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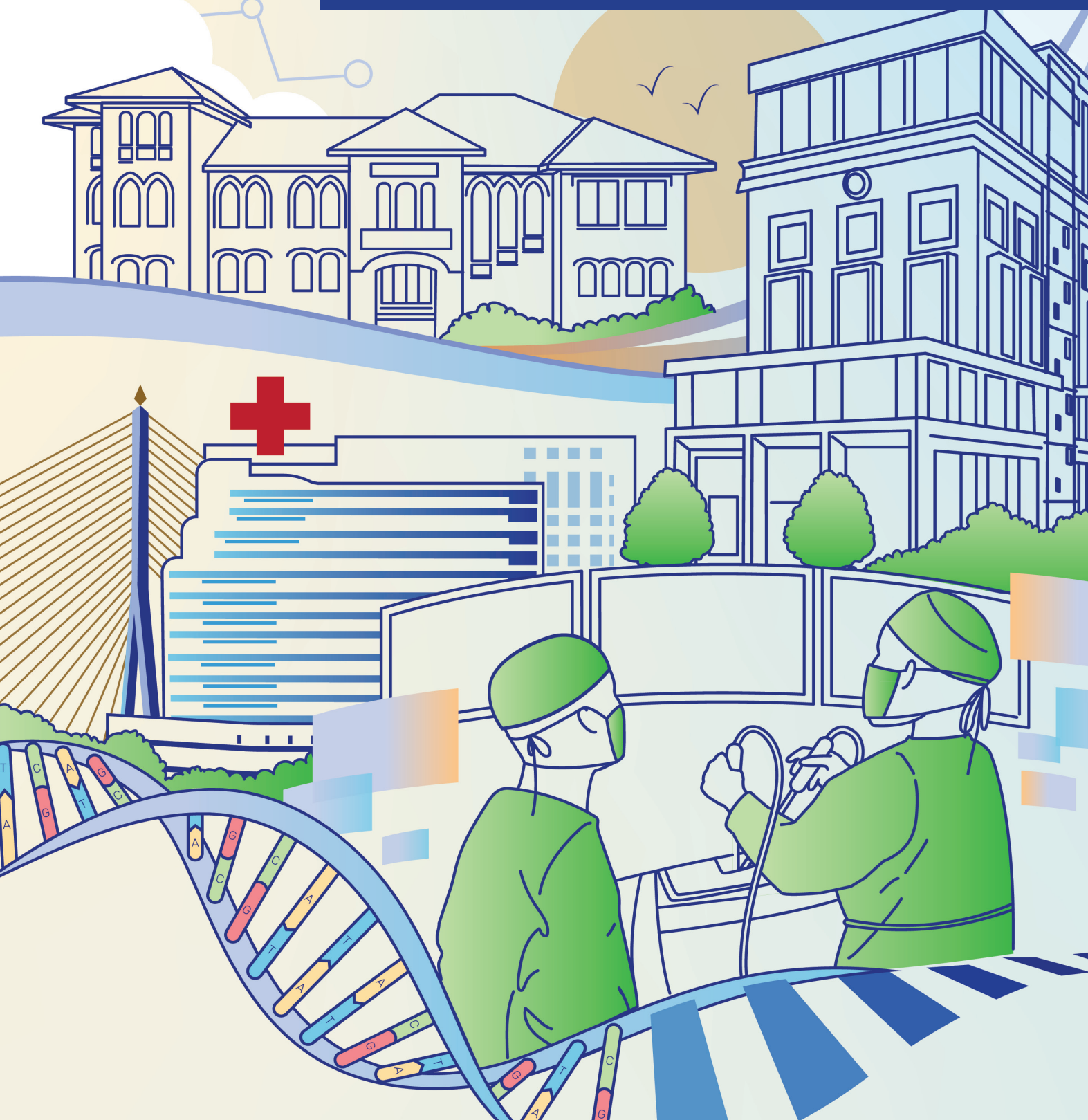

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ORIGINAL ARTICLES

CASE REPORT

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Original Article

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Efficacy of Novel Blue Silver Nanoparticles Hydrogel versus Reference Hydrogel: a Prospective Randomized Controlled Trial for Acute and Chronic Wound Management

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ABSTRACT

OBJECTIVE: Hydrogel dressings are commonly used as wound dressings and provide a moist environment in the wound area. Silver nanoparticles (AgNPs) are widely considered as useful therapeutic agents for the prevention and eradication of wound colonization by microorganisms. Recently, there has been a hydrogel dressing that consists of carboxymethyl cellulose hydrogel with blue AgNPs. It provides a moist and optimal healing environment for pain relief and protection from infection. This study aimed to evaluate the use of blue AgNPs hydrogel in acute and chronic wound care.

METHODS: From September 2017 to September 2018, 62 wound sites from 39 patients were randomized to receive daily application of either the blue AgNPs hydrogel (31 wound sites from 20 patients) or a commercially available reference hydrogel (31 wound sites from 19 patients). The primary outcome was wound area reduction, expressed as the wound healing rate; secondary outcomes included pain intensity and infection prevention.

RESULTS: The blue AgNPs and reference hydrogels were comparable in terms of wound area reduction and pain scores during the changing of wound dressings, with no significant differences ($p > 0.05$). Patients in the blue AgNPs hydrogel group showed low rates of bacterial infection for both gram-negative and gram-positive strains; in particular, there was almost complete prevention of infection by gram-positive strains at day 21 after treatment initiation.

CONCLUSION: The blue AgNPs hydrogel may be effective in preventing bacterial infections of both gram-negative and gram-positive strains at 14–21 days. Thus, the blue AgNPs hydrogel is a promising material for therapeutic applications in wound care.

KEYWORDS: antimicrobial agents, hydrogel, nanoparticles, wound dressing

INTRODUCTION

Wound healing, as a protective function of the skin upon injury, is a complex process, whereby damaged tissue is restored by the formation of connective tissue and regrowth of the epithelium[1]. For acute wounds, the wound healing process is completed in a timely fashion, whereas chronic wounds are those that fail to heal within 4 weeks[2].

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A wound dressing can be directly applied to the wound, enhancing the healing process. Various types of wound dressing materials, such as films, foams, hydrogels, and hydrocolloids, have been employed for the treatment of skin ulcers. In the management of acute and chronic wounds, a range of materials can be utilized to stimulate wound healing and establish an optimal environment for tissue regeneration. Commonly used materials for acute and chronic wounds include traditional dressings, hydrocolloids, hydrogels, foams, alginates, antimicrobial dressings, and negative pressure wound therapy[3]. Hydrogels are advanced wound dressings composed of water-insoluble hydrophilic materials, which are typically synthetic or composite polymers. Their soft and elastic nature facilitates easy application and promotes epithelium progression by maintaining a moist environment. Hydrogels are an optimal choice for wound dressings as they effectively create a moist environment at the wound site, assist in the removal of wound exudates, prevent infection, and establish a suitable environment for tissue regeneration[4-6]. According to Dumville et al., hydrogel dressings have demonstrated promising potential in accelerating the healing process of lower grade diabetic foot ulcers when compared to basic wound contact dressings[7]. Shu et al. highlighted three key advantages of using hydrogel dressings for burn wound treatment. Firstly, hydrogel dressings possess excellent absorbent properties, capable of absorbing a significant amount of wound exudate relative to their dry weight. This feature helps maintain a moist environment during wound healing, particularly beneficial for dry wounds. Secondly, the versatility of hydrogel dressings allows for customization to suit the specific shape and condition of the wound. Lastly, hydrogel dressings provide non-adhesive adherence to wounds, thereby reducing both temperature and pain. Additionally, their transparent nature allows for wound observation[8].

Silver nanoparticles (AgNPs) have attracted interest for use in clinical applications because of potential biological properties, including antibacterial activity and wound healing efficacy. When AgNPs are applied to a wound, they attach to and penetrate the cell membrane of bacteria and preferentially attack the respiratory chain and cell division, ultimately leading to cell death[9-10]. Several reports have demonstrated that the antibacterial potency of AgNPs is size-dependent[11-12]. Small AgNPs are more likely than large AgNPs to cross the cell membrane and enter the cell, increasing the toxicity to bacteria. Smaller AgNPs have a larger specific surface area; therefore they exert stronger antibacterial effects than larger AgNPs[13]. Although numerous studies on the efficacy of hydrogel with AgNPs have been published[14-16], information on a hydrogel with AgNPs produced and developed in a developing country is lacking.

Recently, a novel stable hydrogel that composed of a patented carbomer, blue AgNPs, glycerol, and water, was developed in Thailand. The blue AgNPs hydrogel is prepared by dispersing carbomer, bio-cellulose powder, and glycerol in distilled water and adding blue AgNPs to the dispersion at a concentration of 30 ppm. The carbomer polymer chosen for the hydrogel preparation is a self-wetting polymer, providing moderate to high viscosity as well as stabilizing and bioadhesive properties for hydrogel applications. The carbomer can also imbue amorphous hydrogels with moisturizing and absorption properties that facilitate the autolysis and softening of dead tissue. Thus, the blue AgNPs hydrogel was designed to optimize a moist wound environment, providing pain relief during wound care, and to prevent wound colonization by microorganisms.

Pain during the changing of the wound dressing is another important issue. Some patients undergo multiple painful changes during their wound care, which can cause unfavorable physiological and emotional effects. A hydrogel dressing can provide pain relief due to an evaporative cooling effect and create a moist environment, which soothes exposed nerve endings in the skin[17]. Moreover, silver dressings may relieve pain by providing a moist and protective air-free wound environment and can be left in place for some period of time[18].

This study was performed to investigate the efficacy of the blue AgNPs hydrogel compared to a reference hydrogel. The reference hydrogel was selected as the comparative group due to its shared substrate characteristics with advanced wound dressings, similar to the blue AgNPs hydrogel being evaluated. By comparing the efficacy of these hydrogels, the study sought to assess their relative performance. It is worth noting that other advanced wound dressings, such as hydrocolloid, hydrofiber, and foam, have been shown to potentially accelerate wound healing, but this particular study focused on comparing the substrate properties of the products. Additionally, the incorporation of blue AgNPs into the hydrogel serves the purpose of providing infection protection. Specifically, the aim of this study was to investigate the clinical efficacy of the blue AgNPs hydrogel in terms of wound healing, pain intensity, and antimicrobial prevention in acute and chronic wounds.

METHODS

This prospective study evaluated the effectiveness of the blue AgNPs hydrogel as a primary aid for acute and chronic wounds compared with that of a reference material. This study was conducted in accordance with the Helsinki Declaration of Human Rights and approved by the Research Ethics Committee of the Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Thailand (study code 046/60). This study was also registered at Thai Clinical Trials Registry (TCTR), number TCTR20230623001.

Recruitment was conducted by attending physicians and nursing staff at the Outpatient Wound Clinic of the Department of Surgery at Vajira Hospital, Thailand, from September 2017 to September 2018. All participants were required to be >10 years of age and have acute or chronic partial- or full-thickness wounds; wounds due to thermal burns and accidental injury were included. Patients who were pregnant, allergic to hydrogel or silver, had a compromised immune system, or had any other connective tissue disease were excluded. Infected wounds with frank pus or necrotic tissues were also excluded.

Once written informed consent was obtained, wound sites were randomly stratified to receive the blue AgNPs hydrogel or the reference hydrogel (as control) using a computerized random number sequence-generating program. Both treatments were applied according to the manufacturer's instructions, followed by standard wound care, typically consisting of cleaning, debridement, and dressing application once daily. Patients underwent dressing changes and were followed up prospectively until full healing or 21 days (figure 1).

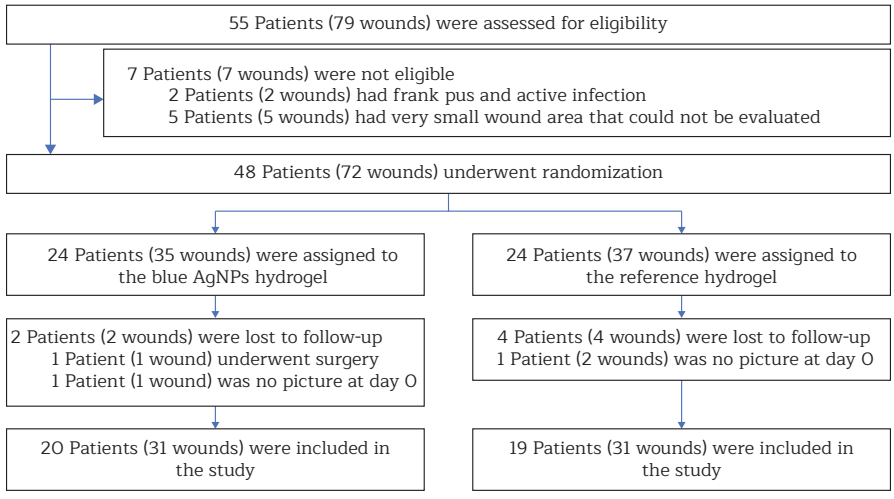

Figure 1 Flow diagram of a single trial of the blue AgNPs hydrogel and the reference hydrogel for acute and chronic wound management. The diagram illustrates a single-center trial with parallel randomized trial of two groups.

The blue AgNPs hydrogel (Novatec Healthcare, Samut Prakan, Thailand) was used as the experimental material. The dressing consisted of carboxymethyl cellulose polymer, blue AgNPs, glycerol, and water. The size- and shape-dependent antibacterial activities of the blue AgNPs hydrogel have been measured using optical density and fluorescence intensity, and their absorbency has been measured with an ultraviolet spectrophotometer. Additionally, characterization results obtained through transmission electron microscopy analysis have documented the different sizes (40–100 nm) and shapes (spherical, cuboid, and planar) of the blue AgNPs hydrogel[19]. The blue AgNPs hydrogel was sterilized by autoclaving in aluminum tubes. A commercially available carbomer-based hydrogel (IntraSite®; Smith & Nephew, Watford, UK) was used as the reference material. IntraSite® gel is composed of 3% carboxy-methylcellulose polymer, 77% water, and 20% propylene glycol. The water in the hydrogel only partially hydrates the polymer, allowing it to maintain its absorptive capacity. As a result, the gel effectively absorbs excess exudate from the wound site, reducing the likelihood of leakage[20].

The primary outcome was wound area reduction, expressed as the wound healing rate. The wound area was evaluated on days 0, 7, 14, and 21 after treatment initiation[21-22]. All assessors were blinded to treatment group allocation prior to measuring the wounds. The wound area was measured by three well-trained practitioners using a centimeter ruler and the scratch wound healing assay, which relies on ImageJ[23-24]. The mean wound area across three practitioners was used for calculation as the percentage of wound area reduction as follows:

$$\% \text{ wound area reduction} = \frac{Ao - At}{Ao} \times 100\%,$$

where *Ao* is the original wound area and *At* is the area of the wound at the time of the observation.

Secondary outcome measures included pain intensity during dressing changes and infection prevention. Pain intensity during dressing changes on days 0, 7, 14, and 21 was assessed using a 10-point visual analogue scale, whereby a score of 0 indicated no pain and a score of 10 indicated severe pain[18,25].

The microbiological flora was sampled using wound surface swabs obtained during dressing changes on days 0, 7, 14, and 21. Bacteria were identified and quantified using standard microbiological techniques. The wound swab was cultured to identify microbial infections using colonization, graded as 1+ (10^2–10^3 CFU/g), 2+ (10^3–10^4 CFU/g), or 3+ (10^5 CFU/g), according to the bacterial growth on a culture plate[26-27].

All values are expressed as mean ± standard deviation, and statistical analyses were performed using SPSS version 18.0 (IBM Corp., Armonk, NY, USA). Differences between treatment groups were evaluated using the Student t-test for data with normal distribution and the Mann-Whitney U test for data with non-normal distribution. p-values < 0.05 were considered statistically significant.

RESULTS

A total of 62 wound sites from 39 patients (age, 57 ± 19 years; range, 14–84 years) were enrolled. The majority of patients had thermal burns and accidental injuries. The baseline characteristics of the enrolled patients are presented in Table 1. In total, 31 wound sites from 20 patients were randomized to receive the blue AgNPs hydrogel and 31 wound sites from 19 patients were randomized to receive the reference hydrogel.

Table 1 Demographics and clinical baseline characteristics

Characteristics	Blue AgNPs hydrogel	Reference hydrogel	P-value
Patients, n	20	19	
Age, years	59 ± 3	54 ± 4	0.317
Sex, F/M	6/14	9/10	
Comorbidities			
Diabetes, n	12	8	
Hypertension, n	9	5	
DLP, n	2	1	
CAD, n	2	2	
Etiology (sites), n (area; cm^2)	31 (8.3±2.3)	31 (4.9±1.1)	0.197
Acute wound (sites), n (area; cm^2)	24 (8.3±2.8)	23 (5.4±1.4)	0.361
Flame burn (sites), n	12	10	
Accident (sites), n	10	10	
Abrasion (sites), n	2	3	
Chronic wound (sites), n (area; cm^2)	7 (8.4±3.7)	8 (3.6±1.1)	0.202
Location (sites), n			
Scalp	2	–	
Neck		1	
Chest	–	2	
Back	1	1	
Leg	11	14	
Forearm	1	6	
Buttock	3	–	
Foot	8	6	
Hand	5	1	

Abbreviations: AgNPs, silver nanoparticles; CAD, coronary artery disease; cm^2, square centimeters; DLP, dyslipidemia; F, female; M, male; n, number of patients

Overall, the two groups showed no significant differences in wound area reduction or residual wound healing rate. Both treatments showed reduced wound area in a time-dependent manner (figure 2). In the blue AgNPs hydrogel group, the area of acute wounds decreased from 8.3 ± 2.8 cm^2 on day 0 to 3.2 ± 2.2 cm^2 (61% wound area reduction) on day 7. This reduction continued gradually, reaching 0.7 ± 1.5 cm^2 (91% wound area reduction) by day 21. Conversely, in comparison, chronic wounds exhibited delayed wound closure. The area of chronic wounds decreased from 8.4 ± 3.7 cm^2 on day 0 to 5.9 ± 3.2 cm^2 on day 7, indicating partial wound closure (30% wound area reduction). Nevertheless, by day 21, significant healing was observed in chronic wounds, with a wound area reduction of 75%. In the reference hydrogel group, the area of acute wounds decreased from 5.4 ± 1.4 cm^2 on day 0 to 2.2 ± 0.8 cm^2 on day 7. This reduction continued gradually, reaching 0.3 ± 0.1 cm^2 (94% wound area reduction) by day 21. Regarding chronic wounds in this group, the area decreased from 3.6 ± 1.1 cm^2 on day 0 to 2.0 ± 0.63 cm^2 on day 7, indicating partial wound closure (42% wound area reduction). By day 21, substantial healing was observed in chronic wounds, with a wound area reduction of 83% (figure 3A).

