Y1 is Y4.

Path Analysis between Y4 and Y5 towards Y2

It can be seen from the Anova test coefficients that the path coefficients Y4, and Y5 are -0.183 and 0.132. There is no significant correlation (0.662 > 0.05 and 0.753 > 0.05), whereas in the Model Summary table, it can be seen that the R square is -

0.104, so the path coefficient ε (variable outside the model) is 0.947.

$\rho_{Y5\varepsilon} = \sqrt{(1 - (-0.104))} = \sqrt{0.896} = 0.947$

This means that none of the proposed hypotheses is accepted because based on testing, none of the path coefficients from Y4 and Y5 to Y2 are meaningful.

Path Analysis between Y4 and Y5 to Y3

It can be seen from the Anova test coefficients that the path coefficients Y4, and Y5 are 0.341 and 0.566. The only significant correlation is Y5 (0.014 < 0.05), whereas in the Model Summary table, it can be seen that the R square is 0.720, so the path coefficient ε (variable outside the model) is 0.529.

$\rho_{Y5\varepsilon} = \sqrt{(1 - 0.720)} = \sqrt{0.28} = 0.529$

This means that the proposed hypothesis is not completely accepted because based on testing, only the path coefficient from Y5 to Y3 is statistically significant. This shows that the only influence on Y3 is Y5.

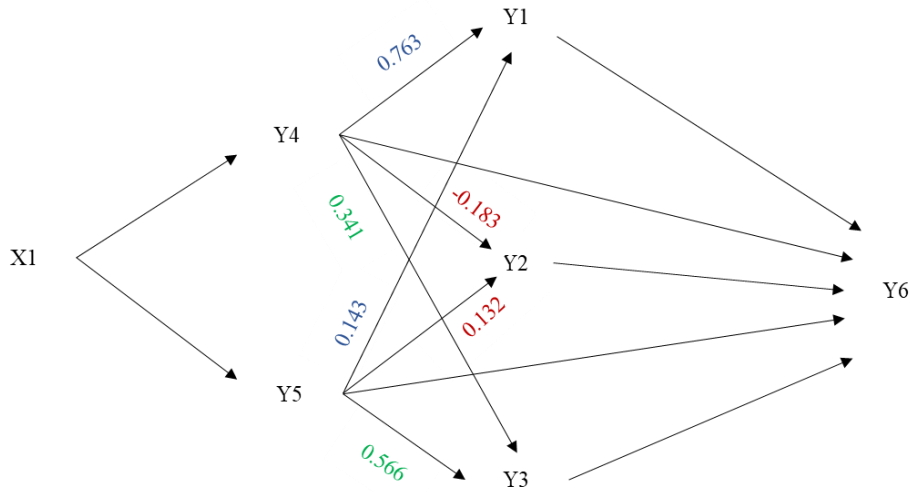

Figure 2. Control Group Analysis Model (X1: Local anesthetic; Y1: Beta Endorphin; Y2: Enkephalin; Y3: Serotonin; Y4: Glutamic Acid; Y5: Substance P; Y6: Pain relief)

In figure 2, X1 will suppress Y4 and Y5 which are excitatory neurotransmitters so that painful stimuli are not transmitted to the brain or do not feel pain (Y6). If Y4 and Y5 are suppressed, Y1, Y2, and Y3 as inhibitory neurotransmitters are also suppressed or not released in the brain's nervous system. Y1, Y2, and Y3, when stimulated, will inhibit pain so that the pain disappears.

Discussion

In the treatment group, it was discovered that patients did not feel pain after undergoing hypnoanesthesia intervention by providing suggestions for the relief of pain in the area where surgery would be carried out. Suggestions for the relief of pain or suggestions for numbness given through visual, sound, and/or touch stimuli are received by the sensory organs and then forwarded to the Thalamus and after breaking through the Reticular Activating System (RAS) alert system in the Formation Reticularis, it is passed on to the Dorso Lateral Prefrontal Cortex as a new perception. , namely pain-free feeling.[10] This pain-free perception is stored in the Ventro Medial Prefrontal Cortex.

