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EDITORIAL

Intriguing Review and Topics in Third Issue of Thai Journal of Obstetrics and Gynaecology 2025

Vorapong Phupong, M.D., FRTCOG.*

** Editor in Chief, Thai J Obstet Gynaecol, The Royal Thai College of Obstetricians and Gynaecologists*

This third issue of Thai Journal of Obstetrics and Gynaecology 2025 contains many interesting articles. The special article is "Potential of pravastatin for the prevention and treatment of preeclampsia". The authors reviewed the risk factors of preeclampsia, pathophysiology, current preventive strategies for preeclampsia, and pravastatin as a novel approach for preeclampsia prevention and treatment[1].

This issue also contains seven original articles and one case report. Sitthisaknawakul et al performed a randomized controlled trial to study the efficacy of using a heat patch to reduce postoperative pain after cesarean delivery and found a heat patch applied on the lower back resulted in significantly reduced pain 8 hours after cesarean delivery[2]. Wongjariyakul et al performed a randomized clinical trial to evaluate the efficacy of preoperative tranexamic acid in reducing intraoperative blood loss in high-risk cesarean deliveries. They found that tranexamic acid effectively reduced intraoperative blood loss in women at high risk of PPH who underwent cesarean deliveries[3]. Banjongpark et al performed a prospective cohort study to determine the incidence of chemotherapy-induced severe neutropenia in the nadir period among gynecologic cancer patients receiving carboplatin and paclitaxel. They found that severe neutropenia occurred in 46.2% per cycle and 74.0% per patient[4]. Wongvivattanakarn et al performed a randomized placebo control trial to study the efficacy of lidocaine-prilocaine cream versus placebo in conjunction with lidocaine injection in relieving pain during episiotomy repair. They found that lidocaine-prilocaine cream in conjunction with lidocaine injection effectively reduced pain during lidocaine injection, perineal muscle repair, and perineal skin repair without adverse reaction[5]. Nampeng et al performed a retrospective analysis to assess the prevalence of sexually transmitted infections (STIs) and identify factors associated with STIs among female sexual assault victims. The result showed that 12.33% tested positive for at least one STI, with Chlamydia trachomatis being the most common[6]. Jaitham et al performed a randomized controlled trial to evaluate the effectiveness of cold pack gel in reducing postoperative pain after cesarean delivery, Pfannenstiel skin incision. The results revealed the cold pack gel could reduce postoperative opioid use without any serious side effects. However, the postoperative pain scores were not decreased[7]. Koedplangtong et al performed a randomized controlled trial to evaluate the efficacy of antenatal perineal massage (APM) in reducing postpartum morbidities, particularly anal incontinence (AI). The results revealed that APM did not reduce AI incidence. But it reduced AI severity and fecal incontinence incidence[8]. Lorsirirat et al performed a randomized, double-blind, placebo-controlled trial to assess the efficacy of oral ginger powder for prevention of postoperative bowel ileus in benign gynecologic abdominal hysterectomy. They found that oral ginger powder could reduce postoperative bowel ileus in benign gynecologic abdominal hysterectomy[9].

The Royal Thai College of Obstetricians and Gynaecologists mid-year meeting already held during 23-25 April 2025 at Centara Grand at Central Plaza Ladprao Bangkok, Thailand. The theme of the meeting was "NextGen OB-GYN: Stepping into Tomorrow". This meeting was successful with 800 delegates.

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Thai Journal of Obstetrics and Gynaecology
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SPECIAL ARTICLE

Potential of Pravastatin for the Prevention and Treatment of Preeclampsia

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ABSTRACT

Preeclampsia (PE) is a severe pregnancy complication affecting 5–10% of pregnancies worldwide and remains a leading cause of maternal and neonatal morbidity and mortality. Although low-dose aspirin is widely used for prevention, its efficacy is limited, necessitating the development of novel therapeutic strategies. This review examines the potential of pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, as a preventive and therapeutic agent for PE.

Pravastatin exerts pleiotropic effects, including upregulation of placental growth factor, suppression of soluble fms-like tyrosine kinase-1, and anti-inflammatory and antioxidative properties. Preclinical studies demonstrate its ability to mitigate PE-like symptoms in animal models, whereas clinical studies suggest its potential to reduce the incidence of severe PE in high-risk pregnancies. However, its effectiveness is limited when administered after 35 weeks of gestation, and its optimal dosage remains undetermined.

Building on existing clinical evidence, well-designed large-scale randomized controlled trials are crucial to establish the safety and efficacy of pravastatin in PE prevention. Further research is needed to evaluate its potential for reducing long-term cardiovascular risk in women with a history of PE. An ongoing clinical trial in Japan (jRCTs031230067) aims to address these gaps and contribute to future PE prevention strategies.

Keywords: preeclampsia, pravastatin, angiogenic factors, cardiovascular risk, randomized controlled trial.

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Introduction

Preeclampsia (PE) is a multisystem pregnancy complication characterized by new-onset hypertension, proteinuria, and organ dysfunction after 20 weeks of gestation. It can result in severe maternal and fetal complications, affecting multiple organ systems, including the liver, kidneys, cardiovascular system, and coagulation pathways. In severe cases, PE may progress to eclampsia, a life-threatening condition characterized by seizures, or to hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome, further increasing maternal and perinatal risks.

Globally, PE affects approximately 5%–10% of pregnancies and remains a leading cause of maternal and perinatal mortality and morbidity. Each year, it is associated with an estimated 50,000 maternal and more than 500,000 perinatal deaths worldwide[1, 2]. Early-onset PE, occurring before 34 weeks of gestation, poses a particularly high risk of adverse neonatal outcomes due to prematurity and fetal growth restriction (FGR). It is also associated with an increased risk of stillbirth and long-term neurodevelopmental impairment in surviving infants[3]. Late-onset PE, occurring after 34 weeks of gestation, significantly contributes to maternal complications such as stroke, placental abruption, and postpartum hemorrhage[3]. These severe maternal and neonatal outcomes underscore the urgent need for effective preventive and therapeutic interventions.