There was no significant difference in the reduction of pain intensity during dressing changes between the two treatment groups. Patients in both the blue AgNPs hydrogel group and the reference hydrogel group exhibited a consistent decrease in pain scores over time for both acute and chronic wounds. In the acute wound subgroup treated with the blue AgNPs hydrogel, the mean pain score at day 14 was minimal (range, 0.25–0.71), and by day 21, pain during dressing changes had completely subsided. Similarly, in the reference hydrogel group, the mean pain scores at day 14 and 21 were negligible (range, 0.05–0.29 and 0.04–0.22 respectively) (figure 3B). In the case of chronic wounds, both treatment groups displayed a declining trend in pain scores, without any significant differences.

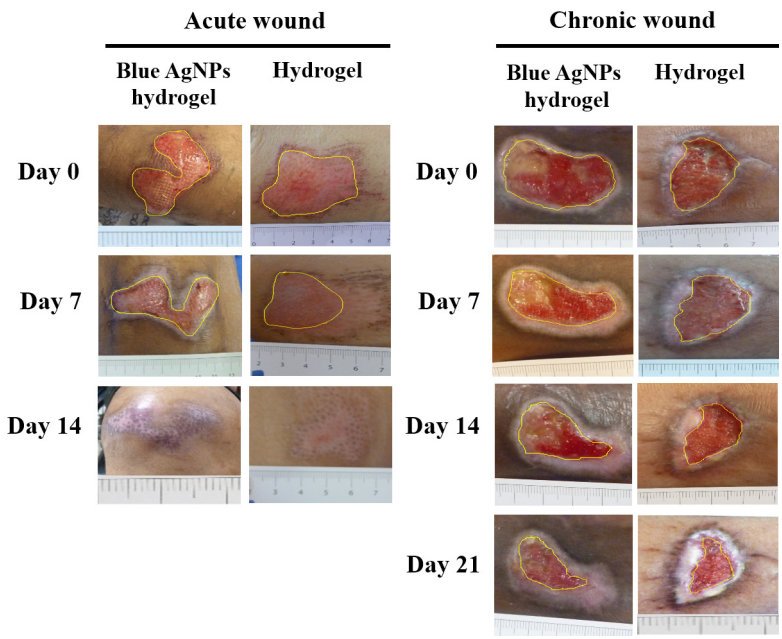

Figure 2 Representative photographs showing wound closure in acute and chronic wounds treated with the blue silver nanoparticles hydrogel or the reference hydrogel. The wound area, outlined in yellow, was assessed using ImageJ during dressing changes on days 0, 7, 14, and 21 after treatment initiation.

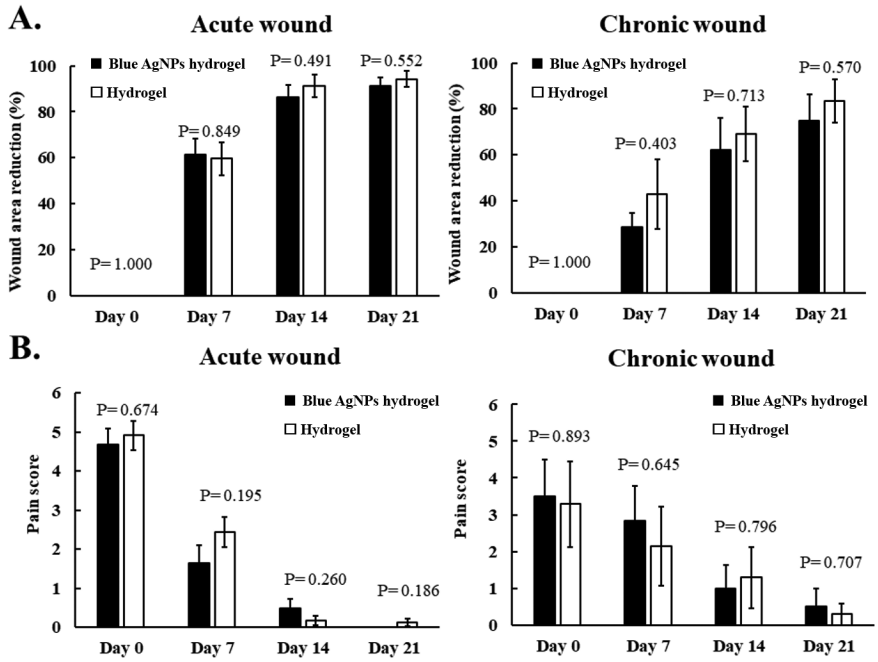

Figure 3 Wound area reduction and pain intensity during dressing changes on days 0, 7, 14, and 21 for acute and chronic wounds. (A) Both the blue silver nanoparticles hydrogel and reference hydrogel induced wound closure over time in acute (n = 24 and n = 23, respectively) and chronic wounds (n = 7 and n = 8, respectively), without significant group differences. (B) Both the blue silver nanoparticles hydrogel and reference hydrogel reduced pain intensity scores over time, with a greater decrease for acute wounds (n = 24 and n = 23, respectively) than for chronic wounds (n = 7 and n = 8, respectively) on days 14 and 21. All data are expressed as mean ± standard deviation.

Regarding infection prevention, the blue AgNPs hydrogel group demonstrated low rates of bacterial infection for both gram-negative and gram-positive strains, as shown in Table 2. In particular, gram-positive strains were more susceptible to prevention than gram-negative strains, with almost complete prevention at day 21 after treatment initiation. Importantly, no clinical signs of wound infection, such as the presence of frank pus or increased pain, were observed in either group. Furthermore, the wounds in both groups exhibited a gradual healing process.

DISCUSSION

This prospective study is the first to report the efficacy of a blue AgNPs hydrogel, produced and developed in a developing country, in wound healing and infection prevention in acute and chronic wounds. The study results show that the blue AgNPs hydrogel can induce complete wound healing in acute and chronic wounds in as short as 14 days. Generally, acute wounds tend to heal within 3 weeks, whereas chronic wounds tend to persist for a minimum of 3 months after the injury[28]. In the present study, 25 (80%) of 31 sites treated with the blue AgNPs hydrogel had completely healed by day 14. This result is similar to the re-epithelialization results observed with chitosan cross-linked materials, for which the rate of wound healing was approximately 82.5% at day 14[29]. The blue AgNPs hydrogel matrix has a cross-linked hydrophilic biopolymer and high water content, providing good conditions for maintaining a humid environment around the wound interface prior to immune cell activation and increasing the speed of wound healing[30-31]. In the present study, the observation period was 21 days because wound area reduction and complete wound healing could be observed within 14–21 days.

Additionally, the time for re-epithelialization using wound dressings with AgNPs has been widely studied. A previous multicenter study demonstrated a significantly faster healing time with a silver-containing soft silicone foam dressing than with standard care; the average time to complete healing was 13.44 days for 75% of patients treated with the foam[32]. Similar re-epithelialization results were shown for AgNPs embedded into a chitosan-polyethylene glycol (PEG) hydrogel, as a substantial layer of dermal skin and mixed pattern of collagen were detected in the AgNPs-impregnated chitosan-PEG hydrogel group at day 14[14].

Table 2 Comparison in bacterial colonization between different wound dressing biomaterials

Bacterial stain	Blue AgNPs hydrogel					Reference hydrogel				
	Wound site (n)	Day				Wound site (n)	Day			
		0	7	14	21		0	7	14	21
Gram-negative										
Acinetobacter baumannii	2	–	–	1+	1+	2	2+	–	–	1+
Escherichia coli	3	1+	–	–	1+	2	1+	1+	1+	–
Klebsiella pneumoniae	4	–	–	1+	1+	1	–	3+	1+	2+
Pseudomonas aeruginosa	1	–	1+	1+	–	1	1+	2+	1+	1+
Gram-positive										
Corynebacterium striatum	2	1+	–	–	1+	1	–	–	2+	1+
Enterobacter cloacae	1	–	1+	–	–	1	–	2+	2+	–
Staphylococcus aureus	3	1+	–	–		5	–	1+	–	1+
Staphylococcus caprae	2	–	1+	1+	–	1	–	–	1+	1+
Staphylococcus epidermidis	6	1+	1+	1+	–	3	1+	1+	–	–
Staphylococcus haemolyticus	7	1+	1+	–	–	2	1+	1+	–	–
Staphylococcus hominis	1	–	3+	–	–	1	–	–	3+	–
Staphylococcus warneri	1	–	1+	–	–	1	–	–	3+	–

Abbreviations: AgNPs, silver nanoparticles; CFU/g, colony-forming units per gram; n, number of wound sites
Microbial colonization was graded according to bacterial growth on a culture plate (–, no growth; 1+, 10^2–10^3 CFU/g; 2+, 10^3–10^4 CFU/g; 3+, 10^5 CFU/g).

As a wound management outcome, pain reduction plays a role in reducing patient anxiety and leads to improved compliance and participation in the treatment[33]. Dried-out dressings and aggressive adhesives are most likely to cause pain during dressing removal. Choosing the appropriate dressing can maintain the moisture balance, providing adequate moisture without causing maceration or desiccation, both of which impede healing[34]. In the present study, the mean pain intensity score during dressing change was not significantly different between the two groups. The pain scores were similar for acute and chronic wounds at late stages; however, a significantly faster reduction was noted for acute wounds.

Microbial infections caused by bacteria and fungi are a serious health problem, especially with respect to the wound-healing process, and can lead to tissue morbidity and sepsis, depending on the severity of the infection[35]. Hydrogels loaded with AgNPs offer a useful starting point in engineering wound dressing materials. AgNPs have potential against a broad range of bacteria and fungi because of their ability to generate reactive oxygen species and bind to bacterial cell membranes, thus leading to membrane damage[36-37]. *Staphylococcus aureus* and *Pseudomonas aeruginosa* are the most common bacteria isolated from chronic wounds[38]. The blue AgNPs hydrogel showed the maximum activity against resistant bacteria isolated from wounds, preventing bacterial infection and accelerating wound healing at day 21.

In summary, the blue AgNPs hydrogel and the reference gel demonstrated similar results in terms of wound healing and pain reduction. However, the blue AgNPs hydrogel demonstrated notable advantages over the reference hydrogel, specifically in its ability to effectively prevent bacterial infections, especially those caused by gram-positive strains. Furthermore, the blue AgNPs hydrogel exhibited no adverse clinical effects. These results indicate that the blue AgNPs hydrogel can play a role in infection prevention and has application prospects in wound care.

A limitation of this study is that it included only a small number of patients from a single center with a variety of wounds in the same or different patients. Additionally, the duration time for wound investigation was short (3 weeks). Moreover, we did not use biopsy for evaluations of wound infection or colonization. Thus, future studies that are multicenter in nature, with a longer examination period (for at least 8–12 weeks), with both treatment materials applied to the same wound (by dividing the wound into two parts), and with tissue biopsy are needed for more refined data.

CONCLUSION

Our findings conclude that the blue AgNPs hydrogel exhibits considerable promise as a therapeutic material in wound care applications. The results of this prospective study demonstrate the ability of the innovative blue AgNPs hydrogel to enhance wound healing, alleviate pain, and prevent infection. These positive outcomes underscore the promising utility of the innovative blue AgNPs hydrogel in clinical wound care. Based on these findings, we believe that the blue AgNPs hydrogel has potential for clinical utilization in the field of wound care. Further research and larger-scale studies should be conducted to substantiate these results and support the future widespread adoption of the blue AgNPs hydrogel in clinical practice.

CONFLICT OF INTEREST

The authors have no financial interest in any of the products or devices mentioned in this article.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions.

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Original Article

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Survey of the Undergraduate Health Status during the Outbreak of COVID-19: a Case Study of an Urban University in Thailand

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ABSTRACT

OBJECTIVE: This study aimed to survey the health status of undergraduates during the outbreak of COVID-19 in Thailand.

METHODS: This cross-sectional descriptive study recruited undergraduate students from a university in an urban area in Thailand. The survey was conducted online by the electronic mailing of questionnaires to the studied participants. The daily health behaviors questionnaire, the 28-item General Health Questionnaire (Thai GHQ28), and the participants' satisfaction with the online learning questionnaire were used in this study.

RESULTS: There was a total of 390 undergraduate students who participated and responded to the survey. The results showed they scored poorly in the areas of controlling food consumption, such as salt and sweet intakes, and exercise or continuous movement. The majority of the surveyed students (303 out of 390 students or 77.7% of the total) have shown a normal health status in response to the Thai GHQ28 except for social dysfunction. There was a strong association between daily health behaviors ($p = 0.015$) and general health ($p = 0.019$) status with the online satisfactory level.

CONCLUSION: At-home online learning was found to be directly associated with the health behaviors and the health status of the surveyed students. Based on the findings, counseling centers should be set up to offer advice to students on how to stay healthy and socially connected during the online learning period.

KEYWORDS: COVID-19, health status, online learning, undergraduate

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) pandemic has greatly affected many aspects of society from the economy to health and lifestyle[1]. People are also overly stressed from travel bans and social isolation, taking in too much information about the pandemic, and hoarding household products[2]. According to previous studies[3-4], COVID-19 heavily affects people's mental health as it causes stress and worries that may even lead to depression.

During the first wave of the COVID-19 outbreak in Thailand, the government enacted social distancing rules and began the "Stay Home, Stop the Virus, Help the Nation" policy on March 2020[5]. The enforcement of this policy caused the

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temporary closure of schools, universities, public transportation, big companies, and the prohibition of public events/gatherings. People began to work from home, and educational institutions implemented online learning to prevent gatherings and limit physical interactions to contain the outbreak. The COVID-19 pandemic has put tremendous pressure on the schooling framework across the world to contain the outbreak. It forced educational institutions to move away from traditional, direct teacher-students classroom learning to long-distance, teacher-students online classes.

Prior to the COVID-19 outbreak, online learning had been developing consistently worldwide, as technology and education co-evolved to provide people with the opportunity to acquire new skills[6]. Since the pandemic, online learning has become an integral part of the lives of teachers and students who want to acquire knowledge and new skills. Although online learning allows physical distancing among teachers and students, preventing the spread of the virus as recommended by various health agencies around the world, there are unintended, negative consequences as well. First, it has a negative impact on student's health due to inactivity. Normal physical activities that students have to engage are absent in the online classroom. In addition, these students lack physical interaction with friends in the form of sports or exercise due to home isolation. At the same time, the students consume more food and drinks that contain high amounts of salt and sugar[7-8] which may lead to obesity. Second, online learning has a negative effect on the students' mental health. Because online learning lacks direct human-to-human interaction (i.e., with friends and teachers) and seems to connect just humans to a computer, there is little or no social engagement. In Thailand, due to the first lockdown from March to December 2020, almost all institutions abruptly canceled their classes. For example, universities were forced to shut down for a long period of time. Conventional learning platform shifted enormously to virtual one insofar as it immediately tackled unprecedented situations. Therefore, a great number of students were confronted with challenges as to deal with online activities and adjust themselves to be familiar with online lessons to carry on their studies during the initial lockdown. Previous studies have associated mental health problems with online learning, caused by factors like uncertainties about the mode of examination, and the constant worry about the future[9-10]. In some cases, instructors are not familiar with or are not prepared to teach online which results in poor presentations to the online students[11]. This in turn causes mental stress among students because they do not understand what is being taught. Some students even used prescription drugs to relieve this stress[12]. A student's mental health may also be directly affected by their family's financial issues due to the closure of their family's business. This is supported by the findings which claim that educational outcome is affected by 4 factors: communication, learning facilities, proper guidance, and family stress[13].

Health concept is a multi-faceted construct and identified by four main dimensions: physical, mental, social, and cultural[14]. However, most studies[15-18] only investigated the impact of online learning and psychological disorders. There is still a lack of information on physical and social health and health behaviors which are also important for the undergraduate students to excel in their studies. The objective of this study is to survey the health and health behaviors of students. The study also aims at analyzing the association between daily health behaviors and Thai GHQ28 during the first wave of COVID-19 pandemic in Thailand. These preliminary results will be used to improve the health of students, provide consultation, and prepare students for online classes in the future.

METHODS

This cross-sectional descriptive study was carried out from August to October 2020. The undergraduate students at the university in Thailand were recruited. The recruited students were enrolled and taking classes at the university during the onset of COVID-19 pandemic.

Total population were 1,564. The sample size was calculated for proportions considering a 95% confidence level, 0.05 margin of error and a finite correction for the student population of 371[19]. The inclusion criteria for this study were that each recruit must be an undergraduate student at the university and is willing to participate in the study. There was a 25% quota of each faculty in the sampling with no exclusion criteria. A simple random sampling from the list of students' email addresses was used to recruit the study participants. Initially, the questionnaires were administered to 500 undergraduates via email. At first, merely 20% of emails were returned. With this, the researcher resent the emails every two weeks and urged them to complete the questionnaires. After three months, the number of responses increased.

This study was conducted using questionnaires on two major topics: students' health and students' satisfaction with online learning. The "students' health" topic was subdivided into two categories: daily health behaviors and general health status. The questionnaires were designed to collect basic information to assess the students' health behaviors and the general health status while studying online at home. The daily health behaviors of the participants were evaluated using a questionnaire of the Health Education Division, Ministry of Public Health of Thailand[20]. The reliability of daily health behaviors questionnaire was 0.7. The questionnaire is made up of six items which consisted of consumption (2 items), physical activity (1 items), stress management (1 items), drug addiction (2 items) dimensions, giving a combined total score of 30. The score of 5 is given for each positive health behavior that is practiced 6-7 times per week, and each one that is never practiced is given 1.