However, the results of research and statistical tests showed that there were no significant differences in changes in Beta Endorphins, Enkephalin, and Serotonin as inhibitory neurotransmitters ($p > 0.05$) or Glutamic Acid and Substance P as excitatory neurotransmitters ($p > 0.05$) before and after hypnoanesthesia intervention. There is no statistically significant difference. It turns out that there can be an empirical relief of pain. At the time of the minor surgical procedure, all research subjects in the treatment group did not feel pain after being given hypnoanesthesia (data source in research video recording).

In this study, the mechanism of pain in the control group occurred in the peripheral nervous system, the transduction process during minor surgical procedures was inhibited by the intervention of local anesthesia with 2% lidocaine so that pain was not passed on to the transmission, modulation and perception processes so that pain was not felt.[15,16] This is in accordance with the results of the t-test in the control group; proving that the control and treatment groups have equality in the final result, namely pain relief.

Based on the results of statistical analysis of the treatment group, it was found that Beta Endorphin, Enkephalin, and Serotonin simultaneously had a significant effect on Substance P by 98.4% and Glutamic Acid by 98.2%. Of the three inhibitory neurotransmitters, the results obtained were that only Beta Endorphin had a strong significant correlation with Substance P ($r = 0.912$) and Glutamic Acid of 0.800.[17–19] These results are in accordance with Gate Control Theory[19] which states that ascending pain signals delivered by excitatory neurotransmitters (Glutamic Acid and Substance P) interact with the inhibition of descending signals by inhibitory neurotransmitters (Beta Endorphin, Enkephalin, Serotonin).

Conclusion

Based on the results of data analysis and discussion in this study, it can be concluded that there is no significant difference between hypnoanesthesia which mechanism is in the central nervous system, and local anesthesia in the peripheral nervous system in minor surgical procedures in both the control and treatment groups, wherein the control and treatment groups have equality in the final result, namely pain relief.

Conflict of Interest

The authors declare no potential conflicts of interest or competing interests. The authors received no financial assistance or grants from public, private, or non-profit funding agencies.

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CASE REPORTS

Complete Heart Block Secondary to Leptospirosis: A Case Report

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ABSTRACT

Complete heart block (CHB) is a rare but potentially life-threatening complication of leptospirosis, a zoonotic bacterial infection caused by spirochetes of the genus Leptospira. While leptospirosis primarily affects the kidneys and liver, cardiac involvement, including CHB, can occur and has significant clinical implications. The pathogenesis of CHB in leptospirosis is multifactorial and may involve direct cardiac invasion by Leptospira organisms, systemic inflammatory response, autoimmune reactions, electrolyte imbalances, and hemodynamic effects. Prompt recognition and management of CHB are essential to prevent adverse outcomes, including hemodynamic instability and sudden cardiac death. Treatment strategies include supportive measures such as hemodynamic support and correction of electrolyte imbalances, temporary pacing for symptomatic bradycardia, antibiotic therapy for the underlying infection, and consideration of permanent pacemaker implantation in refractory cases.. Cardiac manifestations may include myocarditis, pericarditis, arrhythmias, conduction blocks and cardiac failure. We are reporting a case of leptospirosis causing complete heart block in a previously healthy young gentleman.

Introduction

Leptospirosis is considered to be a widespread zoonotic disease globally, particularly in tropical and subtropical regions where conditions favor the survival and transmission of the causative bacteria, Leptospira spp. The true prevalence of leptospirosis is difficult to estimate due to underreporting and misdiagnosis in many parts of the world. However, it is believed to be a significant cause of morbidity and mortality, especially in regions with poor sanitation and hygiene practices.[1]

Severe infection with leptospirosis may cause multiorgan failure like pulmonary haemorrhage, acute kidney injury, neurological complications as well as cardiac involvement. Cardiac manifestations may include myocarditis, pericarditis, arrhythmias, conduction block and cardiac failure.[2]

One rare but serious complication of leptospirosis is the occurrence of complete heart block. Complete heart block is a conduction system disorder of the heart that results in the failure of electrical impulses to transmit from the atria to the ventricles. This can lead to symptoms such as dizziness, syncope, or even sudden death if not promptly managed.[3]

A cross sectional study done in India shown that ECG abnormalities may predict the development of acute respiratory distress syndrome, renal failure requiring dialysis, multiorgan dysfunction syndrome and prolonged hospital stay.[1-2] Therefore, it is important for a clinician to be aware of cardiac complications from leptospirosis so that appropriate measures can be taken to improve the morbidity and mortality.