Despite decades of research, delivery of the placenta remains the only definitive treatment for PE, which presents challenges when the condition occurs preterm. Premature delivery is associated with an increased risk of neonatal complications, including respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and necrotizing enterocolitis (NEC), often necessitating specialized neonatal intensive care[4]. Additionally, women with a history of PE have a significantly higher lifetime risk of cardiovascular disease (CVD), stroke, and metabolic syndrome, suggesting shared pathophysiological mechanisms between hypertensive pregnancy disorders and long-term cardiovascular dysfunction[5]. Emerging evidence also suggests that offspring born to mothers with PE may have an increased predisposition to hypertension and metabolic disorders in adulthood, with intergenerational health implications[6].

In this paper, we provide an overview of the risk factors for PE, current understanding of its pathophysiology, and the preventive role of low-dose aspirin. Furthermore, we focus on the potential use of pravastatin as a novel and promising strategy for PE prevention. Given its pleiotropic effects, including endothelial protection, anti-inflammatory properties, and improvement of placental function, pravastatin has gained attention as a potential intervention to modify the disease course. We examine the current evidence supporting pravastatin use for PE prevention and discuss its future clinical implications.

Risk factors

Although substantial progress has been made in recent years, the precise pathophysiological mechanisms underlying PE remain unclear. However, several maternal risk factors have been identified, including advanced maternal age, nulliparity, twin pregnancy, assisted reproductive technologies such as in vitro fertilization (IVF), obesity, pre-existing hypertension, type 1 and type 2 diabetes mellitus, chronic kidney disease, and autoimmune diseases such as systemic lupus erythematosus and antiphospholipid syndrome, and a family history of PE[7-12]. Additionally, lifestyle factors such as excessive gestational weight gain, poor diet, and physical inactivity have been implicated in increasing PE risk[13]. Genetic predisposition, epigenetic modifications[14], and environmental influences are believed to contribute to the heterogeneity of PE phenotypes, further complicating prevention and treatment strategies[15].

Despite these advances, effective disease-modifying therapies remain limited, and the search for novel pharmacological interventions to improve

maternal and fetal outcomes remains a major research priority. In parallel with research on PE risk factors, studies on PE prediction have also advanced. Notably, early-onset PE has a high detection rate when biomarker assessments are incorporated[16-18].

Pathophysiology of PE

Pathophysiology of PE and the role of angiogenic factors

PE and its related condition, FGR, have been associated with the placenta-derived circulating factor soluble fms-like tyrosine kinase-1 (sFlt-1), also known as soluble vascular endothelial growth factor receptor-1. Vascular endothelial growth factor (VEGF) receptors include VEGF receptor-1 (Flt-1), which mediates angiogenic signaling, and sFlt-1, which functions as an antagonist by inhibiting VEGF signaling.

In 2003, researchs led by Maynard and Karumanchi, and, led by Kaori Koga and Minoru Osuga, independently reported that maternal serum sFlt-1 levels are associated with hypertensive disorders of pregnancy (HDP)[19, 20]. The following year, Karumanchi et al. published a study demonstrating longitudinal changes in maternal sFlt-1 levels during pregnancy in normotensive and preeclamptic women[21]. Given its critical role as a bottleneck factor in PE development, sFlt-1 is considered a key regulator in the final stage of the disease, which results from a multifactorial interplay involving maternal and fetal immunity, genetics, and other contributing factors.

The two-step theory of PE pathogenesis

The "Two-Step Theory" is widely accepted as a unifying hypothesis explaining PE pathogenesis, encompassing both early placental malformation and later dysregulation of angiogenic factors[22] (Fig. 1).

1. Early placental malformation: During early placentation, failure of extravillous trophoblast (EVT) invasion into the uterine myometrium and inadequate remodeling of the spiral arteries result in insufficient vascular expansion. Consequently, reduced maternal blood flow to the intervillous space creates a hypoxic environment.

2. Vascular dysfunction in mid-to-late pregnancy: In response to hypoxic stress, the placenta overproduces angiogenesis inhibitors such as soluble endoglin and sFlt-1, which circulate in the maternal bloodstream. These factors impair maternal endothelial function, leading to hypertension and proteinuria—hallmarks of PE.

Furthermore, in 2013, Nakashima and Saito from the University of Toyama demonstrated that under physiological oxygen conditions in early pregnancy, autophagy deficiency leads to impaired EVT invasion, contributing to poor spiral artery remodeling[23]. These findings provide critical insights into early pathogenic mechanisms underlying PE and enhance understanding of its pathogenesis.

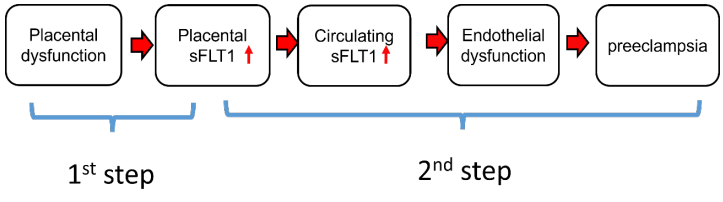

Fig. 1. Two-step theory of preeclampsia.

Role of placental growth factor (PlGF) and the sFlt-1/PlGF ratio

PlGF, a key proangiogenic factor primarily produced by the placenta, plays a critical role in pregnancy. Low maternal circulating PlGF levels are associated with PE. The balance between proangiogenic factors, such as PlGF, and antiangiogenic factors, such as sFlt-1, is essential

for maintaining a healthy pregnancy. Studies indicate that maternal PlGF and sFlt-1 levels differ significantly between normotensive and preeclamptic pregnancies throughout gestation[21].