The 28-item General Health Questionnaire (Thai GHQ28) of the Department of Mental Health, Ministry of Public Health, Thailand[21] was employed in this study. The reliability of the Thai GHQ28 is 0.8. The questionnaire requests the participants to indicate the status of their health in general over the past few weeks. The questionnaire is subdivided into four behavioral dimensions assigned with a 4-point scale to indicate the following frequencies of experience: not at all, no more than usual, rather more than usual, and much more than usual. These four dimensions are somatic symptoms (items 1-7), anxiety (items 8-14), social dysfunction (items 15-21), and severe depression (items 22- 28). Scores were assigned as follows: not at all = 0, no more than usual = 0, rather more than usual = 1 and much more than usual = 1.

A questionnaire was also developed to assess the participants' satisfaction with the online learning method. The questionnaire comprised of 13 items from the following topics: instructors (5 items), contents (2 items), learning processes (2 items), learning materials and resources (2 items), and measurement and evaluations (2 items). The content validity of the online learning questionnaire was verified by three experts in the field of education. Reliability was performed with 30 undergraduate students in the university having the same characteristics. The reliability of the online learning questionnaire was 0.8. The five-point Likert scale was used to investigate the questionnaire. The scale ranges 5 to 1 from strongly agree to strongly disagree or dissatisfied.

Data were collected between August to October 2020 using Google Forms that were emailed to the students. The data were extracted from the Google Forms and analyzed in SPSS Statistics for Windows, Version 28.0 (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). Each question of the daily health behaviors questionnaire has a maximum score of

5.0. An average score of < 2.9, 3.0-3.4, 3.5-3.9 and ≥ 4.0 was considered to be poor behavior, quite poor behavior, good behavior and very good behavior, respectively. The total score of the daily health behaviors questionnaire was 30.0. An average score of 0-17.9, 18.0-20.9, 21.0-23.9 and 24.0-30.0 was considered to be "poor behavior", "quite poor behavior", "good behavior", and very good behavior, respectively[20]. The minimum score for the Thai GHQ28 general health survey is 0, and the maximum is 28. Total scores of 5 or below was classified as normality, while participants with scores of ≥ 6 were classified as abnormality[21]. Scorings of online learning questionnaire are classified as follows: < 80% indicating dissatisfied and ≥ 80% indicating satisfied. Analyzed data were presented as average, standard deviation, frequencies, and percentages. The association between online learning with the students' daily health behaviors and the students' general health (Thai GHQ28) was established using Chi-square. This study was approved by the Human Research Ethics Committee at the Vajira Hospital (COA 116/2563). Informed consent process was also sent to the respondent online. For confidentiality, the data were anonymized and just the pooled/total outcomes are presented.

RESULTS

A total of 390 undergraduate students participated in this study, composed of 107 medical students, 163 nursing students, 93 sciences and health technology students, and 27 students from non-health sciences majors. The majority of the surveyed subject were females with an average age of 21.4 years. Most of the participants had an average body mass index (BMI) of 21.7 kg/m^2. Almost half of the respondents (46.4%) experienced weight gain from self-weight assessment during online learning at home. The basic profile of the undergraduate students has been shown in Table 1.

Table 1 Basic profile of undergraduate students

Basic characteristics	n	(%)
Sex		
Female	325	83.3
Male	65	16.7
Age (years)		
< 20	218	55.9
20–30	153	39.1
> 30	19	5.0
BMI (kg/m^2)		
< 18.5	91	23.3
18.5–22.9	179	45.9
23.0–24.9	44	11.3
25.0–29.9	58	14.9
> 30	18	4.6
Faculty		
Medicine	107	27.4
Nurse	163	41.8
Sciences and Health Technology	93	23.8
Other	27	7.0
Self-weight assessment while online learning at home		
Increase	181	46.4
Not change	124	31.8
Decrease	85	21.8

Abbreviations: BMI, body mass index; kg, kilogram; m, meter; n, number

The mean total score of daily health behaviors was 21.3 out of 30 (S.D.= 3.4) which indicated that most of them were in good health behaviors. An average score for each item of the daily health behaviors was ranged from 2.7–4.7 out of 5. These data illustrated that the surveyed subjects performed poorly in controlling food, salt and sweet intakes, and also fared poorly in exercise or continuous movement until feeling tired. On the other hand, they scored excellent on items of no smoking or inhaling cigarette smoke and no alcohol drinking. The details on health behaviors in the daily lives of the surveyed undergraduate students during the COVID-19 pandemic are depicted in Table 2.

The majority of the surveyed students (77.7%) have a normal health status as indicated by the scores in the total Thai GHQ28 questionnaire. More than two-thirds of the participants (66.7%, 67.4%, and 83.3%) did not exhibit the symptom of somatic, anxiety, and severe depression, respectively. However, about two-thirds of the studied subjects (68.7%) experienced some form of social dysfunction. The details of the general health status of the surveyed undergraduate students are shown in Table 3.

Table 2 Assessment of health behaviors in daily life of the surveyed undergraduate students during the COVID-19 virus pandemic

Items	Mean (SD)	Meaning
1. Controlling of food intake, controlling of salinity and sweetness food and salty at every meal	2.7 (1.3)	poor
2. Always eat fresh fruits and vegetables at least half a kilogram a day	3.0 (1.2)	quite poor
3. Exercise or continuous movement until feeling tired	2.7 (1.1)	poor
4. Stress management by always being optimistic	3.7 (1.0)	good
5. No smoking or inhale cigarette smoke	4.6 (0.9)	excellent
6. No alcohol drinking	4.7 (0.8)	excellent
Total score	3.6 (0.5)	good

Abbreviation: SD, standard deviation

Table 3 General health status of the surveyed undergraduate students

Dimension of symptoms	n	(%)
Somatic symptom		
No	260	66.7
Yes	130	33.3
Anxiety		
No	264	67.4
Yes	126	32.6
Social dysfunction		
No	122	31.3
Yes	268	68.7
Severe depression		
No	325	83.3
Yes	65	16.7
Total		
Normality (score < 6)	303	77.7
Abnormality (score ≥ 6)	87	22.3

Abbreviation: n, number

The majority of the participants (305 from 390 or 78.2%) reported dissatisfaction with the online class experience, while only around one-fifth (21.8%) felt satisfied. When analysis subgroups, it was found the most dissatisfaction with the online class in undergraduate student who had a good behavior and normality health status.

The results obtained from Chi-square analyses indicated the relationship between satisfactory of online learning with the daily health behaviors and general health status of the surveyed students. The association was found to be statistically significant for both variables (p = .015 and p = .019 respectively). These data were presented in Table 4.

DISCUSSION

The findings of this study reveal that during the COVID-19 pandemic, most students had normal average BMI. However, almost half of the students (46.4%) reported weight gain during the homebound online study and the rest were either unchanged (31.8%) or decreased in weight (21.8%) (table 1). This result of weight gain was in accordance with the poor score in the item of controlling food consumption (table 2). On the other hand, their eating behaviors were in the acceptable range for consuming fruit and vegetables, good for stress management, and excellent in avoiding smoke and alcohol (table 2). These results indicated that the undergraduates maintained healthy lifestyle pertinent to stress management, smoking, and alcohol consumption. Such lifestyle lasted approximately eight months during the online platform.

Further analysis to find reasons for the poor daily health behaviors of the surveyed students in terms of foods, salt and sweet as well as low or lack of physical activities are discussed as follows. As soon as the government announced the lockdown and the physical distance policy, people may begin to excessively purchase and store household goods. They might be worried that they would not have enough food to eat and were too scared to go to buy food at the stores, afraid of being infected with the virus. This is in agreement with previous studies which reported that people were aware and scared of being under lockdown without enough food items to survive, and therefore they tended to buy household products including food in excessive amounts during the pandemic[2,22]. These long shelf-life food products are known to be highly processed, calorie-dense and with high salt, sugar and preservatives[7,8,23]. Thus, having excessive foods stored at home may result in increased consumption of food and snacks in the sample population[24]. Furthermore, the government's social distancing policy and classroom cancellation and online study forced students to be homebound. This could lead to boredom and/or stress; hence, they may opt to eat more foods to relieve their

Table 4 Relationship of satisfactory of online learning with daily health behaviors, and general health status of the surveyed students

Variables	Dissatisfy online learning n (%)	Satisfy online learning n (%)	P-value* (Chi-square)
Daily health behaviors			0.015 (χ^2 =10.495)
Poor behavior	40 (13.1)	17 (20.0)	
Quite poor behavior	91 (29.8)	12 (14.1)	
Good behavior	92 (30.2)	25 (29.4)	
Very good behavior	82 (26.9)	31 (36.5)	
General health status			0.019 (χ^2 =5.502)
Normality	229 (75.1)	74 (87.1)	
Abnormality	76 (24.9)	11 (12.9)	

Abbreviation: n, number

*P-value < 0.05 = statistically significant

burdens. The outcome of this is shown in this survey, which finds that almost half of the students have gained weight during the lockdown (table 1). Low or lack of physical activities may also contribute to weight gain. During normal circumstances, students in the sample population had engaged in several physical activities such as commuting to and from class and working and had the opportunity to exercise with their friends. These activities drastically decreased during the lockdown; instead, the students spent most of their time in front of computer screens, resulting in less physical activity more sedentary lifestyle. In addition, the closure of parks and outdoor arenas prevented students from outdoor exercises. However, it is noteworthy that the studied participants have an excellent score on health behavior concerning cigarette and alcohol intake (table 2). This could reflect that the majority of the surveyed students were female; therefore, were most likely to abstain from smoke and drink[25].

The general health status assessment from the Thai GHQ28 found that 22.3% of the samples had abnormal symptoms which were slightly higher than the samples of similar age in the previous study which is reported to be 20.7%[26]. This study reveals that more than two-third (68.7%) of the surveyed students experienced some form of social dysfunction, indicating that they had difficulty adjusting in the early stages of social distancing. This is not a surprising outcome because most of these students may be independent individuals who enjoy doing things on their own. When their normal, carefree lifestyles came to a sudden stop due to the lockdown, they could feel disconnected. They needed to adjust to the new lifestyle to accommodate the pandemic, for instance, wearing a face mask and online study. This new lifestyle seems to draw people apart further; for example, people may not recognize each other with a face mask on, while online classes completely separate classmates and teachers. These numbers, however, may drop with time because most people will adapt, modifying their lifestyles to be more socially connected. It is also found that after the peak pandemic, people started to adopt the lifestyle before the outbreak, increasing chances to socialize themselves. This could mean that poor social activities would no longer be an issue for the students. Additionally, the advisers should provide something to the students with abnormal health status.

Overall, the majority of the surveyed students were dissatisfied with homebound, online learning. Many factors contributed to the large number of dissatisfactions with online learning as revealed by the students in this study. Form the questionnaire, online learning lacks engagement with the teachers and their peers and offers less class time. Additionally, the lack of necessary equipment, lack of internet service, and insufficient online materials also further heighten the dissatisfaction of students. Moreover, the evaluation of students' progress, such as examinations, is difficult to conduct and potentially subject to an unfair practice. This data concurred with prior published data showing that the majority of students are dissatisfied with online classes[27-28]. To ascertain whether homebound, online learning influences daily health behaviors and general health status or not, a Chi-square analysis was performed on the acquired scores. The results of this study indicated that homebound, online learning and health status are related, as depicted in Table 4. These findings were consistent with previous research which found that online learning during the COVID-19 pandemic lockdown led to mental health problems[15] in terms of depression, anxiety, and stress[16,29-30]. Based on these findings, the students need to recognize potential health problems during homebound online studies such as unhealthy food consumption, poor physical activity, and social connectivity. Meanwhile, students who were satisfied with online instruction had better daily health behaviors. In addition, there was a higher proportion of normality in the general health status comparing

to those dissatisfied with online learning platform. Educational institutions should establish counseling centers to provide information to those who need guidance in maintaining healthy behaviors for a similar situation in the future.

The limitation of this study was surveyed in only one university in Thailand. The population given here may not be enough to generalize the findings to a larger scale. This could be due to the difficulties in collecting data, especially during the lockdown. Online data collection has proved to be problematic because of the lack of participation or response rate compared to face-to-face communication or questionnaires.

CONCLUSION

Homebound, online learning during the COVID-19 lockdown for some period of time has directly affected the students' health. The majority of the surveyed students (77.7%) had normal health status. However, the undergraduate students maintained a healthy lifestyle for stress management, smoking, and alcohol consumption. Almost half of the students (46.4%) gained weight and two third of them experienced social dysfunctions during this short period of study. More harmful effects would surely occur among students and the general population if the lockdown and home isolation were to continue for a longer period. Based on these findings, counseling centers should be established in schools and universities to provide advice to students and the general public on how to maintain a healthy lifestyle during a pandemic lockdown.

CONFLICT OF INTETEREST

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Neonatal Bacterial Meningitis among Term Neonates with Early Onset Sepsis: Prevalence, Clinical Features and Outcomes at a Tertiary Care Center in Thailand: a Retrospective Study over a 7-Year Period (2013-2019)

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ABSTRACT

OBJECTIVE: To determine the prevalence and clinical features associated with early onset neonatal bacterial meningitis (EONBM) in term infants with early onset neonatal sepsis (EOS).

METHODS: This was a retrospective descriptive study of term neonates with EONBM (defined as diagnosis of proven meningitis within 72 hours of age) at Vajira Hospital during 2013–2019. Data from medical records including demographic data, cerebrospinal fluid (CSF) analysis, microbiological results, and neonatal outcomes were reviewed.

RESULTS: There were 1,203 term neonates with EOS. Of these, 18 neonates were diagnosed with EONBM, which corresponded to a prevalence of 15.0 cases per 1000 term neonates with EOS. A total of 409 (34.0%) neonates with EOS underwent lumbar puncture (LP) within 72 hours of age, of which 4.4% had EONBM. Of the 18 neonates with EONBM, 1 (5.6%), 2 (11.1%), and 15 (83.3%) neonates had positive CSF Gram stain, latex agglutination test, and CSF white blood cell > 20 cells/millimeter^3 (mm^3), respectively. All neonates with EONBM had negative blood and CSF culture. Median gestational age and birthweight were 39.0 (interquatile range [IQR] 37.0–39.0) weeks and 3.3 (IQR 2.9–3.4) kg, respectively. Apnea (adjusted odds ratio [aOR] 57.2; 95% confidence interval [CI] 7.1–460.9), history of maternal chorioamnionitis (aOR 13.66; 95% CI 2.08–89.59), and absolute neutrophil count ≥ 18,000 cells/mm^3 (aOR 7.05; 95% CI 2.13–23.30) showed a significant association with EONBM.

CONCLUSION: The prevalence of EONBM in this cohort of term neonates with EOS was relatively low. The current literature does not provide the definite elucidation of risk factors associated with EONBM. A promptly performed LP remains a challenge in neonates with clinical or laboratory indices suggestive of EOS.

KEYWORDS: bacterial meningitis, early onset neonatal sepsis, lumbar puncture, term neonates

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INTRODUCTION

Bacterial meningitis is one of the leading causes of neonatal morbidity and mortality[1-2]. The incidence of neonatal bacterial meningitis varies among regions depending on maternal risk factors, gestational age (GA), and clinical setting. Developed countries have a lower incidence of neonatal bacterial meningitis (0.3 per 1000 live births)[3] compared to developing countries (as high as 0.8 per 1000 live births)[4]. In Thailand, the prevalence of culture proven neonatal meningitis cases was 0.37 per 1000 live births in single university hospital[5]. The prevalence of neonatal meningitis exhibited limitation in Thailand.

Early clinical manifestations of meningitis are typically non-specific (such as temperature instability, lethargy, apnea, respiratory distress, bradycardia, or tachycardia) and are difficult to differentiate from those of early onset neonatal sepsis (EOS)[6]. More specific neurological signs, such as bulging anterior fontanelle and seizures, are late manifestations of meningitis; therefore, cerebrospinal fluid (CSF) analysis via lumbar puncture (LP) plays an important role in the diagnosis of neonatal bacterial meningitis[7].

According to the guidelines of the American Academy of Pediatrics (AAP)[8] and National Institute of Health and Care Excellence (NICE)[9], the indications for LP in EOS include infants with culture-positive bacteremia, infants who do not show improvement with initial antimicrobial therapy, or infants whose clinical course or laboratory indices are suggestive of sepsis. Due to undetermined clinical course of sepsis in neonates, the decision to promptly perform LP greatly depends on institutional policy and the discretion of the attending physician[10]. Better characterization of the epidemiology and clinical course of early onset neonatal bacterial meningitis (EONBM) is a key imperative for early and appropriate investigations and diagnosis.

METHODS

A retrospective descriptive study was conducted at the neonatal care units at the Vajira Hospital, a teaching university hospital and tertiary care center in Thailand (COA 092/2563). The inclusion criterion was term newborns (GA ≥ 37 weeks) who were born at Vajira Hospital during January 1st, 2013–December 31st, 2019 and were diagnosed with EOS according to international classification of disease (ICD) 10 (P360–365, P369) and subsequently diagnosed with EONBM. EOS is defined as infection in bloodstream occurring within the first 3 days of life[11]. Culture-confirmed EOS defined as positive blood culture within 72 hours[11].

Culture-negative EOS defined as ≥ 2 clinical signs of sepsis (temperature instability, irritability, lethargy, feeding difficulties, capillary refill > 2 seconds, apnea, tachycardia or tachypnea), abnomal laboratory finding (c-reactive protein [CRP] > 10 milligram/liter (mg/L), white blood cell (WBC) ≤ 5,000 cells/millimeter^3 (mm^3), physician assigned ICD-10 diagnosis P369 and complete course of antibiotics (at least 7 days) was administered[12-15].

EONBM is defined as proven meningitis in infants who had positive CSF culture, or gram stain results, or latex agglutination test, or CSF WBC > 20 cells/mm^3 without CSF red blood cell (RBC) > 500 cells/mm^3 [16]. Exclusion criterion was infants in whom LP was performed due to other conditions apart from suspicion of neonatal sepsis and meningitis. Infants with incomplete and missing data was excluded. Data pertaining to demographic data, CSF analysis, microbiological results, and neonatal outcomes were retrived from medical records. The data of infants who underwent LP according to ICD 9 with 8,232 were collected.