Case studies and medical reports have indicated that leptospirosis can be a rare yet significant cause of complete heart block. This may be due to the direct effects of bacterial infection on cardiac tissues or due to the body's immunological response to the infection. However, the exact mechanisms linking leptospirosis and complete heart block require further investigation.

Case

This is a case of 25-year-old gentleman, a non-smoker, with no known medical illness who was referred from a district hospital for further management of severe leptospirosis complicated with complete heart block secondary to myocarditis, acute kidney injury and acute liver injury.

He initially presented to the district hospital with complaint of epigastric pain for five days associated with fever, headache, yellowish discoloration of sclera, bilateral eye redness, lethargy, myalgia and fainting episodes. Otherwise, there were no diarrhea and vomiting. There were also no chest pain, palpitation and shortness of breath. He was previously well. He is an immigrant, travelling to Malaysia for odd jobs. There were rats found around his house.

During the admission in the district hospital, he was hypotensive requiring double inotropes. ECGs done noted persistent 3rd degree heart block with multiple significant ventricular standstill despite no electrolytes abnormalities. Cardiac biomarkers sent were also negative. He also developed multiple episodes of syncopal attack while in ward. He was subsequently admitted to Critical Coronary Unit (CCU) for percutaneous temporary pace maker and close monitoring. Leptospira serology IgG and IgM were positive. While in CCU, he had developed one episode of breaktrough seizure requiring elective intubation.

He was subsequently referred to our tertiary hospital for further management. Noted that his renal function was worsening with increasing creatinine from 150 to 749 with metabolic acidosis and anuria thus intermittent hemodialysis was initiated. His liver enzymes were also worsening with worsening of coagulation profile.

Abdominal Ultrasound noted increased in liver echogenicity and moderate ascites with no evidence of abscess and intraabdominal collection. He has normal kidney size bilaterally with no evidence of obstructive uropathy.

Echocardiogram noted Ejection Fraction 65% with normal chambers size and no evidence of ventricular hypertrophy.

He was managed with IV Ceftriaxone 2g daily and T Doxycycline 100mg twice daily and has shown a good response in terms of improving septic parameters and decreasing inotropic requirements after about one week. His liver enzymes were returning to normal values and he was able to wean off from hemodialysis. He was able to be extubated. However, he had persistent complete heart block

despite improving general conditions so he was planned for a permanent pacemaker insertion.

Results

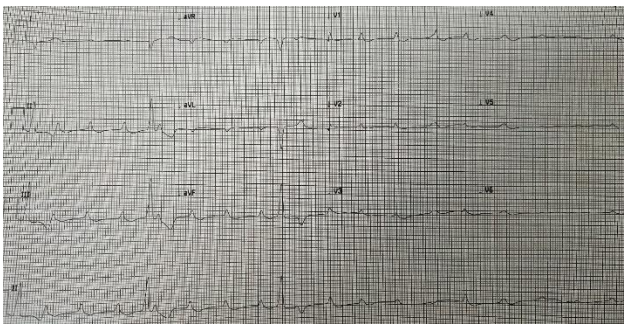

Figure 1: First ECG showing complete heart block and ventricular standstills

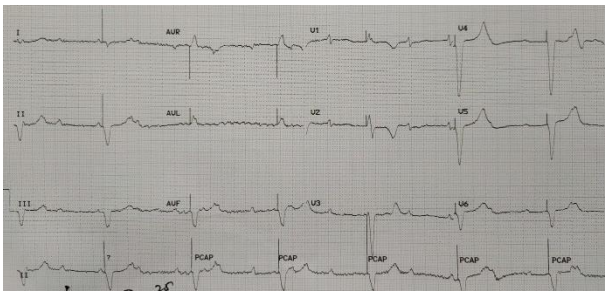

Figure 2: ECG after Temporary Pace Maker insertion

Discussion

Leptospirosis is a well-known zoonosis caused by a spirochete of the genus Leptospira. Weil's syndrome was described in 1886 which consists of jaundice, splenomegaly, renal dysfunction, conjunctivitis and skin rash and few years later the causative organism was found by Inada which described the organism as Spirochaeta which is now known as leptospirosis.[4]