In women who later develop PE, maternal PlGF levels progressively decline from mid-pregnancy onward, whereas sFlt-1 levels increase relative to normotensive controls. Leveraging this biomarker imbalance, a 2016 European multicenter study reported that the sFlt-1/PlGF ratio serves as a reliable predictor of PE onset in high-risk pregnant women[24]. A previous study also found that sFlt-1/PlGF ratio at 16-18 weeks of gestation in elderly gravida has a high sensitivity for predicting preeclampsia, especially early onset preeclampsia[25]. This biomarker is now widely used in clinical practice for early detection and risk stratification of PE. Subsequent validation studies in Asia have reported similar findings[26, 27].

Current preventive strategies for PE

Low-dose aspirin for PE prevention

Aspirin remains the most widely accepted preventive measure for PE. The Aspirin for Evidence-Based PE Prevention (ASPRE) trial, a multicenter, double-blind, placebo-controlled study, demonstrated that daily administration of 150 mg aspirin during early pregnancy reduced the incidence of PE before 37 weeks by 62%[28]. However, the overall effectiveness of aspirin remains limited, necessitating the development of alternative preventive strategies.

Several international guidelines currently recommend low-dose aspirin (81 mg/day) for high-risk women, including those issued by the American College of Obstetricians and Gynecologists[29], the World Health Organization, the International Society for the Study of Hypertension in Pregnancy[30], and the U S Preventive Services Task Force[31].

Need for novel preventive and therapeutic approaches

A simulation study estimated that universal aspirin use among pregnant women in the United States could prevent approximately 13% of PE cases[32]. Although this represents a significant advancement, it underscores the need for additional preventive and therapeutic strategies. Among emerging candidates, pravastatin has gained increasing attention for its potential role in PE prevention and treatment.

Pravastatin as a novel approach for PE prevention and treatment

Classification and pharmacological properties of statins[33]

Statins are classified based on their potency as either standard or strong statins:

- Standard statins, including pravastatin, simvastatin, and fluvastatin, lower serum low-density lipoprotein (LDL) cholesterol levels by approximately 15%.
- Strong statins, such as atorvastatin, pitavastatin, and rosuvastatin, reduce LDL cholesterol levels by approximately 30%.

Statins are also categorized based on solubility into water-soluble and lipophilic statins. Among the six currently marketed statins, only pravastatin and rosuvastatin are water-soluble. Unlike lipophilic statins, which undergo hepatic metabolism, water-soluble statins exhibit minimal hepatic metabolism, making them a suitable option for patients with hepatic impairment.

Why Is pravastatin the preferred statin for PE?

Statins, also known as 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are lipid-lowering agents that inhibit HMG-CoA reductase, a key enzyme in cholesterol biosynthesis. The first statin, mevastatin, was discovered in 1973 by Akira Endo in Japan[34], marking a major breakthrough in cardiovascular pharmacotherapy. Although mevastatin was never commercialized, subsequent research led to the development of eight statins, six of which remain in clinical use. Pravastatin was one of the statins

developed in Japan[35]. During pregnancy, physiological hypercholesterolemia occurs to support fetal and placental growth, necessitating an increased lipid supply[36]. If statin therapy is considered during pregnancy, standard statins may be preferable to strong statins due to their milder cholesterol-lowering effects. Furthermore, PE is often associated with hepatic dysfunction, raising concerns regarding drug metabolism and potential hepatotoxicity. Water-soluble statins, which can be administered to patients with hepatic impairment, offer a distinct advantage. Among the available statins, pravastatin uniquely meets both of these criteria (Table 1).

Table 1. Currently used statins.

statin	strong/standard	Water/fat soluble
Rosuvastatin	strong	Water soluble
Pitavastatin	strong	Fat soluble
Atorvastatin	strong	Fat soluble
Fluvastatin	standard	Fat soluble
Simvastatin	standard	Fat soluble
Pravastatin	standard	Water soluble

Considerations for statin use during pregnancy

Can pravastatin be used during pregnancy?

Over the past decade, various animal models and clinical reports have investigated pravastatin use in pregnant women. However, randomized controlled trials (RCTs) have been limited, primarily due to the classification of statins as Category X by the United States Food and Drug Administration (FDA) for use during pregnancy. Consequently, pravastatin use for PE prevention in pregnant women has faced significant regulatory barriers.

Nevertheless, accumulating evidence suggests that pravastatin does not exhibit strong teratogenic potential[37]. Additionally, retrospective studies have reported that infants born to women who inadvertently received pravastatin during early pregnancy did not show an increased risk of congenital abnormalities[38-40].

Given the promising findings from animal models demonstrating the potential of pravastatin for PE prevention and treatment, as well as the low likelihood of teratogenicity in humans, pravastatin has been evaluated as a therapeutic option for PE. In 2021, the FDA issued a statement removing contraindications for statin use during pregnancy.

Pravastatin as an affordable PE treatment

Another key advantage of pravastatin is its cost-effectiveness, making it an accessible treatment even in resource-limited settings. Given the global burden of PE and its associated maternal and fetal complications, the affordability and safety profile of pravastatin may facilitate widespread adoption in both high-income and developing countries.

Mechanisms in PE prevention

Regulation of Angiogenic Factors: Pravastatin upregulates PlGF and downregulates sFlt-1, thereby improving placental blood flow[41, 42].

Anti-inflammatory Effects: Pravastatin reduces inflammatory cytokine production, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), mitigating maternal vascular inflammation[43].

Reduction of Oxidative Stress: Pravastatin suppresses oxidative stress-induced placental damage, supporting its protective role during pregnancy[44].

Preclinical evidence

Elucidating PE pathogenesis is crucial for developing effective therapeutic strategies. Animal models play a key role in understanding disease mechanisms and evaluating potential treatments. A pregnancy-induced hypertensive mouse model was previously established through placenta-specific overexpression of sFlt-1 (Fig. 2)[41].

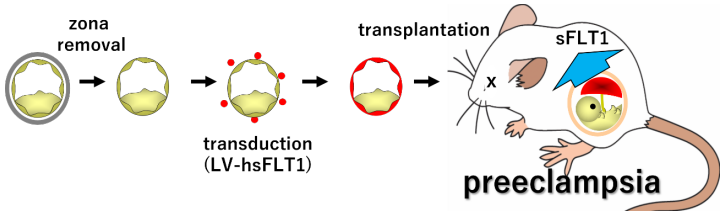

Fig. 2. Establishment of a preeclampsia mouse model.