Using a previously report prevalence of early onset neonatal bacterial sepsis and meningitis of 9.2%[17], we calculate the sample size required to estimate proportion with an error 0.046 and an alpha 0.05. The sample size required for estimating the prevalence of EONBM was 152 cases.

Descriptive statistics were analyzed by using Statistical Package for social science (SPSS) software version 22.0 (SPSS Inc., Chicago, IL., USA). Categorical data are presented with numbers and percentages, and continuous data are presented with the median and interquartile range (IQR). The maternal and neonatal characteristics and neonatal outcomes between infants with EONBM and without non-EONBM were compared using Chi-square, Fisher's exact test, Student's t-test, or Mann-Whitney U Test. The factors significantly associated with EONBM were identified. Variables with a p-value less than 0.05 in univariate analysis were entered into a multivariate logistic regression model. A p-value less than 0.05 was considered statistically significant.

RESULTS

The total of 15,959 neonataes born during the study period. A total of 1,203 term neonates with EOS were identified during the study reference period. Of these, 18 neonates were diagnosed with EONBM, which corresponded to a prevalence of 15.0 cases per 1000 term neonates with EOS. A total of 409 (34.0%) neonates with EOS had undergone LP within 72 hours of age and 4.4% of these had EONBM (figure 1).

Out of 18 infants with EONBM, 1 (5.6%) infant had positive CSF gram stain results identified as Gram-negative rod, 2 (11.1%) infants had positive latex agglutination test (one was identified as *Haemophilus influenzae* and the other one was identified as *Streptococcus* group B *with Streptococcus pneumoniae*). Fifteen (83.3%) infants had CSF WBC > 20 cell/mm^3. However, all infants with EONBM had negative blood and CSF culture.

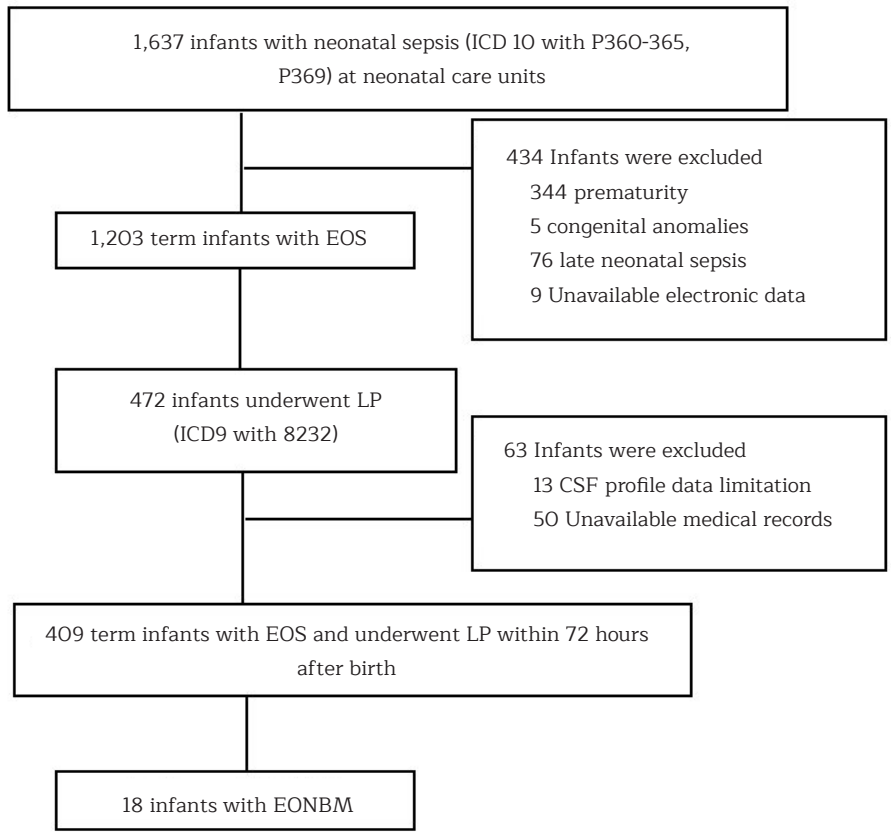

Figure 1 Flowchart demonstrating selection of study. Lumbar puncture, Early onsetneonatal sepsis, Early onset neonatal bacterial meningitis

Maternal and neonatal characteristics of term infants with EOS compared between those with and without EONBM are shown in Table 1. Among infants who had EONBM, the proportion of infants with maternal history of chorioamnionitis (11.1% versus (vs) 1.8%, p = 0.055) and prolonged premature rupture of membrane > 18 hours (16.7% vs 17.9%, p = 0.186) was higher than that among infants without EONBM. None of the mothers of infants with EONBM underwent adequate intrapartum antibiotic prophylaxis (IAP). The median GA and birthweight (BW) of infants in the EONBM group were 39.0 (IQR 37.0–39.0) weeks and 3.3 (IQR 2.9–3.4) kilograms, respectively. The most common clinical signs were respiratory distress (9/18 infants, 50.0%), feeding intolerance (7/18 infants, 38.9%), apnea (2/18 infants, 11.0%), and hyperthermia (2/18 infants, 11.0%). The proportion of infants who developed apnea in the EONBM group was significantly greater than that in non-EONBM group (11.1% vs 1.0%, p = 0.025). None of the neonates with EONBM required respiratory support.

Table 1 Maternal and neonatal characteristics and clinical features with early onset neonatal bacterial meningitis (EONBM) compared with non-EONBM. (n = 409)

Characteristics	EONBM (n = 18)	Non-EONBM (n = 391)	P-value
Maternal data			
Antenatal care	18 (100.0)	356 (92.0)	0.328
Primigravida	8 (44.4)	189 (48.5)	0.739
Chorioamnionitis	2 (11.1)	7 (1.8)	0.055
PROM > 18 hours	3 (16.7)	31 (7.9)	0.186
Vaginal delivery	11 (61.1)	234 (60.0)	0.834
Adequate IAP	0 (0)	21 (5.4)	0.148
Birth before arrival	1 (5.6)	5 (1.3)	0.238
Neonatal data			
GA (weeks)	39.0 (37.0-39.0)	38.0 (38.0-39.0)	0.511
Birth weight (kg)	3.3 (2.9-3.4)	3.0 (2.7-3.3)	0.223
Male gender	11 (61.1)	164 (41.9)	0.110
Small for gestational age	0 (0)	14 (3.6)	0.778
Apgar scores at 5 minutes < 7	1 (5.6)	3 (0.8)	0.166
Clinical features*			
Respiratory distress	9 (50.0)	140 (36.0)	0.316
Feeding intolerance	7 (38.9)	219 (56.3)	0.155
Apnea	2 (11.1)	4 (1.0)	0.025
Hyperthermia	2 (11.1)	45 (11.6)	> 0.999
Hypothermia	0 (0)	13 (3.3)	> 0.999
Seizure	0 (0)	3 (0.8)	> 0.999
Lethargy	0 (0)	21 (5.4)	0.613
Shock	0 (0)	2 (0.5)	> 0.999
Late onset sepsis	0 (0)	20 (5.1)	> 0.999

Abbreviations: EONBM, early onset neonatal bacterial meningitis; GA, gestational age; IAP, intrapartum antibiotic prophylaxis; kg, kilogram; n, number; PROM, premature rupture of membrane
Data reported as number and percentage or median and interquartile range (IQR).
* Some infants had ≥ 1 clinical features .

Laboratory indices of term infants with EOS compared between those with and without EONBM are shown in Table 2. The proportion of infants with absolute neutrophil count (ANC) ≥ 18,000 cells/mm^3 in the EONBM group was significantly greater than that in the non-EONBM group (61.1% vs 30.0%, p = 0.005). In EONBM group, all infants with history of chorioamnionitis (2/2 infants, 100%) and 5 of 11 infants with ANC ≥ 18,000 cells/mm^3 (5/11, 45%) had respiratory distress, respectively. The neonatal outcomes of term infants with EOS compared between those with and without EONBM are shown in Table 3.

The results showing factors associated with EONBM in term infants with EOS are shown in Table 4. By multivariable regression, apnea (adjusted odds ratio [aOR] 57.2; 95% confidence interval [CI]: 7.1–460.9), history of maternal chorioamnionitis (aOR 13.7; 95% CI: 2.1–89.6), and ANC ≥ 18,000 cells/mm3 (aOR 7.1; 95% CI 2.1–23.3) were significantly associated with EONBM.

Table 2 Laboratory data of infants with EONBM compared with non-EONBM (n=409)

Laboratory data	EONBM (n = 18)	Non-EONBM (n = 391)	P-value
ANC ≥ 18,000 cell/mm^3	11 (61.1)	117 (30.0)	0.005
Platelet ≥ 150,000 cell/mm^3	18 (100)	35 (88.9)	0.238
Positive hemoculture	0 (0)	4 (1.0)	> 0.999
CSF WBC > 20 cell/mm^3	15 (83.3)	72 (19.5)	< 0.001
CSF RBC < 500 cell/mm^3	17 (94.4)	193 (52.3)	< 0.001
CSF protein > 100 mg/dL	4 (22.2)	165 (45.2)	0.086
CSF glucose < 30 mg/dL	0 (0)	1 (0.3)	> 0.999
CSF glucose ratio < 0.6	2 (11.1)	9 (2.5)	0.090

Abbreviations: ANC, absolute neutrophils count; CSF, cerebrospinal fluid; EONBM, early onset neonatal bacterial meningitis; mg/dL, milligrams per decilitre; mm, millimeter; n, number; RBC, red blood cell; WBC, white blood cell
Data reported as number and percentage.
*Calculated from 14 infants with EONBM (excluded 4 cases because of no laboratory results).

Table 3 Neonatal outcomes of infants with early onset neonatal bacterial meningitis (EONBM) compared with non-EONBM (n = 409)

Neonatal outcomes	EONBM (n = 18)	Non-EONBM (n = 391)	P-value
Antibiotic duration (days)	10.0 (7.0-14.0)	7.0 (7.0-10.0)	0.006
Oxygen supplement	7 (38.9)	98 (25.1)	0.189
Respiratory support	0 (0)	9 (2.3)	> 0.999
Length of stay (days)	10.5 (7.0-14.0)	9.0 (8.0-11.0)	0.253
Cost (bath)	17,416.0 (14,809.0-22, 509.0)	16,083.0 (13,496.0-20, 102.0)	0.286

Abbreviations: EONBM, early onset neonatal bacterial meningitis; n, number
Data reported as number and percentage or median and interquartile range (IQR).

Table 4 Factors associated with EONBM in term infants with EOS

Factors	Univariate OR (95%CI)	P-value	Multivariate aOR (95%CI)	P-value
Low birth weight	Factors	0.209	3.0 (0.7-12.2)	0.126
PROM ≥ 18 hours		0.683	0.99 (0.2-4.9)	0.990
Chorioamnionitis		0.006	57.2 (7.1-460.9)	< 0.001
Apnea		0.022	13.7 (2.1-89.6)	0.006
ANC ≥ 18,000 cell/mm^3		0.009	7.1 (2.1-23.3)	0.001

Abbreviations: ANC, absolute neutrophil count; CI: confidence interval, EONBM, early onset neonatal bacterial meningitis; EOS, early onset neonatal sepsis; OR, odds ratio; PROM, premature rupture of membrane

Analysis adjusted for all factors in the table.

DISCUSSION

In this study, we investigated the prevalence and clinical features of early bacterial meningitis in term neonates with proven and clinical EOS within 72 hours of age at our center over a period spanning 7 years (2013–2019). The prevalence rate was relatively low. Moreover, this study highlights the favorable outcomes of meticulous implementation of AAP 2012 guidelines for management of neonates with suspected or proven early onset bacterial sepsis[8] and Centers of Disease Control and Prevention (CDC) about prevention of perinatal group B streptococcal disease 2010 guidelines[18]. These guidelines have been followed as a standard practice at our hospital for almost a decade prior to a newly published AAP guidelines in 2020[19].

In a prospective surveillance study conducted in Australia and New Zealand (1992–2002), the incidence of EONBM was 92 cases per 1000 infants with only proven EOS. This was despite more strict diagnostic criteria of EONBM, which included clinical presentation consistent with meningitis and either a positive CSF culture or a positive blood culture in association with a total CSF WBC > 100 cells/mm^3 [17]. Similar to our study, a study conducted in Iran found a low incidence of early bacterial meningitis in neonates younger than 3 days (12.8 cases per 1000 neonates with suspected sepsis)[20]. Our study helps characterize the epidemiology and clinical features of early meningitis in term infants with EOS. The difference among previous[17,20] studies is that the study population comprised of term/preterm infants who are known to have an increased risk of sepsis and meningitis and infants with just suspected sepsis[20].

The differences in the reported prevalence rates of early bacterial meningitis in neonates with EOS are likely attributable to use of different CSF parameters for diagnosis of bacterial meningitis and differences with respect to the study population (term and/or preterm infants), definition of EOS (proven or presumed or suspected sepsis), and age at diagnosis of meningitis.

With respect to the criteria for diagnosis of neonatal meningitis, we included all reliable methods that aid in the diagnosis of bacterial meningitis, i.e., positive CSF culture, CSF Gram stain, polymerase chain reaction (PCR) detected organisms, or CSF WBC > 20 cells/mm^3 [16]. In order to improve the accuracy of CSF pleocytosis for diagnosis of neonatal bacterial meningitis, we excluded traumatic tapping, which is defined as CSF RBC > 500 cells/mm^3, prior to the use of CSF WBC > 20 cells/mm^3. A similar approach was used in an epidemiological study of neonatal meningitis in Morocco[21] and a multicenter retrospective cohort study in China[22].

Because traumatic LP attempts are common in newborns and can affect the interpretation of CSF WBC count, several methods have been used to adjust CSF WBC counts based on CSF and peripheral RBC counts. However, these techniques

do not improve the diagnostic utility and can result in loss of sensitivity with marginal gain in specificity[23].

Similar to our study, The Neonatal Research Network (NRN) showed that EOS cases are caused by organism other than group B *streptococcus* (GBS) or *Escheirchia coli* (E coli), other *Streptococcal species* (12.8%) and *Haemophilus species* (3.8%) are commonly identified[24].

Meningitis is commonly associated with neurological manifestations including seizures, bulging fontanelle, irritability, abnormal consciousness, and dystonia[6,23,25]. However, none of the infants with EONBM in our cohort showed neurological symptoms. This may be attributable to subtle clinical presentation in the early stage of meningitis.

Respiratory distress in newborns is one of the most common signs of EOS and sometimes is the reason for early LP as part of sepsis screening. Eldadah et al. [26] investigated 203 infants (GA ranging from 23–40 weeks) with respiratory distress who underwent LP within the first 24 hours after birth and found that none of them had meningitis. Weiss et al. [27] studied 1,495 preterm infants (GA: 27–36 weeks) with respiratory distress in whom LP were performed as part of sepsis evaluation; only 4 (0.3%) infants were found to have had true meningitis. In the study by Xu et al[22], none of the full-term neonates who were clinically diagnosed as early onset meningitis presented with symptoms of respiratory distress. This is consistent with our study in which respiratory distress was not a differentiating clinical feature between EONBM and non-EONBM groups, and thus was not found to be a risk factor for meningitis. Therefore, the results of previous study and our study suggest that performing an early LP can be delayed in infants with isolated respiratory symptoms[28].

In the 2012 AAP[8] and NICE[9] guidelines, one of the challenging indications for LP is infants whose clinical course or laboratory indices are suggestive of sepsis. For almost the past decade, the decision to promptly perform LP varies from one center to another, and from one physician to another[10].

Of note, after implementation of the current guidelines[8,9,17] which have partially altered the clinical and laboratory features of EOS over time, symptoms of apnea or maternal history of chorioamnionitis or ANC ≥ 18,000 cells/mm^3 in term infants with EOS showed a significant association with increased incidence of EONBM. Krebs et al.[29] reported clinical signs of meningitis in infants with BW < 2,500 grams found that apnea (20.6%). Overall JC[30] reported predisposing factors significantly associated with meningitis were complications during labor and delivery, maternal peripartum infection, and chorioamnionitis. In contrast, Garage et al.[31] reported a low predictive value of peripheral WBC count for late preterm/term neonatal meningitis (defined as only culture-proven meningitis). The difference from previous study[31] is that EONBM was defined as CSF pleocytosis apart from positive CSF culture. Our aim was to include infants who were pretreated with antibiotics before performing an LP. Consistently, Nigrovic et al[32]. reported infants pretreated had lower rates of positive CSF culture than nonpre-treated infants (84 vs 58%). The general practice in our hospital was to perform an LP on clinically stable infants with suspected EONBM, antibiotic treatment is usually started before performing LP. Similar to the ANC ≥ 18,000 cells/mm^3 in term infants with EOS that showed a significant association with increased incidence of EONBM, Ajayi et al[33]. reported that term infants with sepsis (N = 196) in maternal chorioamnionitis showed the ANC 17,800 ± 6,000 cells/mm^3 in timepoint 2.

For this reason, clinical presentations such as respiratory distress should be considered in conjunction with a laboratory parameter (such as ANC) or maternal risk factors (such as chorioamnionitis) while considering early LP in infants with suspected EONBM. Our study showed that a total of 39% (472/1,203) infants

with EOS had undergone LP within 72 hours of age. The LP is an invasive procedure, the indications for LP in the current guidelines of AAP[8] and NICE[9] is not recommend that an LP should be performed in all infants with EOS or was one as part of the septic work up in EOS. Respiratory distress is the one of most common clinical presentation of EOS, however, it is difficult to differentiate between infectious (EOS, meningitis) and non-infectious course (transient tachypnea of the newborn) in the early clinical course. Clinical judgment is required in deciding when to perform an LP[34]. This might be the result of selection bias or information bias.

Some limitations of our study should be considered. Firstly, this may have potentially introduced an information or misclassification bias. The diagnosis of EONBM was mostly not based on gold standard diagnosis for meningitis from microbiology. The result may be better if the database from microbiology was choosen. The information of all cases with positive hemoculture who underwent LP was incomplete. Secondly, this was a retrospective study with possibility of incomplete data or inappropriate ICD coding. Thirdly, this was study was conducted at a single academic tertiary care center, which may limit the generalizability of our findings to other general healthcare settings. The interpretation of the factors associated with EONBM was cautious because of the small of cases and wide confidence interval.