Leptospirosis can be found throughout the world but the prevalence tends to be higher in tropical regions with high rain fall. However, despite traditional belief, recent reports indicated that it is also currently emerging as an important infection in developed countries.[5] Risk factors of leptospirosis may include workers in agricultural sector, sewerage workers, livestock handlers and people with chronic disease and open skin wounds. Incubation period is usually 10 days with a range of 2 to 30 days.

Most cases are usually self-limited, by but some patients may develop fatal complications with severe disease. Patients may present with mild influenza like illness, Weil's syndrome characterized by jaundice, renal failure, pulmonary haemorrhage and myocarditis, meningitis and pulmonary haemorrhage with acute respiratory distress syndrome.

World Health Organization has introduced Faine's criteria for diagnosis of leptospirosis, based on clinical history and epidemiological history supported by laboratory parameters.[5-6] Our patients demonstrated a score of 30 which are headache (2), fever (2), conjunctival suffusion (4), jaundice (1), rainfall (5), animal contact (1) and positive ELISA IgM (15) which mean that he falls into presumptive diagnosis of leptospirosis.

Cardiac involvement is one of the known complications of leptospirosis. A study conducted in India had found that 56% of leptospirosis patients had cardiac involvement and 52% of them had ECG abnormalities.[7] Among cardiac involvement can be found in leptospirosis may include myocarditis, heart failure, atrial fibrillation, atrioventricular conduction blocks and non-specific ventricular repolarization abnormalities. Our previously healthy young gentleman presented with complete heart block as one of the complications of leptospirosis. From our literature review, this is the first reported case of leptospirosis presented with persistent complete heart block requiring pacemaker insertion.[8]

Pathophysiology of cardiac involvement in leptospirosis is currently poorly understood. Post mortem studies has shown myocardial

inflammation and vasculitis in leptospirosis patients.[4] Echocardiographic evidence of myocardial dysfunction has not been adequately described which is also demonstrated in our patient which shown normal echocardiography.

The clinical implications of CHB in leptospirosis are significant, as it can result in hemodynamic instability, syncope, and sudden cardiac death if left untreated. Early recognition and prompt management of CHB are essential to prevent adverse outcomes. However, diagnosing CHB in the context of leptospirosis may pose challenges, particularly in resource-limited settings where advanced cardiac monitoring and specialized care may not be readily available. Clinicians should maintain a high index of suspicion for cardiac complications, including CHB, in patients with severe leptospirosis, especially those presenting with unexplained syncope or hemodynamic instability.[9-12]

It is important to note that leptospirosis with cardiac involvement, either demonstrated by ECG or clinically, tends to predict poor outcome with multi organ involvement.[13-14] This is also presented in our patients in which he had worsening renal function in ward that requires intermittent renal replacement therapy.

Severe leptospirosis requires adequate antibiotics together with careful management of renal, hepatic, hematologic and central nervous complications.[15-16] First line antibiotics for leptospirosis include IV Penicillin, Doxycyline, Ampicillin and Ceftriaxone. It's important to tailor treatment to the individual patient based on their clinical presentation, disease severity, and response to therapy. Close monitoring and timely intervention are crucial for improving outcomes in patients with CHB complicating leptospirosis.[17-19]

Patients should also be constantly monitored for any cardiac arrhythmias, renal function abnormalities as well as deranged liver enzymes. In our patient, despite the infection is resolving, the complete heart block persist thus necessitate the need of Permanent Pacemaker insertion.

Conclusion

Despite common presentation of leptospirosis with cardiac involvement is common, the presentation of complete heart block as a complication alone is rare. As currently there is no definite diagnostic method, high level of suspicion is required so that appropriate treatment of leptospirosis and supportive management of its complication can be constituted early.

Conflict of Interest

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