Despite sFlt-1 overexpression, implantation and live birth rates remained unaffected. However, these transgenic mice exhibited elevated blood pressure, proteinuria, and intrauterine FGR, closely resembling the clinical manifestations of PE. Additionally, both blood pressure and proteinuria normalized postpartum, further supporting this model as representative of human PE.

Using this model, we explored potential therapeutic interventions. As discussed earlier, pravastatin has been reported to exert effects beyond cholesterol-lowering, including roles in angiogenesis. Notably, pravastatin inhibits angiogenesis at high concentrations but promotes angiogenesis at low concentrations in vitro[45].

Evaluation of pravastatin in a PE mouse model

Based on these findings, we investigated the effects of pravastatin in a mouse model of PE. The dosage was adjusted according to body weight to ensure it remained within clinically relevant levels for humans. Pravastatin administration successfully prevented the onset of PE symptoms. Although post-onset administration did not result in statistically significant therapeutic effects, a trend toward reduced blood pressure elevation was observed.

Further experiments using both a PE mouse model and human umbilical vein endothelial cells demonstrated that pravastatin induces the expression of PlGF, an essential angiogenic factor. Additionally, pravastatin treatment reduced circulating sFlt-1 levels in PE mice. In this PE model, where placenta-specific overexpression of sFlt-1 led to FGR, pravastatin administration improved FGR[41]. Subsequently, other research groups have reported that statin treatment increases VEGF and PlGF levels in animal models[46], further supporting these findings.

In our experiments, pravastatin administration did not affect live birth rates. However, FGR was observed, with fetal weights approximately 15% lower than those in the control group. No gross morphological abnormalities were detected in the fetuses, and both male and female offspring exhibited normal reproductive capacity postnatally. Additionally, no studies have reported an increased incidence of fetal malformations in statin-treated mouse models.

Clinical evidence

Several clinical studies have reported promising results regarding the potential benefits of pravastatin in the prevention and treatment of PE.

Lefkou et al reported that adding pravastatin to low-dose aspirin and low-molecular-weight heparin prolonged pregnancy, improved birth weight, and enhanced neonatal outcomes in women with antiphospholipid syndrome and a poor obstetric history[47]. Costantine et al conducted two small randomized placebo-controlled trials and demonstrated

that pravastatin use reduced the incidence of PE[42, 48]. Döbert et al found that pravastatin administration after 35 weeks of gestation did not prevent PE, highlighting the importance of early intervention[49]. From an Asian perspective, the INOVASIA study reported favorable outcomes in the secondary prevention of PE, demonstrating significantly lower rates of preterm delivery and neonatal morbidity, as well as improved birth weight and Apgar scores among pravastatin-treated mothers[50].

Recent meta-analyses further support the potential role of pravastatin in preventing PE. A systematic review of 14 studies involving 1,570 pregnant women found that pravastatin notably reduced the incidence of PE by 61%, preterm birth by 45%, intrauterine growth restriction by 45%, and neonatal intensive care unit admissions by 77%[51]. Additionally, randomized trials have demonstrated that pravastatin improves angiogenic balance by increasing PlGF levels and reducing sFlt-1, key mediators of endothelial dysfunction in PE. Furthermore, a clinical study (jRCTs031230067) was recently initiated in Japan to evaluate the efficacy of pravastatin in preventing PE recurrence in women with a history of HDP.

Regulatory considerations and future directions

Despite these promising results, research on pravastatin use during pregnancy faces regulatory challenges. The U.S. FDA previously classified statins as Category X in pregnancy due to concerns regarding fetal harm. However, accumulating clinical and epidemiological data indicate that pravastatin is not teratogenic.

In July 2021, the FDA revised its stance, removing strong contraindications for statin use during pregnancy, particularly for women with significant cardiovascular risk factors. This regulatory shift has paved the way for larger RCTs to further evaluate the safety and efficacy of pravastatin in PE prevention.

Collectively, these findings support pravastatin as a promising therapeutic option for PE. Future research should focus on large multicenter trials to optimize dosing strategies, determine the ideal timing for intervention, and assess long-term maternal and neonatal outcomes.

Conclusion and future perspectives

Current evidence strongly suggests that pravastatin is a promising therapeutic option for PE but also highlights certain limitations.

Although pravastatin has preventive effects, its efficacy in the treatment of post-onset PE remains unclear. Administration during the late stages of pregnancy (after 35 weeks) does not provide a preventive benefit. However, the optimal dosage and administration regimens remain to be determined. Large-scale RCTs with long-term follow-up are essential to establish the efficacy and safety of pravastatin in PE prevention, particularly in high-risk populations. From a long-term perspective, pravastatin may also play a role in reducing future cardiovascular risk in women with a history of PE. Additionally, pravastatin is a low-cost medication, as its patent has expired, making it an economically feasible option for widespread clinical use. Given its potentially high efficacy in PE prevention, pravastatin could have a significant impact on healthcare economics by reducing maternal and neonatal complications, lowering hospitalization costs, and improving long-term health outcomes.

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Potential conflicts of interest

The author declares no competing interests.

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OBSTETRICS

Efficacy of Heat Patch Applied on Lower Back for Reducing Postoperative Pain after Cesarean Delivery: A randomized controlled trial

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ABSTRACT

Objectives: To study the efficacy of using a heat patch to reduce postoperative pain after cesarean delivery.

Materials and Methods: Women who underwent cesarean delivery under a spinal block were randomly allocated into two groups, comprising one group who received a heat patch and one who received standard postoperative care. The heat patch group received a 40-degree Celsius heat patch applied to the lower back (dermatome T10 to L1) 6 hours postoperatively, while the control group received standard postoperative pain control. The primary outcome was assessed based on postoperative pain scores at 8 hours using a 10-cm visual analogue scale (VAS).