CONCLUSION

This study found a relatively low prevalence of EONBM in term neonates with EOS. The decision to promptly perform lumbar puncture is still a subjective decision. Understanding of the epidemiology, clinical course, and related laboratory indices of EONBM can help inform more precise investigations for diagnosis of EONBM.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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DATA AVALABILITY STATEMENT

All of the data generated and analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Original Article

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Melatonin Niosome Gel vs. Chloral Hydrate for Sedation in Children Undergoing Auditory Brainstem Response: a Randomized Controlled Trial

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ABSTRACT

OBJECTIVE: To compare the success rate of auditory brainstem response (ABR) testing after the application of melatonin niosome gel (MNG) versus chloral hydrate in children aged 1 to 6 years.

METHODS: A double-blinded, randomized, controlled trial was conducted. Participants in the MNG group were given 250 mg of MNG (5 mg melatonin) for sedation prior to the ABR test, and those in the chloral hydrate group were given chloral hydrate syrup, 50 mg/kg with an additional dose of 25 mg/kg if they didn't fall asleep within 30 min. The study was conducted in the morning; all the participants were prepared in accordance with protocols similar to the regular ABR protocols.

RESULTS: Twenty-four children were enrolled, and 16 participants passed the screening and were randomized into 2 groups. The success rate of ABR in the MNG group was 25.0% compared to 100.0% in the chloral hydrate group (p-value = 0.01). Twenty-five percent of the subjects in the chloral hydrate group required a second dose of choral hydrate. The average sleep onset latency of the chloral hydrate group was 25.1 min, which was approximately the same as the MNG group (25.4 min). The average sleep duration of the chloral hydrate group was 89.3 min, which was significantly longer than the MNG group (45.6 min), with a mean difference of 43.6 min (p-value = 0.01). There were minor adverse events in both groups, including vomiting (12.5 – 25.0%) and irritability (25.0%), without any serious adverse events reported.

CONCLUSION: The sedative effect of trans-mucosal MNG was unfavorable comparing with the chloral hydrate. The sublingual delivery was intolerance for uncooperative children and sedation for neurodevelopment disordered children were challenging. However, the sleep onset latency by behavioral observation induced by MNG tended to be comparable to chloral hydrate. Further adjustment of trans-mucosal administration and dosage could provide adequate pediatric sedation.

KEYWORDS: auditory brainstem response, chloral hydrate, melatonin niosome gel, pediatric sedation

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INTRODUCTION

The auditory brainstem response (ABR) test is a diagnostic tool used to detect retro-cochlear pathology, and estimate hearing threshold. During the ABR test, muscle movements affect the electrical wave forms that are recorded. Therefore, it is recommended for patients to be asleep during the procedure. Sedative agents are usually administered to children aged between 6 months and 6 years to induce calmness during the test. For children, younger than 6 months, ABR testing can be performed while the patient sleeps naturally[1].

Sedative agents used for children include chloral hydrate, fentanyl, opioids, ketamine, midazolam, and nitrous oxide[2]. Chloral hydrate is commonly used for ABR testing. According to Valenzuela and Reynold's studies[1,3], the success rates of the ABR test after chloral hydrate administration in children older than 6 months were 66.0% and 95.0%, respectively. Sleep onset latency ranged from 20.0 to 49.0 min (with an average of 30.0 min)[3]. The adverse events of chloral hydrate are prolonged sleepiness lasting more than 8 hours (11.0%)[4], vomiting (15.0%)[4] and agitation (34.0%)[5]. Some patients with chronic neurological abnormalities such as cerebral palsy and developmental abnormalities are difficult to sedate with chloral hydrate and cannot fall asleep through the procedure as reported in a pediatric electroencephalogram study[6].

Oral melatonin is also a sedative agent for pediatric non-invasive procedures, with the advantage of the low side effects of central nervous system (CNS) suppression. This agent is also used for ABR testing with success rates of 65.0 – 86.7%[7] and a mean ABR examination time of 52.0 min[8]. The limitation of oral formulation is variation of gastrointestinal absorption and poor bioavailability (< 33.0%) due to extensive first-pass hepatic metabolism[9-11]. The melatonin niosome gel (MNG) is the muco-adhesive gel providing strong affinity for mucosal surface contributed by molecular interaction between gel and mucin/mucosa[12] to increase contact time, improve absorption and prolonged release of medication. Trans mucosal MNG provides direct absorption of melatonin through the oral mucosa, bypassing the first pass metabolism, resulting in high bioavailability with prolonged effect[11]. The MNG has 6 times higher maximal plasma concentration (C-max) than the oral formulation and mean half-life of 1.2-1.5 hour covering the routine ABR testing duration[11,13]. In addition, the trans-mucosal MNG in young adults' study reported no significant local and systemic adverse events[11]. The dosage of MNG was formulated according to the pharmacokinetic study of MNG in young adults applied to the oral melatonin dose [11,14-15]. This study aimed to evaluate the efficacy of MNG for ABR testing. The secondary outcomes were to study the effects of both medications on daytime sleep induction, including sleep onset latency and sleep duration, in addition to drug safety and any adverse events.

METHODS

This research was designed as a double-blinded, randomized controlled trial for children in an otorhinolaryngology clinic who undergo ABR testing at a university hospital. The study was conducted at the clinical research ward (Academic Clinical Research Office; ACRO) of Srinagarind Hospital, Faculty of Medicine, Khon Kaen University. Inclusion criteria were 1) aged between 1 and 6 years old. 2) No abnormalities of pinna and external auditory canal, craniofacial anomalies, or cleft palate conditions that contribute to conductive hearing loss and require additional air conduction testing. 3) No history of allergic reactions to melatonin or chloral hydrate, as determined by medical records. 4) No history of gastric ulcer[16]. 5) No use of medications interacting with sedative agents, such as warfarin[16], carbamazepine[16], cimetidine[16], fluvoxamine[16], furosemide[17], nifedipine[18], rifampicin[19], fluconazole[19], ketoconazole[19], and quinolone[20]. 6) No use of medications with CNS suppressing effects, such as opioids, benzodiazepines, and barbiturates[16].

7) No history of severe adverse events during previous sedation, including respiratory arrest and upper airway obstruction. Exclusion criteria were 1) Participants with the American Society of Anesthesiologist physical status classification of class III or below, such as patients with severe systemic disease and definitely restricted function[21]. 2) Participants who had a previous history of arrhythmias, arrhythmia detected on physical examination, or taking tricyclic antidepressants[19]. 3) Patients with severe renal impairment, indicated by a glomerular filtration rate less than 50 ml/min/1.73m^2 (according to KDIGO 2012 criteria) calculated by the Schwartz equation to estimate glomerular filtration rate in children[22]. 4) Patients with severe liver dysfunction, including those with cirrhosis or acute hepatitis[16]. 5) Participants who had abnormal blood test results, including blood urea nitrogen, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, and direct bilirubin.

The sample size calculation was based on the previous studies of ABR when the success rate of chloral hydrate and oral melatonin sedation were 65.8%[3] and 86.7%[14], respectively. The two-sided test for a superior clinical trial was used with a statistical power level of 80.0% and error level (α) of 0.05. The calculated number of participants for each group was 64.

The parents or caregivers were informed about the testing procedures, including advice for preparations before the ABR test (fasting from food, water, and milk for at least 2 hours prior, avoiding falling asleep before the test, and the signs of illness that are contraindications for sedation), the medication given before the ABR test and the potential risks or side effects of both sedative agents. For the participants with an unsuccessful ABR test, an additional ABR test was scheduled with chloral hydrate sedation, according to the institutional standard. Subsequently, the research assistants obtained consent from the parents and caregivers of the participants.

The participants were categorized according to the presence of neuro-developmental disorders, including autistic spectrum disorder[23], Down's syndrome[24], attention deficit hyperactivity disorder (ADHD)[25], and cerebral palsy[26]. Stratified randomization was employed by using a permutated block randomization method (block of four) (figure 1). The codes for each participant were kept in sealed opaque envelopes, concealed from sleep assessors, audiologists and physicians, and were given to the 1st research assistant nurse who administered the sedative medication.

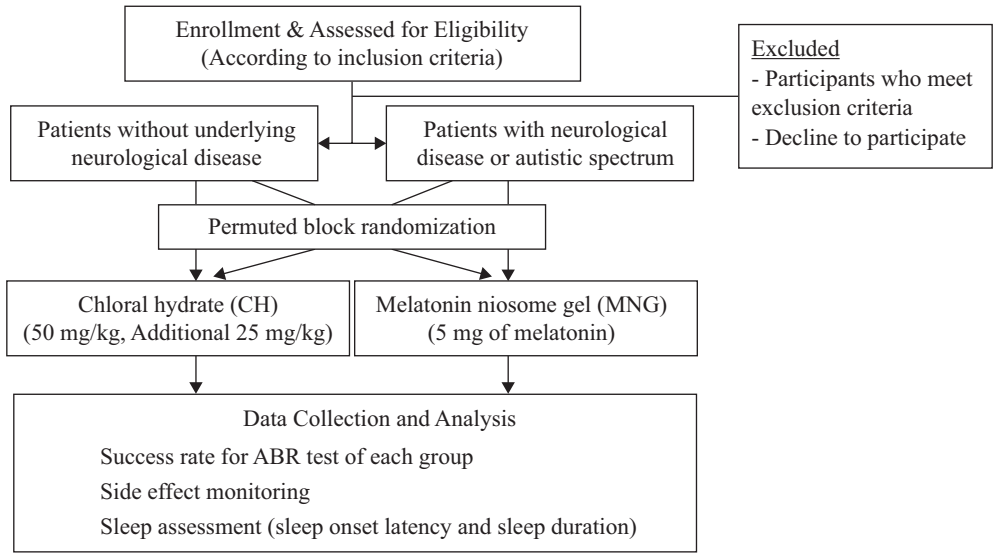

Figure 1 The consort flow diagram of study populations.

This study was a double-blinded randomized controlled trial. The researchers, sleep assessors, audiologists, and all parents were blinded from the intervention given to the participants.

The MNG was stored at a temperature of 2-8°C throughout the study period. The stability of the substances was assessed every 3 months. The MNG included melatonin, 0.08% w/w cholesterol, 0.08% w/w sorbitan monostearate, 9.0% w/w polyvinylpyrrolidone, 9.0% w/w hydroxypropyl methylcellulose, 8.0% w/w poloxamer 407, and 3.0% sucralose (flavoring agent). Glygerine, polyethylene glycol 400, and water were used as the solvents of the melatonin in muco-adhesive niosome gel.

The reference dose of oral melatonin adjusted by age[14-15] prior to the ABR testing was as the following:

- Children aged up to one year received 5 mg of oral melatonin
- Children aged between 1 and 6 years received up to total 10 mg of oral melatonin
- Children aged older than 6 years old received up to total 20 mg of oral melatonin

The study included participants aged between 1 and 6 years old which met the total dose of 10 mg oral melatonin by age range. Although the pharmacokinetic of melatonin in children were different from adult in drug metabolism and elimination, the MNG has bypassed the first pass metabolism and exclude the issue of different hepatic clearance between children and adults[11,27]. Therefore, the MNG dose were calculated from young adult pharmacokinetics data. According to the study of trans-mucosal melatonin, the MNG (5 mg) provided maximum plasma concentration (C-max) of 3 times greater than 10 mg oral formulation[11,13]. Another trans-mucosal buccal application study provided (C-max) of 2.3 times greater than same dose of oral formulation[28]. Therefore, trans-mucosal MNG (5 mg dose) would provide C-max at least 1.2-3 times as 10 mg oral formulation and prolonged effect covering ABR testing duration (mean $T_{1/2}$ of 1.5 hour). The MNG (5 mg) was administered before the ABR test. Participants received 5 mg of melatonin (in 250 mg of the melatonin niosome gel) administered at the sublingual area or the mucosal area between the gum and the inner cheek (buccal mucosal area). This method is referred to as trans-mucosal drug delivery. According to British medical association[16], the recommended maximal daily dose was 10 mg oral melatonin for children. In addition, the studies by Schmidt et al.[14] and Guerlain et al.[15] also applied total dose up to 10 mg oral melatonin for children aged between 1 and 6 years old prior to ABR test. As a result, a single dose of trans-mucosal MNG (5 mg) which provided higher C-max than 10 mg oral formulation reached the maximum dosage recommended for this age range and no additional dose applied.

The chloral hydrate syrup (100 mg/ml) was stored in amber glass bottles; each bottle contained 10 ml of the drug and was stored at a temperature of 15°C–25°C. The first dose of chloral hydrate syrup (100 mg/ml) was 50 mg/kg per oral, not exceeding 1 gram[16]. The participants were observed for 30 min (corresponding to the time of maximal effect)[29]. The second dose of chloral hydrate (25 mg/kg) was administered if the participants were not sedated or could not complete the test. The total doses of chloral hydrate did not exceed 100 mg/kg[16].

A successful ABR test was defined as the participants could complete the test on both ears after the sedation. If the participants could not initiate the test (within 60 min after the first dose of sedation), or could not complete the test, they were recorded as failed ABR tests.

Evaluation of sleep parameters and daytime sleep induction was conducted through direct observation and a sleep monitoring device (Philips Respironics Actiwatch 2) for the objective parameters. In direct observation, the sleep onset latency (SOL) was recorded from the time of drug administration until the onset of sleep (observed through the behaviors of eye closing, decreased body movements and consistent, rhythmic breathing for 5 min). Sleep duration was recorded

from the onset of sleep until the time of waking, which was observed through the behaviors of eye opening and increased body movements.

The sleep monitoring device contains acceleration-responsive piezoelectric sensors to record the intensity, frequency, and duration of movement that could assist in the evaluation of a patient's sleep. The devices were attached to the non-dominant wrist of participants and monitored their movement in order to interpret whether participants were asleep or awake. The devices reported SOL, sleep duration, and wakefulness after sleep onset (WASO) as outcomes. The adverse events were monitored from the drug administration until the post-test monitoring period, and were classified as common terminology criteria for adverse events (CTCAE) version 5.0[30].

Data were analyzed using descriptive statistics for continuous data, reported as means and standard deviations, while categorical data were presented as numbers and percentages. Statistically, the Independent T-Test was used to compare the sleep parameters and Fisher's Exact Test was used to compare the success rate of the ABR test, with a p-value of < 0.05 considered statistically significant. Statistical analysis was performed using IBM SPSS statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, Released 2021).

This study underwent an ethical review conducted by the Human Research Ethics Committee at Khon Kaen University (reference number HE621458) and was registered in the Thai Clinical Trial Registry (TCTR) (reference number TCTR20211121003).

RESULTS

The study was conducted between July 21, 2020 and October 5, 2020 and included a total number of 24 participants. Four participants were excluded due to abnormal laboratory tests. The number of participants who met the research criteria was 20. The research was suspended by the Data and Safety Monitoring Board to investigate cases that couldn't complete the test due to overall success rate obtained from the study which was lower than routine practice (62.5% and 70.0%, respectively). Among the included participants, 1 case was lost to follow-up, and the ABR schedule was suspended in 3 cases. Sixteen participants were investigated, including 8 children in each study group. The average ages were 2.6 and 2.1 years in the MNG group and the chloral hydrate group, respectively (table 1). There were 2 cases with neuro-developmental disorders (autistic spectrum disorder and ADHD) in the MNG group. The laboratory parameters and vital signs,

Table 1 The baseline characteristics of the participants in both study groups

Characteristic	Number of cases (%)	
	Melatonin niosome gel (N = 8)	Chloral hydrate (N = 8)
Male	6 (75.0)	7 (87.5)
Female	2 (25.0)	1 (12.5)
Age (μ ± SD)	2.6 ± 0.9 yr	2.1 ± 1.1 yr
Weight (μ ± SD)	15.0 ± 0.7 kg	12.3 ± 1.2 kg
Height (μ ± SD)	93.8 ± 2.8 cm	87.8 ± 3.7 cm
Neurological disorder	2 (25.0)	0
Underlying disease	5 (62.5)	3 (37.5)
Drug allergy	0	0
Current medication	3 (37.5)	2 (25.0)
Non-dominant hand	Left 7 (87.5) Right 1 (12.5)	Left 8 (100.0) Right 0

Abbreviations: cm, centimeter; kg, kilogram; N, number; SD, standard deviation; yr, year old; μ, means

except systolic blood pressure (SBP), were in the age-appropriate range for all participants[31] (table 2). The rise of SBP was temporary and didn't indicate a health issue. The mean dose of chloral hydrate was 652.0 mg and the additional dose of chloral hydrate was administered in 2 cases (25.0 %) with the mean dose of 357.0 mg (table 3). The success rate of the chloral hydrate group (100.0 %) was greater than the MNG group (25.0 %) (table 4) with a statistically significant difference (p-value = 0.01).

The effects on daytime sleep induction (table 4) include: The average SOL was 25.4 min and 25.1 min in the MNG group and the choral hydrate group, respectively, without any statistically significant differences between the groups. The sleep onset latency from the sleep monitoring device (table 4) were 21.3 min and 6.8 min in the MNG group and the choral hydrate group, respectively. However, the mean difference of 14.5 min was not statistically significant. According to the time gap between drug administration and starting of record by the devices which affected the SOL parameter, the author prioritized behavioral observation method for the SOL assessment.