Results: Seventy-eight postoperative women, 39 in each group, were recruited between September 2023 and March 2024. The heat patch group expressed significantly less postoperative pain than the control group 8 hours after cesarean delivery (3.5 ± 0.3 vs 4.7 ± 0.4; mean difference 1.2; 95%CI: 0.4-2.1; p = 0.006). The time to first ambulation in the heat patch group was significantly shorter than the control group (1,073 ± 267.7 min vs 1,261.9 ± 205.3 min; mean difference 189 min; 95%CI: 81.4-296.6; p < 0.001). The heat patch group required fewer additional analgesic drugs compared to the control group (56.4% vs 82.1%; p = 0.014). No adverse events were reported.

Conclusion: A heat patch applied on the lower back resulted in significantly reduced pain 8 hours after cesarean delivery.

Keywords: heat patch, postoperative pain, cesarean delivery.

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การศึกษาประสิทธิภาพของแผ่นแปะร้อนบริเวณหลังส่วนล่างในการลดความเจ็บปวดหลังผ่าตัดคลอดบุตร: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

วิลาณี สิทธิศักดิ์นวกุล, สาธิดา จันทนวิลัย

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของแผ่นแปะร้อนในการลดความเจ็บปวดหลังผ่าตัดคลอดบุตร*

วัสดุและวิธีการ: *สตรีที่เข้ารับการผ่าตัดคลอดบุตรด้วยวิธีระงับความรู้สึกบริเวณกระดูกไขสันหลัง จะถูกสุ่มแบ่งออกเป็น 2 กลุ่ม ได้แก่ กลุ่มที่ได้รับการติดแผ่นแปะร้อน และกลุ่มที่ได้รับการดูแลหลังผ่าตัดตามมาตรฐาน โดยกลุ่มที่ได้รับการติดแผ่นแปะร้อน จะได้รับแผ่นความร้อน 40 องศาเซลเซียส ติดที่บริเวณหลังส่วนล่าง (เดอร์มาโทม T10 ถึง L1) ที่เวลา 6 ชั่วโมงหลังผ่าตัดคลอด ขณะที่กลุ่มควบคุมได้รับการดูแลความเจ็บปวดหลังผ่าตัดตามมาตรฐาน โดยจุดประสงค์หลักในงานวิจัยคือคะแนนความเจ็บปวดหลังผ่าตัดที่ระยะเวลา 8 ชั่วโมง โดยใช้ภาพอนาล็อกมาตราส่วน 0-10เซนติเมตร (visual analog scale; VAS)*

ผลการศึกษา: *สตรีหลังผ่าตัดจำนวน 78 คน กลุ่มละ 39 คน ระหว่างเดือนกันยายน 2566 ถึงเดือนมีนาคม 2567 กลุ่มที่ได้รับการติดแผ่นแปะร้อนที่เวลา 8 ชั่วโมงหลังผ่าตัดคลอด มีอาการปวดหลังผ่าตัดน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ (กลุ่มทดลอง 3.5 ± 0.3 vs กลุ่มควบคุม 4.7 ± 0.4; mean difference 1.2; 95%CI: 0.4-2.1; p = 0.006)) ระยะเวลาในการลุกเดินครั้งแรกในกลุ่มที่ได้รับการติดแผ่นแปะความร้อนน้อยกว่ากลุ่มควบคุมอย่างมีนัยสำคัญ (1,073 ± 267.7 นาที vs 1,261.9 ± 205.3 นาที; mean difference 189นาที; 95%CI: 81.4-296.6; p < 0.001) กลุ่มที่ได้รับการติดแผ่นแปะร้อนมีปริมาณการใช้ยาแก้ปวดเพิ่มเติมน้อยกว่าเมื่อเปรียบเทียบกับกลุ่มควบคุม (56.4% vs 82.1%; p = 0.014) ไม่มีรายงานเหตุการณ์ไม่พึงประสงค์*

สรุป: *การใช้แผ่นแปะร้อนที่บริเวณหลังส่วนล่างช่วยลดอาการปวดอย่างมีนัยสำคัญที่ 8 ชั่วโมงหลังการผ่าตัดคลอด*

คำสำคัญ: *แผ่นแปะร้อน, ความเจ็บปวดหลังผ่าตัด, การผ่าตัดคลอดบุตรทางหน้าท้อง*

Introduction

Cesarean delivery is one of the most common surgical procedures in Obstetrics. A prevalent issue that many women face after undergoing a cesarean section is pain. Discomfort arises from various factors, including pain at the incision site, lower back pain, and pain due to uterine contractions, which adversely affect a woman's comfort during the postpartum phase. The pain from uterine contractions is referred to the dermatomes that are supplied by T10, T11, T12, and L1[1]. Nowadays, there are various methods of dealing with pain after cesarean section. Treatment of postoperative cesarean delivery pain is divided into pharmacologic and non-pharmacologic treatment.

Pharmacological treatments are often favored for managing pain after a cesarean section due to their capacity to alleviate discomfort in a relatively short time frame. Typically, non-steroidal anti-inflammatory drugs and paracetamol-based medications are used.

Non-pharmacological strategies should also be integrated into pain management to complement pharmacological treatments and reduce reliance on analgesics. A systematic review conducted by Cochrane on complementary and alternative therapies for post cesarean pain has identified various non-pharmacological methods. These include acupuncture or acupressure, aromatherapy, electromagnetic therapy, massage therapy, music therapy, reiki, relaxation, and transcutaneous electrical nerve stimulation (TENS)[2].

One of the non-pharmacologic methods for pain reduction is heat therapy; it is simple, cost-effective, requires no special skills, and is readily available with few side effects when applied appropriately[3,4].

The mechanism by which heat alleviates pain is explained by the gate theory of pain. Heat provides relief to the mother by activating heat receptors in the skin and deeper tissues, which interrupts the transmission of pain signals to the brain by effectively closing the pain control gate system within the spinal cord[4]. Furthermore, heat promotes vasodilation, leading to increased blood flow[5]. It also relaxes superficial muscles and reduces muscle spasms. In addition, heat can stimulate touch and temperature receptors, which promote a pleasurable feeling and decrease the level of pain[6]. The optimum temperature range for superficial heat therapy is between 40 and 45°C[7].

Current research indicates that heat can help reduce pain in various cases, such as those involving lower back pain, muscle strain, pain during labor, dysmenorrhea, and pain after surgical procedures like hernia surgery and cystoscopy[8-14]. However, there is still insufficient information regarding the study of heat application for pain relief after cesarean delivery. Additionally, a systematic review conducted by Cochrane in 2020[2] examined several strategies for alleviating pain following cesarean delivery, as previously noted. However, it revealed that, while numerous methods exist, the application of heat for pain management post-cesarean delivery was not included in this study. Based on all the research and information mentioned, it is clear that studies focusing on the use of heat for reducing pain after cesarean section remain limited.

Materials and Methods

This study was conducted as a randomized controlled trial involving postpartum women aged 18 years or older who had undergone operative procedure cesarean delivery at Khon Kaen Hospital from September 2023 to March 2024. The inclusion criteria specified that participants were at least 18 years old, had the ability to read, write, and understand Thai, had a low transverse uterine incision, and underwent cesarean delivery with a spinal block and morphine, and exhibited none of the exclusion criteria applied, such as 1) the woman experienced intraoperative complications including postpartum hemorrhage, intensive care unit admission, high block anesthesia, 2) pelvic infection:

chorioamnionitis, 3) maternal fever, 4) myoma uteri, 5) uterine anomaly, 6) history of uterotonic drugs used except syntocinon, 7) cutaneous lesions on the lower back, 8) vascular disease like vasculitis, 9) heat hypersensitivity, 10) sensory nerve loss, 11) postoperative cesarean section resulting in hematoma at the surgical wound, and 12) adhesions from previous cesarean sections intraoperatively. This study received approval from the Khon Kaen Hospital Institute Review Board for Human Research (reference number: KEF66019). Participants provided informed consent before enrolling in the study at the postpartum ward. Participants were randomly allocated by computer generation using a block of four into two groups. Group 1: The intervention group received a heat patch placed on the lower back (dermatome T10-L1) 6 hours post cesarean delivery. Group 2: The control group received standard postoperative care without a heat patch. Allocation concealment was achieved using sealed opaque envelopes.

The current study used a Japanese iron-filled heat patch that begins to warm up a few minutes after being opened, reaching its maximum temperature within 20 minutes to 1.5 hours and maintaining warmth for up to 10 hours[15]. Enhanced blood circulation is achieved by warming the specific area, which promotes vasodilation and, ultimately results in pain reduction.

This study selected the Japanese iron-filled heat patch due to its simplicity, safety, cost-effectiveness, and affordability[16]. Earlier studies have demonstrated various methods of heat application to alleviate pain, including hydrocollator packs, radiant heat systems, heat wraps, and heat patches[8-14]. In this research, a heat patch was selected because previous findings indicated that the Japanese iron-filled heat patch could help reduce pain during the active phase of the first stage of labor[8]. Consequently, the heat patch was chosen as the intervention for this investigation.

In the Anesthetics Department of Khon Kaen Hospital, the local anesthetic bupivacaine is used in combination with opioid morphine for women undergoing cesarean delivery. The effect of bupivacaine assists in blocking both motor and sensory functions, ensuring that the patient does not experience pain prior to the surgery, with an onset period of 2-4 hours[17]. The analgesic morphine has been proven to be effective in alleviating pain for as long as 24 hours post-administration[18]. Consequently, patients will start to experience pain again roughly 2-4 hours after the surgery, once the effects of the bupivacaine anesthetic have diminished. Therefore, the researchers decided to start data collection once the mothers began to regain motor and sensory function for safety during the study. Pain scores will be recorded 6 hours post-surgery to establish a baseline pain score. After that, a heat patch will be applied, and pain scores will be measured again 2 hours after the patch is applied, allowing the heat patch to gradually release heat and increase the temperature to 40-45°C, which takes about 20 minutes to 1.5 hours after application[15]. The researchers will then consider the primary outcome as the pain score measured 8 hours after surgery (2 hours after applying the heat patch).

Baseline characteristics were documented, including age, body mass index (BMI), underlying, prior abdominal surgery, parity, operative time and indications of cesarean section, as well as surgeon, intraoperative blood loss, and other obstetric problems.

The intervention was initiated 6 hours after post-cesarean delivery. For the heat patch, a 9.5x13 cm, 40-45°C patch was placed on the postpartum women's clothing over the lower back during the dermatome T10-L1 and was not applied directly to the skin area for 6 hours until 16 hours post-cesarean delivery. The total time to apply the heat patch was 10 hours.

The person tasked with applying the heat patch had to be a general physician or an obstetric resident. Those who applied the patches were given

instructions and clarifications in this study before applying them. After attaching the patch, the postpartum women wore a belly band over the area where the patch was attached to prevent slipping out of place. Before the experiment, investigators tested the pregnancy's consciousness and sensory perception. The nurse at the postpartum ward will assist in measuring the pain score for both the study group and the control group, starting at 6 hours after the cesarean section.

Skin temperature and appearance at heat patch placement were monitored every 2 hours by thermoscan. A Xiaomi mijiai Health thermometer (China) was used to control the temperature not to exceed 50°C. Postpartum women were evaluated for complications of the heat patch by verbal interviews and were asked about their pain scores at 6-, 8-, 12-, and 24-hours post cesarean delivery by using a visual analog scale (VAS). The heat patch was immediately removed if there was any abnormal skin reaction (clear water blisters, burned skin, or loss of sensation) or temperature over 50°C. In the control group, standard care with no heat patch was provided. Both groups received the same standard of post-operative management. Additional medications used for analgesia in this study included tramadol, ibuprofen, and acetaminophen. Both groups received additional analgesia postoperatively. On postoperative day 1, tramadol 50 mg was administered intravenously as needed, every 6 hours, for a VAS pain score greater than 4. After starting a step diet, acetaminophen 500 mg (1–2 tablets) was given orally as needed for pain every 4–6 hours, and ibuprofen 400 mg (1 tablet) was given orally three times a day if the VAS score remained greater than 4. The amount of additional analgesic use was measured within 24 hours after surgery. At the end of the study, the data were concluded by the principal investigator.