Table 2 Physical examination of the participants

Variable		Number of cases (%)	
		Melatonin niosome gel (N = 8)	Chloral hydrate (N = 8)
Breath Sound		Normal 8 (100.0) Abnormal 0	Normal 8 (100.0) Abnormal 0
Heart Sound		Normal 8 (100.0) Abnormal 0	Normal 8 (100.0) Abnormal 0
Anterior Rhinoscopy		Normal finding 7 (87.5) Clear nasal discharge 1 (12.5)	Normal finding 7 (87.5) Clear nasal discharge 1 (12.5)
Retrognathia		1 (12.5)	1 (12.5)
Right Tonsil	Grade 1	4 (50.0)	2 (25.0)
	Grade 2	3 (37.5)	3 (37.5)
	Grade 3	0	3 (37.5)
	Grade 4	1 (12.5)	0
Left Tonsil	Grade 1	3 (37.5)	4 (50.0)
	Grade 2	3 (37.5)	3 (37.5)
	Grade 3	2 (25.0)	1 (12.5)
	Grade 4	0	0
Body Temperature (μ ± SD)		36.6 ± 0.3 °C	36.4 ± 0.2 °C
Blood Pressure (μ ± SD)		SBP 126.1 ± 12.1 mmHg DBP 68.4 ± 7.1 mmHg	SBP 131.1 ± 13.9 mmHg DBP 81.0 ± 11.3 mmHg
Pulse Rate (μ ± SD)		87.0 ± 24.6 BPM	121.8 ± 13.6 BPM
Respiratory Rate (μ ± SD)		20.5 ± 4.0 per min	26.1 ± 5.5 per min

Abbreviations: BPM, beats per minute; °C, degree Celsius; DBP, diastolic blood pressure; min, minute; mmHg, millimeter of mercury; N, number; SBP, systolic blood pressure; SD, standard deviation; μ, means

Table 3 Dosage and volume of the administered medication

Dose	Mean drug dose in mg (μ ± SD)	
	Melatonin niosome gel (N = 8)	Chloral hydrate (N = 8)
1st Dose	250.0	652.0 ± 184.0
2nd Dose	0	357.0 ± 106.0 Second dose administration 2 (25.0%)

Abbreviations: mg, milligram(s); N, number; SD, standard deviation; μ, means

Table 4 The sleep parameters among the study groups by direct observation and sleep monitoring device and the success rates of ABR testing

Variable	Duration in min (μ ± SD (range))		Mean difference (min)	P-value*
	Melatonin niosome gel	Chloral hydrate		
Sleep onset latency	25.4 ± 19.6 (10.0 – 59.0)	25.1 ± 19.5 (9.0 – 60.0)	0.3	0.98
Sleep duration	45.6 ± 33.8 (0 – 96.0)	89.3 ± 24.2 (55.0 – 126.0)	43.6	0.01
Sleep onset latency (By Actigraphy)	21.3 ± 22.7 (3.0 – 51.0)	6.8 ± 9.6 (2.0 – 30.0)	14.5	0.14
Sleep duration (By Actigraphy)	30.3 ± 37.1 (0 – 89.0)	77.5 ± 20.4 (36.0 – 100.0)	47.3	0.01
WASO (By Actigraphy)	3.1 ± 0.9 (1.3 – 4.3)	4.6 ± 3.2 (1.5 – 8.8)	1.5	0.38
Duration of ABR test	71.5 ± 3.5 (69.0 – 74.0)	63.3 ± 26.7 (19.0 – 91.0)	8.3	0.69
Success rate	25.0 %	100.0 %	Risk Ratio 0.25	0.01**

Abbreviations: ABR, auditory brainstem response; min, minute; SD, standard deviation; WASO, wakefulness after sleep onset; μ, means
*Independent T-Test
** Fisher's Exact Test

The average sleep duration by observation was 45.6 min and 89.3 min in the MNG group and the chloral hydrate group, respectively. The mean difference in sleep duration was 43.6 min and showed statistical significance (p-value = 0.01). According to Actiwatch, sleep duration was 30.3 min and 77.5 min in the MNG group and the chloral hydrate group, respectively. The mean difference of 47.3 min was statistically significant (p-value = 0.01).

WASO, measured by Actiwatch, were 3.1 min and 4.6 min for the MNG group and the chloral hydrate group, respectively, without any statistically significant difference. There were several minor adverse events (CTCAE grade 1) in both groups (table 5). Vomiting (1 case) and irritability (2 cases) were reported in the MNG group and resolved during the post-test monitoring period. In the chloral hydrate group, vomiting (2 cases) and irritability (2 cases) were also reported. There was no significant difference in the adverse events between groups.

DISCUSSION

Our study applied the current trend of melatonin trans-mucosal delivery for children in order to improve absorption, bioavailability, and more prolonged effect. It was designed to compare MNG sedation with the routine practice. However, the preliminary analytic results were

Table 5 Adverse events after the administration of medication

Adverse events	Number of cases (%)		P-value*
	Melatonin niosome gel (N = 8)	Chloral hydrate (N = 8)	
Nausea	0	0	-
Vomiting	1 (12.5) **	2 (25.0) **	0.99
Headache	0	0	-
Irritability	2 (25.0) **	2 (25.0) **	0.99
Total	3 (37.5)	4 (50.0)	-

Abbreviation: N, number
* Fisher's Exact Test
** CTCAE grade 1

not as effective as expected. The small number of sample size might not represent the entire ABR testing population. The previous studies of oral dosage including, Casteil et al.[8] reported a 65.0% ABR success rate in 29 children aged 1 to 6 years. Chaouki et al.[32] administered 5 mg melatonin (with a repeated dose if necessary) in children aged 5 months to 4 years and reported a 72.7% ABR success rate. Hajjij et al.[33] administered 2-5 mg melatonin for children aged 6 months to 3 years and 5-10 mg for children aged 3 to 6 years resulted in 83.4% success rate. The systematic review by Behrman et al.[7] also reported a 65.0% - 86.7% success rate in children aged 1 month to 14.5 years. In our study, the factors associated with unsuccessful test was the sublingual administration was intolerance for uncooperative participants. The proper adjustment of MNG administration could improve the efficacy such as aiming for buccal administration which was more tolerable for children. Moreover, the neuro-developmental patients, including autism spectrum disorders and ADHD, were also difficult cases for sedation as it could lead to chronic insomnia[24,26]. In terms of daytime sleep induction effect, MNG induced comparable sleep onset latency to chloral hydrate (approximately 25.0 min by behavioral observation). However, the sleep duration of MNG (average 45.6 min) was not sufficient for the ABR testing duration (69.0 – 74.0 min). According to oral formulation, Casteil et al.[8] reported average sleep onset latency of 41.0 min and a sleep duration of 33.0 min in children aged 1 to 6 years. Guerlain et al.[15] report 35.0 min of sleep onset latency and 23.0 min of sleep duration in children aged 1 to 13 years. Compared with the oral dosage, MNG tended to induce earlier onset of sleep with comparable sleep duration. The adjustment of MNG administration and dosage are also needed to facilitate pediatric sedation.

CONCLUSION

The sedative effect of trans-mucosal melatonin niosome gel in pediatric auditory brainstem response test was unfavorable comparing with chloral hydrate. The contributing factors including sublingual administration which was intolerance for uncooperative children and neurodevelopmental disordered children were also challenging for sedation. Nevertheless, the sleep onset latency by behavioral observation tended to be comparable with the chloral hydrate. The adjustment of drug administration and dosage would provide adequate sedation and ensure its suitability for clinical applications.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, SL, upon reasonable request.

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Original Article

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Caring at Cardiology Clinic versus Heart Failure Clinic: Impact of Implementation of Guideline-Directed Medical Therapy in Heart Failure with Reduced Ejection Fraction in Outcomes of Death and Heart Failure Readmission

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ABSTRACT

OBJECTIVE: This study aimed to determine whether the heart failure (HF) clinic setting can improve guideline-directed medical therapy (GDMT) use and reduce HF readmission and mortality rates in patients with heart failure with reduced ejection fraction (HFrEF).

METHODS: This was a retrospective cohort study including patients with HFrEF admitted to Vajira Hospital between May 2016 and December 2021. Data were collected from electronic medical records to compare the usage of GDMT, including beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs)/ angiotensin receptor blockers (ARBs)/ angiotensin receptor-neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), and sodium glucose transporter 2 inhibitors (SGLT2s), after discharge from the inpatient department at 1-, 3-, 6-, and 12-month follow-up between the HF clinic and general cardiology clinic groups. Moreover, readmission, mortality rates and composite endpoint of mortality and HF admission rate at the 1-year follow-up were recorded.

RESULTS: In total, 234 patients with HFrEF were included in this study (88 in the HF clinic group and 146 in the general cardiology clinic group). After 1-year follow-up, the incidence rates of mortality in the HF clinic and general cardiology clinic groups were 3.45 and 11.66 per 100 person-years, respectively ($p = 0.040$), and the incidence rates of readmission were 23.77 and 79.01 per 100 person-years, respectively ($p < 0.001$). The HF clinic group showed reduced risk for the composite outcome of readmission and mortality (0.37, 95% confidence interval (CI): 0.23–0.60) ($p < 0.001$), mortality (0.30, 95% CI: 0.09–1.02) ($p = 0.054$), and readmission (0.33, 95% CI: 0.21–0.53) ($p < 0.001$) than the general cardiology clinic group. At the 12-month follow-up, the HF clinic could up-titrate GDMT to target doses higher than the general cardiology clinic (beta-blockers 68.20% vs. 32.90% ($p < 0.001$), ACEIs/ARBs/ARNIs 12.50% vs. 3.40% ($p = 0.003$), MRAs 9.10% vs. 4.10% ($p = 0.001$), and SGLT2s 4.50% vs. 7.50% ($p = 0.648$)).

CONCLUSION: Patients in the HF clinic showed a significant improvement in survival and HF readmission rates and had a higher use of GDMT with a shorter duration to achieve the target doses.

KEYWORDS: guideline-directed medical therapy, heart failure clinic, heart failure reduced ejection fraction, readmission

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INTRODUCTION

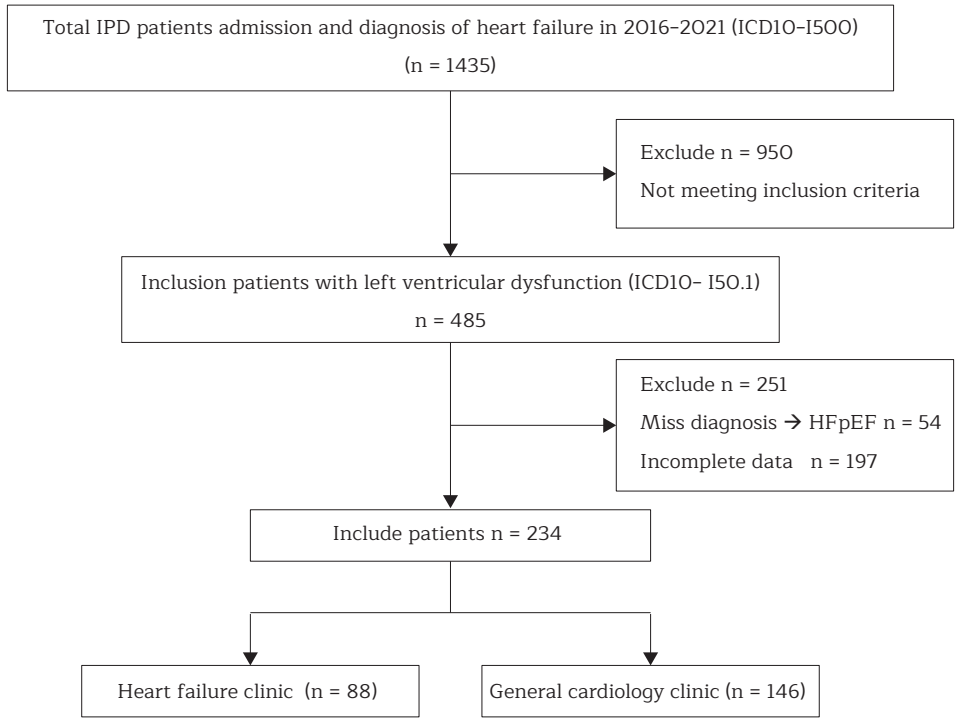
Heart failure (HF) is a growing public health concern. Heart failure with reduced ejection fraction (HFrEF), defined as left ventricular ejection of less than 40%, has been reported to account for more than half of the HF cases; its incidence continues to increase[1]. Many global guidelines from various associations, including the American College of Cardiology, the European Society of Cardiology, and the Thai Heart Association, provide cardiologists with information on best practices for managing patients with HFrEF[2-5]. Appropriate use and titration of drugs, including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), mineralocorticoid receptor antagonists (MRAs), and sodium glucose transporter 2 inhibitors (SGLT2s), have been reported to improve left ventricular function, reduce HF rehospitalization, and decrease mortality[6-8]. However, titration of these drugs in real-world clinical practice is often insufficient[9] due to various factors, including doctor inertia and overcrowding of patients at outpatient departments[10-14]. This can increase the risk of adverse outcomes, including readmission and mortality, which cause disability and increase treatment costs[15].

In Thailand has not HF clinic in every hospital. Benefits of HF clinic compared to general cardiology clinic can include comprehensive management of HF patients including sophisticated medical and device therapies ,patients centered education, cardiac rehabilitation, adequate monitoring. To address this problem, HF clinics have been established to improve treatment quality[16]. These clinics provide intensive care and a multimodal approach, resulting in decreased readmission and mortality[17]. However, data on the drug profile in HF clinics are limited. Thus, this study aimed to fill the gap in knowledge focusing on guideline-directed medical therapy (GDMT) usage in HF clinics and general cardiology clinics, specifically the rate of GDMT dose escalation. Additionally, this study aimed to compare the 1-year readmission rates, mortality and composite of mortality and readmission of HF outcomes between the HF clinic and general cardiology clinic groups to confirm that the HF clinics can improve outcomes.

METHODS

This was a retrospective cohort study including patients with HFrEF who were admitted to the Internal Medicine Department, Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand, between May 2016 and December 2021. The inclusion criteria included patients aged ≥ 18 years and those with a first diagnosis of HFrEF with evidence of left ventricular ejection fraction (< 40%) as indicated by echocardiography. The exclusion criterion was patients with incomplete data, such as less than 1-year follow-up or no echocardiogram data. All patients were considered eligible for participation in the study and were selected based on the criteria in the database of the inpatient department's electronic medical record summary discharge record form (figure 1). In Vajira Hospital, inclusion of patients for HF clinic is HFrEF (ejection fraction < 40%) with at least 1 condition of the following: rehospitalization 2 times within a year, poor compliance, many comorbidities, difficult medication titration. This study was approved by the Institutional Review Board of the Faculty of Medicine, Vajira Hospital, Navamindradhiraj University (COA 014/2565).

Data were collected from electronic medical records to compare the use of GDMT, including beta-blockers, ACE inhibitors/ARBs/ARNIs, MRAs, and SGLT2s, after discharge from inpatient care at 1-, 3-, 6-, and 12-month follow-ups between the HF clinic and general cardiology clinic groups. The primary outcomes were the 1-year readmission rate for HF, mortality, composite outcome of readmission and mortality and the secondary outcomes were the pattern of GDMT use and



Abbreviations: HFpEF, heart failure preserved ejection fraction; ICD 10, international classification of disease 10th revision; IPD, inpatient department

Figure 1 Study patients selection

the time to escalate to the target doses at 1-, 3-, 6-, and 12-month follow-ups. Sample size was calculated based on cohort study for binary data formula of Bernard[18] and use the percentage of rehospitalization and mortality between general cardiology clinic group and HF clinic group reference from Howlett et al.[17] for calculated the sample size.

Baseline characteristics and categorical variables were presented as numbers and percentages. Continuous variables were presented as means and standard deviations if normally distributed and median and interquartile range if not normally distributed. We use Kolmogorov-Smirnov test or Shapiro-Wilk test to test the normality of quantitative variables. Categorical variables were compared using Chi-square or Fisher's exact tests, and continuous variables were compared using the independent samples t-test if normally distributed or the Mann–Whitney U test if not normally distributed. The primary outcomes, 1-year readmission and mortality, were analyzed using Cox proportional hazards models or Kaplan–Meier curves, with a significance level of $p < 0.05$ and a power of 90%. At first, we use univariate analysis to explain the association between each variable (including practice in 2 clinics and all other factors) and outcomes. After that, the variables associated with outcomes ($p < 0.05$) or trend closely associate with outcomes ($p < 0.1$) were include in multivariate analysis. Then we check the multicollinearity assumption of the Cox regression in our multivariate analysis the factor that correlate with other factors were excluded and choose factor that they correlate to represent the factor that we exclude. Data analysis was performed using the Statistical Package for the Social Sciences version 24 (IBM Corporation, Somers, NY, USA).

RESULTS

A total of 234 patients with HFrEF were included in this study (88 in the HF clinic group and 146 in the general cardiology clinic group). The baseline characteristics of patients in both groups are shown in Table 1.

Table 1 Baseline and clinical characteristics of study patients in heart failure clinic and general cardio clinic

Variables	Heart failure clinic (N = 88)	General cardio clinic (N = 146)	P-value
Sex			0.290[c]
Male	62 (70.50)	93 (63.70)	
Female	26 (29.50)	53 (36.30)	
Age (years)	60.31 ± 13.30	66.21 ± 13.48	0.001[t]
Weight (kg)	67.00 ± 16.40	64.02 ± 14.36	0.146[t]
Body mass index (kg/m^2)	24.82 ± 5.14	23.89 ± 4.46	0.145[t]
At 1st time			
Systolic blood pressure (mmHg)	125.33 ± 23.06	137.62 ± 23.88	< 0.001[t]
Heart rate (bpm)	88.92 ± 21.14	93.53 ± 21.25	0.109[t]
Left ventricular ejection fraction (%)	27.25 ± 5.72	28.21 ± 6.69	0.263[t]
At 12 months			
Systolic blood pressure (mmHg)	122.09 ± 18.67	125.33 ± 22.87	0.278[t]
Heart rate (bpm)	73.72 ± 13.85	78.71 ± 17.03	0.025[t]
Smoking	13 (14.80)	14 (9.60)	0.229[c]
Alcohol	14 (15.90)	6 (4.10)	0.002[c]
Comorbidities			
Diabetes mellitus type 2	29 (33.00)	70 (47.90)	0.025[c]
Hypertension	86 (97.70)	131 (89.70)	0.022[c]
Dyslipidemia	75 (85.2)	120 (82.20)	0.546[c]
Coronary artery disease	39 (44.30)	70 (47.90)	0.590[c]
Stroke	6 (6.80)	19 (13.00)	0.137[c]
Asthma/Chronic obstructive pulmonary disease	0 (0.0)	2 (1.40)	0.529[c]
Atrial fibrillation	18 (20.50)	36 (24.70)	0.460[c]
Hyperthyroid	2 (2.30)	1 (0.70)	0.558[c]
Chronic kidney disease	15 (17.00)	51 (34.90)	0.003[c]
Medication drug			
Antiplatelet	64 (72.70)	104 (71.20)	0.806[c]
Anticoagulant	23 (26.10)	44 (30.10)	0.512[c]
Statins	77 (87.50)	127 (87.00)	0.909[c]
Furosemide dose			0.655[c]
< 40 mg	30 (34.10)	54 (37.00)	
≥ 40 mg	58 (65.90)	92 (63.00)	
Cause of heart failure			0.941[c]
Ischemic	36 (40.90)	62 (42.46)	
Non ischemic	49 (55.68)	80 (54.79)	
Unknown	3 (3.4)	4 (2.73)	
Reimbursement scheme			0.644[c]
Universal coverage	57 (64.77)	89 (60.95)	
Social security	26 (29.54)	45 (30.82)	
Government or state enterprise officer	5 (5.68)	12 (8.21)	

Abbreviations: bpm, beats per minute; kg/m^2, kilogram per square meter; mg, milligram; mmHg, millimeters of mercury; n, number

Data are presented as number (%), mean ± standard deviation or median (interquartile range). P-value corresponds to [t]Independent samples t-test, [m]Mann-Whitney U test, [c]Chi-square test or [f]Fisher's exact test.