The primary outcome was the pain score at 8 hours post cesarean delivery. Secondary outcomes included pain score at 6, 12, and 24 hours post cesarean delivery, additional analgesic drugs required, time to first ambulation, time to first flatus, and adverse effect of heat patch.

Statistical analysis

$$n_{trt} = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \left[\sigma_{trt}^2 + \frac{\sigma_{con}^2}{r}\right]}{\Delta^2}$$

$$r = \frac{n_{con}}{n_{trt}}, \Delta = \mu_{trt} - \mu_{con}$$

The calculation of the sample size for this study was based on a pilot study with 15 women per group. The average pain score in the treatment group was 5.05 with a standard deviation (SD) of 2.28, whereas the control group exhibited a mean pain score of 3.55 with an SD of 1.51. With a power of 90% and an alpha error of 5%, accounting for a 10% dropout rate, the study required a total population of 78 participants, with 39 in each group. Continuous variables were assessed using the student t-test and were expressed as mean and SD. Categorical variables were analyzed with chi-square or Fisher's exact test, with results presented as percentages. The mean difference in the pain score between groups was analyzed and presented with 95% confidence intervals. A p value < 0.05 was considered statistically significant. STATA version 17 was used for all analyses.

Results

Seventy-eight women were enrolled in the study. All participants were randomly allocated to either the study group (heat patch) or the control group, with 39 individuals in each group. No participants withdrew from the study (Fig. 1). The demographic data of both groups were not significantly different (ages, body mass index, underlying disease, prior abdominal surgery, parity, gravidity, gestational age, operative time, indication of cesarean delivery, surgeon, and intraoperative blood loss (Table 1).

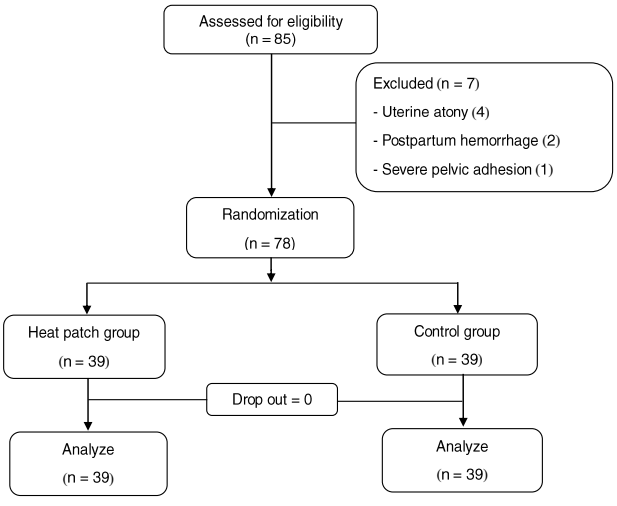

Fig. 1. Study flow diagram.

Table 1. Baseline characteristics of participants.

Baseline characteristics	Heat patch group (n = 39)	Control group (n = 39)	p value
Age (years), mean ± SD	26.9 ± 4.8	29.2 ± 5.2	0.050[a]
BMI (kg/m^2), mean ± SD	26.9 ± 3.8	28.8 ± 5.7	0.088[a]
Underlying diseases, n (%)	0 (0.0)	4 (10.3)	0.115[c]
Prior abdominal Surgery, n (%)			
Yes	14 (35.9)	22 (56.4)	0.069[b]
Gravidity, n (%)			
1	14 (35.9)	10 (25.6)	0.584[c]
2	18 (46.1)	19 (48.7)	
3	7 (18.0)	9 (23.1)	
4	0 (0.0)	1 (2.6)	
Parity, n (%)			
Nulliparous	16 (41.0)	13 (33.3)	0.482[b]
Multiparous	23 (59.0)	26 (66.7)	
GA (weeks), mean ± SD	38.4 ± 1.0	38.0 ± 1.4	0.321[a]
Operative time min, mean ± SD	42.9 ± 11.7	46.9 ± 13.9	0.164[a]
Indication of CD, n (%)			
Cephalopelvic disproportion	15 (38.4)	12 (30.7)	0.475[b]
Previous CD	11 (28.2)	18 (46.2)	0.101[b]
Breech	6 (15.4)	3 (7.6)	0.288[b]
Fetal macrosomia	2 (5.1)	1 (2.6)	0.556[c]
Failed induction	2 (5.1)	0 (0.0)	0.494[c]
Non reassuring FHS	1 (2.6)	4 (10.3)	0.358[c]
Vaginal condyloma	1 (2.6)	1 (2.6)	1.000[c]
Bad obstetric history	1 (2.6)	0 (0.0)	0.500[c]
Surgeon, n (%)			
Staff	23 (59.0)	18 (46.2)	0.257[b]
Residents	16 (41.0)	21 (53.8)	
Intraoperative blood loss ml, mean ± SD	348.7 ± 92.1	318 ± 87.7	0.135[a]
Another obstetric problem, n (%)	0 (0.0)	0 (0.0)	-

[a] Two-sample t-test, [b] chi-square test, [c] Fisher's exact test
BMI: Body mass index, SD: Standard deviation, CD: Cesarean delivery, GA: gestational age

The primary outcome was pain scores at 8 hours post cesarean delivery. There was a statistically significant difference in reducing postoperative pain between the heat patch group and the control group (3.5 ± 0.3 vs 4.7 ± 0.4, p = 0.006) (Table 2). In terms of the secondary outcome, postoperative pain score at 6 hours or before applying the heat patch tended to be higher in the study group but not significant (5.4 ± 0.3 vs 4.9 ± 0.4, p = 0.181), and pain score in the heat patch group was lower than in the control group at 12 and 24 hours post cesarean delivery (3.6 ± 0.3 vs 4.3 ± 0.4, p = 0.104) and (3.2 ± 0.3 vs 4.0 ± 0.3, p = 0.100), respectively, though not statistically significant (Table 2).