Differences in patient gender (70.50% vs. 63.70% males, respectively) and age (average age 60.31 vs. 66.21 years, respectively) were observed between the HF and general cardiology groups. The baseline systolic blood pressure was lower in the HF group (systolic blood pressure = 125.33 vs. 137.62 mmHg, p < 0.001). No significant difference in the baseline left ventricular ejection fraction was observed between the two groups. The HF group had a higher alcohol consumption and lower prevalence of diabetes and chronic kidney disease than the general cardiology group. Cause of heart failure in both HF group and general cardiology group was more common in non ischemic caused. No significant differences in other cardiovascular diseases, such as coronary artery disease, atrial fibrillation, and cerebrovascular disease, were observed between the two groups. Furthermore, no significant difference in the baseline use of other drugs apart from GDMT such as antiplatelets, anticoagulants, and diuretics (furosemide dose), was observed between the two groups.

Table 2 shows the primary outcomes. The results showed that the mortality rate was 3.45 events/100 person-years in the HF clinic group and was 11.66 events/100 person-years (p = 0.040) in the general cardiology clinic group, respectively. The readmission rate was 26.37 events/100 person-years in the HF clinic group, and was 79.01 events/100 person-years (p < 0.001) in the general cardiology clinic group, respectively. The composite outcome rate of mortality and readmission was 28.74 events/100 person-years in the HF clinic group, whereas it was 91.79 events/100 person-years in the general cardiology clinic group (p < 0.001).

Table 3 shows the results of the multivariate Cox regression analysis. The HF clinic group had adjusted hazard ratios versus general cardiology clinic for mortality (0.27, 95% confidence interval (95% CI) 0.07–0.99, p = 0.048), readmission (0.40, 95% CI 0.24–0.67, p = 0.001), and composite outcome of mortality or readmission (0.37, 95% CI 0.23–0.60, p < 0.001). The Kaplan–Meier analysis was showed in Figures 2, 3, and 4.

Table 2 Incidence rate of one-year outcomes for heart failure clinic versus general cardio clinic

1-year outcome	Heart failure clinic (n = 88)	General cardio clinic (n = 146)	P-value
	Incidence rate/ 100 person years	Incidence rate/ 100 person years	
Mortality	3.45	11.66	0.040
Readmission	26.37	79.01	< 0.001
Composite (mortality/readmission)	28.74	91.79	< 0.001

Abbreviations: n, number

Table 3 Multivariable Cox regression analysis for adjusted one-year outcomes for heart failure clinic versus general cardio clinic

1-year outcome	Univariable analysis			Multivariable analysis		
	HR	95%CI	P-value	HR_{adj}*	95%CI	P-value
Mortality	0.30	(0.09 - 1.02)	0.054	0.27	(0.07 - 0.99)	0.048
Readmission	0.33	(0.21 - 0.53)	< 0.001	0.40	(0.24 - 0.67)	0.001
Composite (mortality/readmission)	0.31	(0.20 - 0.48)	< 0.001	0.37	(0.23 - 0.60)	< 0.001

Abbreviations: CI, confident interval; HR, hazard ratio; HR_{adj}, adjusted hazard ratio
*Adjusted for age, weight, BMI, SBP baseline, stroke, asthma, AF, and CKD
**For heartrate at 12 months, alcohol, DM, and HT that have a statistical significant at baseline do not include in the multivariate analysis because they don't have any association with any outcomes in the univariate analysis.

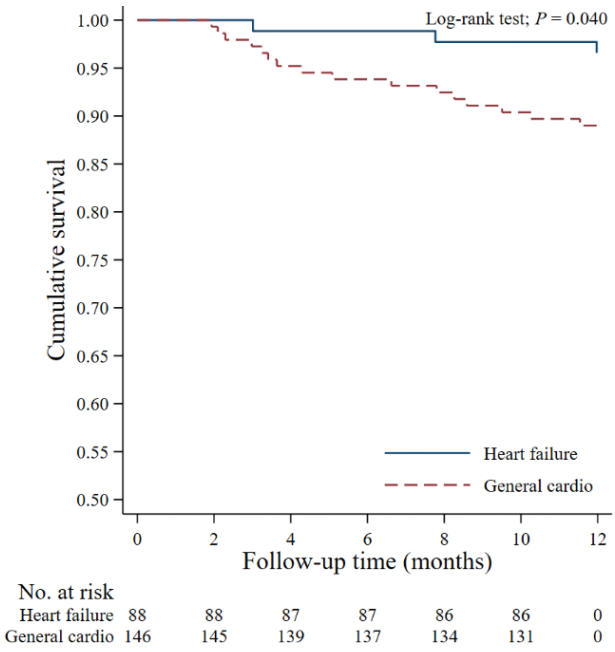


Figure 2 Cumulative survival and follow up time

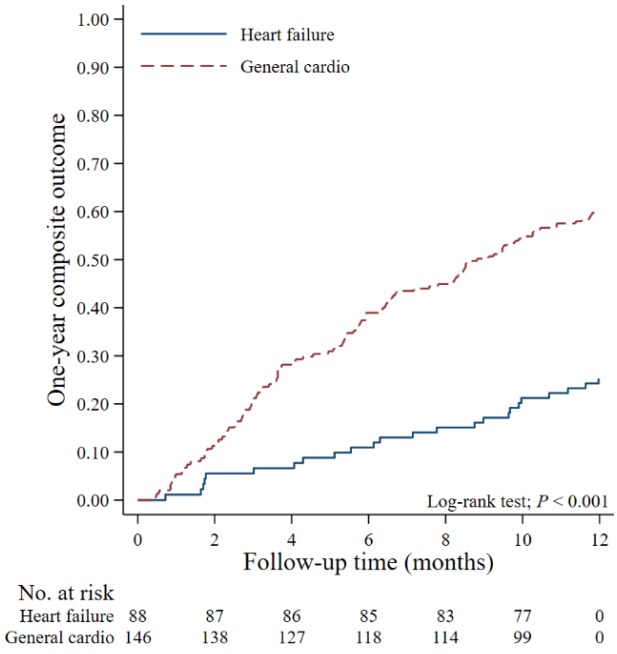


Figure 3 1 year composite outcome of mortality and HF admission and follow up time

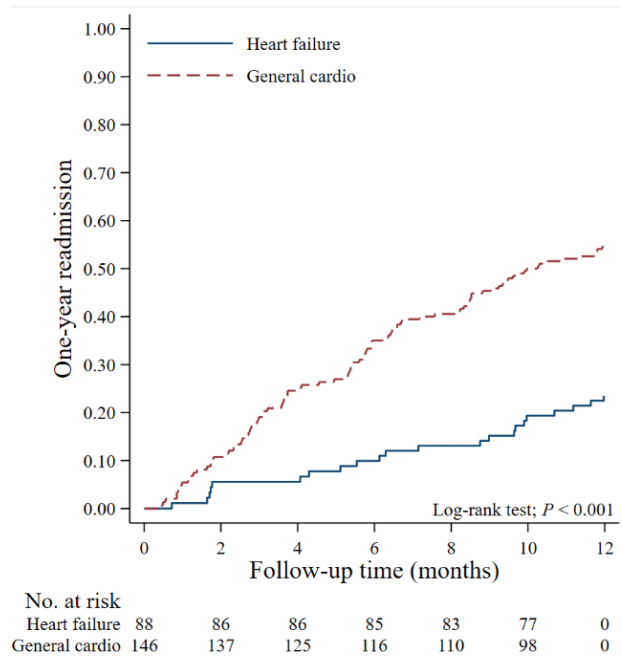


Figure 4 1 year readmission and follow up time

Regarding the secondary outcomes were pattern of GDMT use and the time to escalate to the target doses at 1-, 3-, 6-, and 12-month follow-ups. The results of pattern of GDMT was showed that in the HF group with use of beta blocker dosage < 50.00% at 1-, 3-, 6-, and 12-month follow-ups was 42.00% (n = 37), 15.90% (n = 14) ,14.80% (n = 13), 8.00% (n = 7) , respectively and group use of beta blocker ≥ 50% at 1-, 3-, 6-, and 12-month follow-ups was 34.10% (n = 30), 27.30% (n = 24), 19.30% (n = 17), 19.30% (n = 17), respectively. In cardiology clinic group with use of beta blocker dosage < 50.00% at 1-, 3-, 6-, and 12-month follow-ups was 58.90% (n = 86), 34.90% (n = 51), 30.10% (n = 44), 27.40% (n = 40), respectively and group use of beta blocker ≥ 50.00% at 1-, 3-, 6-, and 12-month follow-ups was 17.80% (n = 26), 25.30% (n = 37), 21.90% (n = 32), 21.20% (n = 31), respectively. In use of ACEI/ARB/ARNI with dosage < 50% in HF clinic groups at 1-, 3-, 6-, and 12-month follow-ups was 69.30% (n = 61), 61.40% (n = 54), 53.40% (n = 47), 45.50% (n = 40), respectively and group use of ACEI/ARB/ARNI with dosage ≥ 50% at 1-,3-,6-, and 12-month follow-ups was 17.00% (n = 15), 18.20% (n = 16), 22.70% (n = 20), 25.00% (n = 22),

respectively. In use of ACEI/ARB/ARNI with dosage < 50.00% in cardiology clinic groups at 1-, 3-, 6-, and 12-month follow-ups was 43.20% (n = 63), 41.80% (n = 61), 39.70% (n = 58), 36.30% (n = 53), respectively and group group use of ACEI/ARB/ARNI with dosage ≥ 50% at 1-, 3-, 6-, and 12-month follow-ups was 15.80% (n = 23), 17.10% (n = 25), 18.50% (n = 27), 19.90% (n = 29), respectively. Other drug were showed in Table 4 and Figures 5 and 6.

Table 4 Percentage of target doses achieved by the drugs in heart failure clinic and general cardio clinic

Dosage used	Heart failure clinic (n = 88)				General cardio clinic (n = 146)			
	Baseline	3 months	6 months	12 months	Baseline	3 months	6 months	12 months
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Beta blocker								
none	1 (1.10)	3 (3.40)	1 (1.10)	4 (4.50)	10 (6.80)	14 (9.60)	23 (15.80)	27 (18.50)
< 50%	37 (42.0)	14 (15.90)	13 (14.80)	7 (8.0)	86 (58.90)	51 (34.90)	44 (30.10)	40 (27.40)
≥ 50%	30 (34.10)	24 (27.30)	17 (19.30)	17 (19.30)	26 (17.80)	37 (25.30)	32 (21.90)	31 (21.20)
100%	20 (22.70)	47 (53.40)	57 (64.80)	60 (68.20)	24 (16.40)	44 (30.10)	47 (32.20)	48 (32.90)
ACEI/ARB/ARNI								
none	11 (12.50)	13 (14.80)	12 (13.60)	15 (17.0)	59 (40.40)	53 (36.30)	55 (37.70)	59 (40.40)
< 50%	61 (69.30)	54 (61.40)	47 (53.40)	40 (45.50)	63 (43.20)	61 (41.80)	58 (39.70)	53 (36.30)
≥ 50%	15 (17.0)	16 (18.20)	20 (22.70)	22 (25.0)	23 (15.80)	25 (17.10)	27 (18.50)	29 (19.90)
100%	1 (1.10)	5 (5.70)	9 (10.20)	11 (12.50)	1 (0.70)	7 (4.80)	6 (4.10)	5 (3.40)
MRA								
none	31 (35.20)	26 (29.50)	24 (27.30)	25 (28.40)	88 (60.30)	75 (51.40)	71 (48.60)	74 (50.70)
< 50%	39 (44.30)	31 (35.20)	30 (34.10)	22 (25.0)	38 (26.0)	43 (29.50)	41 (28.10)	40 (27.40)
≥ 50%	15 (17.0)	27 (30.70)	28 (31.80)	33 (37.50)	17 (11.60)	23 (15.80)	29 (19.90)	26 (17.80)
100%	3 (3.40)	4 (4.50)	6 (6.80)	8 (9.10)	3 (2.10)	5 (3.40)	5 (3.40)	6 (4.10)
SGLT2								
none	83 (94.30)	85 (96.60)	80 (90.90)	83 (94.30)	137 (93.80)	132 (90.40)	131 (89.70)	132 (90.40)
< 50%	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
≥ 50%	2 (2.30)	0 (0.0)	3 (3.40)	1 (1.10)	3 (2.10)	4 (2.70)	3 (2.10)	3 (2.10)
100%	3 (3.40)	3 (3.40)	5 (5.70)	4 (4.50)	6 (4.10)	10 (6.80)	12 (8.20)	11 (7.50)

Abbreviations: ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; BB, beta blockers; MRA, mineralocorticoid receptor antagonist; n, number; SGLT2 I, sodium -cotransporter2 inhibitors

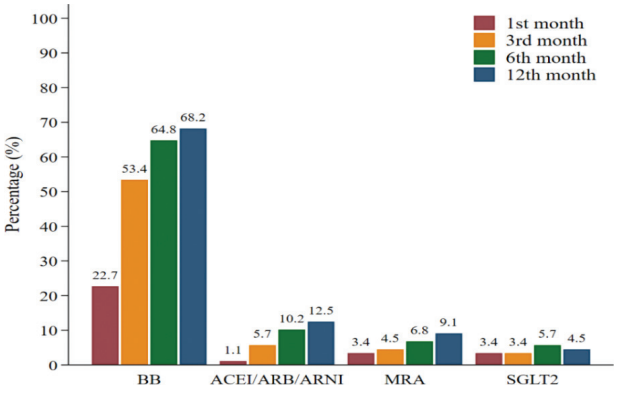


Figure 5 Time to achieve target drug dose in heart failure clinic

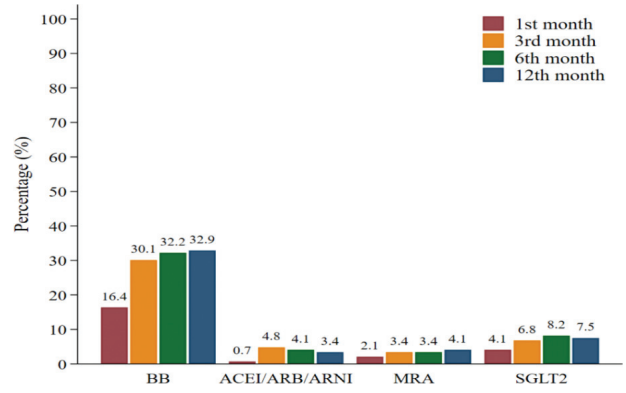


Figure 6 Time to achieve target drug dose in general cardio clinic

DISCUSSION

With the rise of digital technology and widespread internet usage, global evidence-based guidelines for GDMT use in HFrEF management have become easily accessible to practicing cardiologists, thereby removing potential barriers to guideline information and improving HFrEF management. However, the implementation of these guidelines in real-world clinical practice, particularly percentage usage and drug titration, is often inadequate. Thus, in this study, we compared the prescription of GDMT between the two groups, with the focus on evaluating the implementation of management and medication adjustment, to determine whether HF clinics can improve the implementation of GDMT and lead to improved outcomes in terms of mortality and readmission.

In this study, the primary outcomes confirmed that the setting of HF clinics had a statistically significant impact on reducing HF readmission and mortality rates compared with the traditional approach of general cardiology care. HF clinics offer several advantages, including improved patient education and self-management skills, better medication adherence, and more effective monitoring and management of symptoms. In this study, drug profiles and the time frame for dose escalation were analyzed to provide new insights into the success of HF clinics in improving patient outcomes. The study results showed that general cardiology clinics had a plateau phase in up-titrating the GDMT dose, with the majority of the dose increase occurring in the first 3 months and little to no additional increase in the subsequent follow-up visits at 6 and 12 months. In contrast, the HF clinic showed a more steady increase in the GDMT dose throughout the 12-month follow-up period, potentially contributing to the better outcomes observed in this group. But the rate of SGLT-2 inhibitor usage in the general cardiology clinic is higher than HF clinic due to patients in general cardiology clinic group have higher underlying DM than HF clinic group and in general cardiology clinic group many patients have background in government or state enterprise officer.

The study findings suggest that the general cardiology clinic group had lower adherence to the management of HF than the HF clinic group. At baseline, the systolic blood pressure was lower in the HF clinic group, and at the 12-month follow-up, the heart rate was higher in the general cardiology clinic group. This finding suggests that there was more room for increasing the dose of medication, but there was a plateau in the management of the disease. The more aggressive approach used in the HF clinic may have led to improved outcomes, such as reduced rehospitalization and mortality rates, compared with the general cardiology clinic.

Furthermore, patients in the HF clinic group were generally younger, whereas those in the general cardiology clinic group had a higher incidence of comorbidities such as chronic kidney disease and diabetes. The decrease in the estimated glomerular filtration rate may have limited clinicians' ability to add and up-titrate drug doses according to guidelines, which could have resulted in suboptimal patient management. This may have contributed to decreased efficacy in treating patients in the general cardiology clinic group, leading to higher readmission and mortality rates than those in the HF clinic group.

Patients in the HF clinic group may experience significant improvements in their quality of life because they are not recurrently admitted to hospitals and are able to stay at home and maintain their normal daily activities. Reducing hospital readmissions can also be cost-effective for patients and the healthcare system. Hospital stays and readmissions can be costly for patients, especially for those who have to pay out of pocket for any part of their care, and the healthcare system. Reducing the need for readmissions can reduce the burden on the healthcare system, allowing for the allocation of resources to other critical areas.

This study emphasizes the crucial role of following treatment guidelines in improving clinical outcomes in patients with HF. The Eliminate Coronary Artery Disease (ECAD) trial showed that simply closely monitoring patients and providing

follow-up care may not be sufficient to achieve optimal results if the drug profile is not optimized[19]. Therefore, it is necessary to ensure that patients receive appropriate medications at appropriate doses according to the current guidelines. This study showed that the rapid up-titration of GDMT could be a safe and well-tolerated approach that leads to improved clinical outcomes in patients with acute HF. These findings are consistent with those of the STRONG-HF trial[20], which emphasized the importance of intensively titrating GDMT in patients with HF. However, it is important to note that drug up-titration should be performed under close medical supervision and with personalized treatment plans based on each patient's unique needs and health status. HF clinics can play a critical role in this process by providing specialized care and monitoring to ensure that patients receive the appropriate GDMT at the optimal dose. This can lead to improved clinical outcomes, including reduced mortality and HF rehospitalization, while minimizing the risk of adverse effects from medication titration.

This study has some limitations. First, this was a retrospective, not randomized study. Thus, other unknown variables may have affected the results. Second, patient allocation to HF clinic care was not randomized, which raises the possibility of referral bias. Third, in this study, only patients who were able to visit HF clinics or those believed to benefit from increased testing were referred, whereas patients in the nonclinic group may have been less willing to undergo such testing for various reasons. Thus, this study may have the potential for selection bias. Further studies are needed to address these limitations.

CONCLUSION

The study results showed that the HF clinic setting had a significant impact on patient outcomes. HF clinics showed better results in reducing readmission and mortality rates. The results showed that HF clinics could steadily increase drug doses throughout the 12-month follow-up period. These findings highlight the importance of guideline adherence in improving patient outcomes in HF treatment and identifying barriers to optimal HF management in general cardiology clinics.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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Case Report

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Ruptured Pseudoaneurysm of Branch of Profunda Femoral Artery during Revision Total Hip Arthroplasty: a Case Report

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ABSTRACT

A ruptured pseudoaneurysm is a rare but potentially fatal complication during revision total hip arthroplasty. We report a case of a 46-year-old female with a rupture of a pseudoaneurysm at the branch of the left profunda femoral artery during revision total hip arthroplasty. The patient presented with dislocation of the left total hip arthroplasty, which failed closed reduction. During the revision surgery, a massive pulsatile bleeding occurred, which required an emergent vascular surgeon consultation to repair the ruptured pseudoaneurysm. It was later confirmed to be located at the branch of the left profunda femoral artery. Although rare, we recommend performing pre-operative CT angiography and consulting with a vascular surgeon before attempting revision total hip arthroplasty in patients with atypical symptoms, such as unusual thigh swelling and unexplained anemia.

KEYWORDS: profunda femoral artery, revision total hip arthroplasty, rupture pseudoaneurysm

INTRODUCTION

With more than 1 million procedures performed worldwide, total hip arthroplasty (THA) is considered one of the most common orthopedic procedures[1]. The total number of procedures performed each year is expected to increase for both primary and revision THA[2-3]. Vascular injury following hip arthroplasty is a devastating complication that results in patient morbidity and mortality. There is a reported incidence of vascular injury of 0.04% for primary THA and even higher at 0.19% for revision THA[4]. Pseudoaneurysms are a rare subset of vascular complications caused by damage to vessel wall integrity, leading to the development of a compartment of blood-fed arterial structure that is not enclosed by the arterial wall[5]. In this article, we present a case of pseudoaneurysm rupture of the profunda femoris artery (PFA) during revision THA.

CASE REPORT

A 46-year-old female was referred to our hospital with an irreducible dislocation of her left THA. One year prior, she had been in a severe motor vehicle accident and was diagnosed with a close fracture of the left pelvis and acetabulum with posterior hip dislocation. She underwent open reduction and internal fixation with plates and screws at the left acetabulum and closed reduction with internal fixation with sacroiliac screws at her left pelvic. Three months after

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the index operation, she continued to experience pain in her left hip. The hip joint aspiration and follow-up radiograph showed infection of her left hip. She underwent multiple debridements and implant removal and received antibiotics. At a 1-year follow-up after debridement, her clinical and laboratory findings showed improvement of the infection, and she was referred to our arthroplasty unit for a THA of her left hip. Three months prior to her current presentation, she underwent an uneventful hybrid THA (figure 1) and was sent to a rural hospital for easier follow-up care and post-operative physical therapy.

On her current presentation, she reported experiencing sudden pain in her left hip while attempting to move from the bed. She was then transferred to a rural hospital, where an orthopedic physician diagnosed her with a left THA dislocation (figure 2) but failed to perform a closed reduction of the hip. Subsequently, she was referred to our hospital for further evaluation and management one week later.

Upon arrival, physical examination showed shortening and swelling of her left leg, but distal neurovascular appeared to be intact. Plain radiographs showed a posterior dislocation of the left THA, with no subsidence of the femoral stem and acetabular cup position remaining the same as on the early postoperative radiograph. Her hemoglobin level was 9.4 g/dL, white blood cell count was 8,800 cells/cumm and platelet count was 388,000 cells/cumm. A CT scan of her hip revealed retroversion of the femoral stem, which could be the cause of the dislocation. After optimizing the patient's condition and preoperative planning over ten days, we decided to perform an open reduction and femoral stem revision, the patient was placed in a lateral decubitus position. The skin was incised through the previous surgical scar from the index THA, and a lateral approach was performed. The displaced femoral head was visible, and a large hematoma was found distal to acetabular cup (figure 3). During hematoma evacuation, a massive pulsatile bleeding had occurred. A vascular surgeon was immediately consulted intraoperatively, the suspected pseudoaneurysm at branch of profunda femoris artery was found and repaired. After successful repair, the hip was reduced and distal vascular flow was evaluated by ultrasound, which showed good blood flow. Total estimated blood loss was 9,000 ml, six liters of crystalloid, five units of packed red cells and six units of fresh frozen plasma were required to resuscitate the patient intraoperatively. The patient was transferred to the ICU for close monitoring for 2 days.

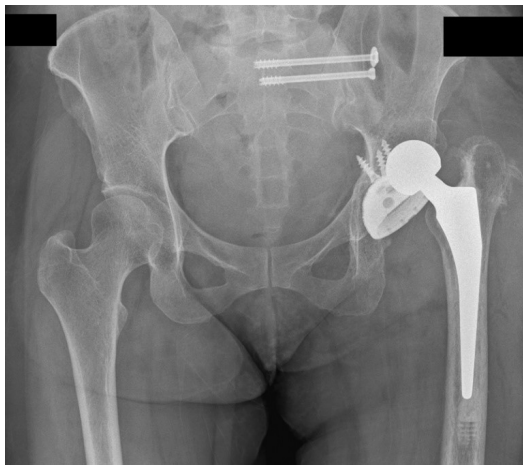

Figure 1 Early postoperative radiograph for left hybrid total hip arthroplasty

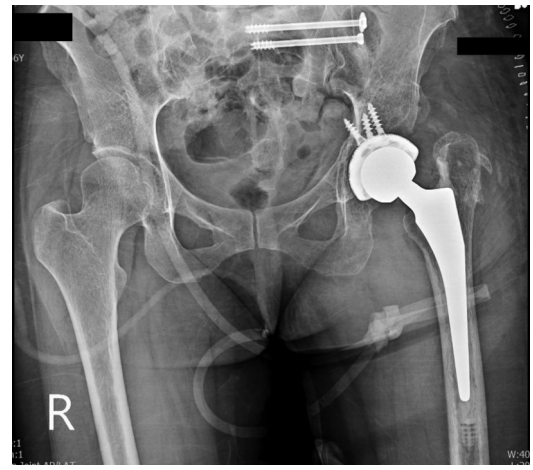

Figure 2 Left total hip arthroplasty dislocation 3 months after index total hip arthroplasty

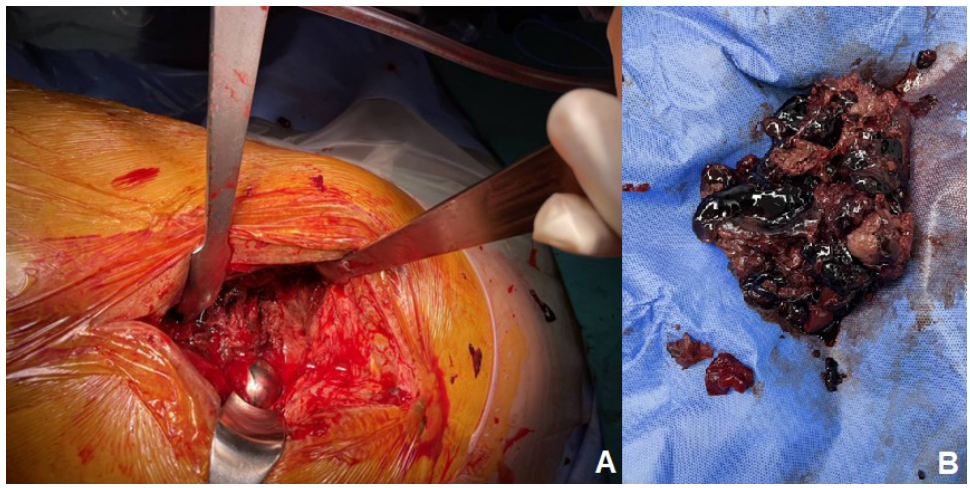

Figure 3 The displaced femoral head was found intraoperative (A). A large hematoma was located distal to acetabular cup and subsequently evacuated (B).

Computer Tomography Angiography (CTA) of the lower limbs showed a 0.5 x 0.7 cm pseudoaneurysm at the branch of the left profunda femoral artery (figure 4). Two weeks after the operation, the patient was stable and allowed to walk only by toe-touch with a walking aid, and she was discharged from the hospital. At the 2-month follow-up, the patient's clinical condition had improved. She could walk with a walking aid without pain or abnormal swelling in her thigh, and her hip remained stable. An appointment was made for a 6-month follow-up to evaluate the hip stability and CTA of the lower limbs.

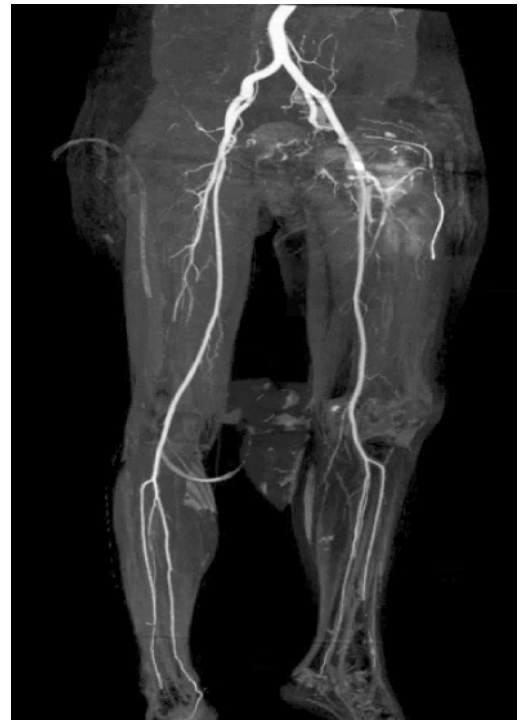

Figure 4 Postoperative Computer Tomography Angiography of the lower limbs showed a 0.5 x 0.7 cm pseudoaneurysm at the branch of the left profunda femoral artery. No evidence of active contrast extravasation.

DISCUSSION

Vascular injury during THA is considerably rare but can cause devastating complications such as persistent limb ischemia, amputation, and death[6]. These vascular injuries consisted of thromboembolic complications, vessel lacerations, arteriovenous fistulas and pseudoaneurysms[7]. Pseudoaneurysms occur after a localized arterial wall injury, which causes local blood to pool in the injured area and become enclosed by a pseudocapsule[5,8]. This pseudocapsule is an abnormal thin vessel wall that is prone to rupture. Several mechanisms are reported to be a cause of the development of pseudoaneurysms after THA. Direct injury caused by instruments

such as retractors, scalpels, or orthopedic hardware, including protruding screws, extruded cement, or component migration, can result in a small puncture to the arterial wall, leading to pseudoaneurysm formation. Indirect injury often occurs due to stretching injuries of the atherosclerotic artery vessels, causing intimal tears in the artery. This can happen during forceful traction in THA operations[6,9].

Injury to vessels during THA has been reported, with the most commonly affected vessels being the common femoral artery, external iliac artery, and profunda femoris artery[6]. Intrapelvic migration of the acetabular component and protruding screws has been documented as a potential cause of pseudoaneurysm in the external iliac artery. Meanwhile, pseudoaneurysms in the common femoral artery and profunda femoris artery frequently occur during femoral preparation, implant migration around the femur, and forceful manipulation of the leg during surgery. Harper et al. reported a patient with Profunda femoris pseudoaneurysm following revision total hip arthroplasty. Patient in his report presents with thigh pain, swelling, and symptomatic anemia which has been evaluate with CT scan and conventional angiography. The patient successfully treated with coil embolization and hematoma evacuation. The authors believe that the injury to the profunda femoris artery may have occurred during the anterior approach at the time of the patient's index THA. Retractor placement, hyperextension during preparation of the femur, and unfamiliarity with the approach have been proposed as potential causes of the injury[10]. Baker et al. also reported a case of a profunda femoris pseudoaneurysm caused by medial migration of broken cerclage wires, 8 years after revision hip surgery. The patient presented with thigh pain, swelling, and anemia. Coil embolization failed in this case, and multiple covered stents were required instead[8]. Nabhani et al. report a case with a deep femoral artery perforating branch pseudoaneurysm after revision hip arthroplasty due to recurrent dislocation. The vessel is located far from the operation site; thus, the authors believe that the cause of the injury was from the repeated manipulation of the patient's leg during the operation[11]. Pollock et al. reported a case of profunda femoral artery pseudoaneurysm following two-stage revision hip surgery for periprosthetic infection, believed to have been caused by a sharp bone fragment encountered during the procedure[12]. (table 1)

Table 1 Literature reviews of profunda femoris artery pseudoaneurysm after total hip arthroplasty or revision total hip arthroplasty

Authors	Year	Sex/ Age	Indication for surgery	Cause	Symptoms	Imaging	Treatment	Time interval
Nozawa et al.[13]	2000	F/70	Post-traumatic OA	Osteotome	Active bleeding, swelling thigh	Angiography	Coil embolization	6 weeks
Harper et al.[10]	2015	M/61	Aseptic loosening femoral stem	Retractor placement, anterior approach	Pain, anemia, swelling thigh	Angiography	Coil embolization	7 weeks
Huynh et al.[14]	2015	M/71	Secondary OA	Retractor placement	Pain, swelling thigh	CT angiogram	Open repair	4 days
Baker et al.[8]	2020	M/84	Periprosthetic femoral fracture	Broken cerclage wire	Pain, anemia, swelling thigh	CT angiogram	Multiple covered stents	8 years
Nabhani et al.[11]	2022	F/50	Recurrent THA dislocations	Recurrent THA dislocations	Pain	CT angiogram	Coil embolization	2 weeks
Pollock et al.[12]	2022	M/69	Second stage revision THA	Sharp bone fragment	Pain, anemia, swelling thigh	CT scan	Open repair	2 weeks

The exact etiology of the pseudoaneurysm in our patient was unclear. Her index total hip arthroplasty proceeded uneventfully, with no signs or symptoms of pseudoaneurysm following the surgery. One purpose is that the pseudoaneurysm may have occurred when the THA was dislocated, and there were multiple forceful attempts to reduce the hip. This could have caused an indirect injury to the blood vessels.

Early detection of pseudoaneurysm formation after hip arthroplasty can often be difficult due to its non-specific symptoms, such as pain, swelling, and refractory anemia[15-16]. For our patient, who presented with a dislocated THA, this could have obscured the symptoms of the pseudoaneurysm. The time to detection is currently reported to range from 4 months to 15 years after the index surgery[10,17]. Performing revision surgery in the presence of a pseudoaneurysm at the surgical site could result in rupturing the pseudoaneurysm sac, which can cause fatal bleeding, as in the case we presented above.

To our knowledge, there are currently no effective screening guideline available to detect pseudoaneurysm or other potential vascular complications prior to performing revision surgery. Diesel et al. have defined high-risk patients for vascular injury during revision THA as those with components or cement migrated more than 5 mm beyond the ilioischial line in pelvic AP or Judet radiographic view. They recommend further evaluation of these groups of patients by CT angiography and vascular surgeon evaluation[18]. However, vascular injuries in THA do not always result from migrated components or protruding implants but can also occur due to indirect mechanisms. Some authors have recommended performing vascular evaluation in every case undergoing revision THA surgery, regardless of the presence of migration[6], but the cost-effectiveness of this approach is questionable.

CONCLUSION

Pseudoaneurysm is a rare vascular complication of THA, and revision surgery poses a higher risk than primary THA. Detecting pseudoaneurysms early on may be difficult because of their nonspecific symptoms, which can resemble those of other causes of painful THA. Atypical symptoms, such as unusual thigh swelling and unexplained anemia in dislocated THA patients, should raise a high degree of suspicion for pseudoaneurysms. In such cases, we recommend performing pre-operative CT angiography and consulting with a vascular surgeon before attempting revision THA.

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None

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In order to maintain the high standards of the Vajira Medical Journal: Journal of Urban Medicine, our editorial team relies on the expertise of numerous professionals. They play a pivotal role in determining the topics to explore, deciding which manuscripts to publish, and making necessary adjustments to ensure the scientific integrity and reliability of the information provided. This fosters the growth and advancement of medical and health science research. I deeply appreciative of the dedication and proficiency exhibited by the individuals who reviewed manuscripts for the journal from September 1st, 2022, through August 31st, 2023.

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