Table 2. Primary and secondary outcomes.

Pain score	Heat patch group (n = 39) mean ± SD	Control group (n = 39) mean ± SD	mean difference (95%CI)	p value
At 6 hours	5.4 ± 0.3	4.9 ± 0.4	0.7 (0.3-1.7)	0.181[a]
(Before using heat patch)				
At 8 hours	3.5 ± 0.3	4.7 ± 0.4	1.2 (0.4-2.1)	0.006[a]
(2 hours after intervention)				
At 12 hours	3.6 ± 0.3	4.3 ± 0.4	0.8 (0.2-1.7)	0.104[a]
(6 hours after intervention)				
At 24 hours	3.2 ± 0.3	4.0 ± 0.3	0.7 (0.1-1.6)	0.100[a]

[a] two-sample t-test
SD: standard deviation, CI: confidence interval

Time to first ambulation and first flatus in the heat patch group were significantly shorter in the heat patch group compared to the control group (1,073 ± 267.7 vs 1,261.9 ± 205.3, p < 0.001) and (1,194.4 ± 398.9 vs 1,636.8 ± 349.4, p < 0.001), respectively (Table 3). Additionally, the study group exhibited significantly lower consumption of additional opioids compared to the control group (22 (56.4) vs 32 (82.1), p = 0.014). Notably, there were no postoperative complications in either group (Table 4).

Table 3. Time to first ambulation and time to first flatus.

	Heat patch group (n = 39) mean ± SD	Control group (n = 39) mean ± SD	mean difference (95%CI)	p value
Time to first ambulation	1,073 ± 267.7	1,261.9 ± 205.3	189.0 (81.4-296.6)	< 0.001[a]
(min)				
Time to first flatus	1,194.4 ± 398.9	1,636.8 ± 349.4	442.4 (273.3-611.6)	< 0.001[a]
(min)				

[a] two-sample t-test
SD: standard deviation, CI: confidence interval

Table 4. Additional analgesic drugs and maternal adverse event.

	Heat patch group (n = 39)	Control group (n = 39)	p value
Additional analgesia, n (%)	22 (56.4)	32 (82.1)	0.014[b]
Maternal adverse events, n (%)			
Blister	0 (0.0)		
Burn skin	0 (0.0)		
Loss of sensation	0 (0.0)		

[b] chi-square test

Discussion

The management of postoperative pain involves multimodal strategies. Non-pharmacological methods are increasingly common due to their lower side effects and higher cost-effectiveness. One such non-pharmacological method for pain reduction is heat therapy. Heat aids in alleviating pain to a certain degree by activating heat receptors, which inhibit pain signal transmission to the brain through the pain control gate system in the spinal cord[4]. Numerous studies have shown that the application of heat is effective for various types of pain, including lower back pain, muscle strain, pain during labor, dysmenorrhea, and pain after surgical procedures[8-14].

Suthisuntornwong et al demonstrated that applying a hot patch to the lower back significantly reduced labor pain during the active phase of the first stage of labor ($p < 0.001$)[8]. Similarly, a study by Kaur et al revealed that warm compression (using a hydrocollator pack) decreased labor pain in the active phase of the first stage of labor ($p < 0.001$) and improved maternal satisfaction[9]. Additionally, Melling et al found that warming (via a radiant heat system) helped to reduce pain after hernia surgery two hours post application and during the first seven postoperative days ($p < 0.05$), potentially aiding in wound healing[10]. A systematic review and meta-analysis of complementary and alternative (CAM) therapies for post cesarean pain of 37 clinical trials (3,076 women) investigated eight distinct CAM therapies for alleviating post cesarean pain (acupuncture or acupressure, aromatherapy, electromagnetic therapy, massage therapy, music therapy, reiki, relaxation, TENS[2], concluding that these therapies might help reduce post cesarean pain for up to 24 hours. Siripanthong et al utilized a cold gel pack to alleviate postoperative pain in cesarean delivery, They found that the cold gel pack effectively reduced postoperative pain 6 hours after the procedure[19]. Further, Singhdaeng et al demonstrated that using an abdominal binder could reduce postoperative wound pain 6, 24, and 48 hours after using the binder, and reduced the used of analgesic drugs in postoperative cesarean delivery, though no significant differences were found in the time to first ambulation between the two groups[20]. However, no studies have investigated the use of heat to reduce pain after cesarean delivery. Therefore, this study aimed to assess the efficacy of using a heat patch to reduce pain after cesarean delivery. After conducting the research, it was found that the heat patch group reported significantly lower postoperative pain levels than the control group 8 hours after cesarean delivery (3.5 ± 0.3 vs 4.7 ± 0.4; mean difference: 1.2; $p = 0.006$). While the difference in pain scores between the groups was statistically significant, it amounted to 1.2 points on the VAS. However, this difference may not be clinically significant. For the secondary outcome, which measured pain scores at 6, 12, and 24 hours after cesarean delivery, it was found that the pain scores did not differ between the two groups. Since the pain score recorded 6 hours post surgery was before the application of the heat patch, it served as a baseline measurement. This may explain why the VAS score in the study group did not show a reduction compared to the control group. At 12 hours post surgery, or 6 hours after the heat patch was applied, the VAS score did not show statistically significant differences. This could be because, by this point, the temperature of the heat patch gradually decreased, falling below the effective temperature range for superficial heat therapy, resulting in insufficient pain relief. Additionally, the pain score measured 24 hours post surgery was taken after the heat patch had been removed. Therefore, this score may have been influenced by the administration of additional analgesics, and it was the pain score measured after the heat patch was removed.

One of the goals of this study was not only to reduce pain but also to promote early ambulation to reduce other postoperative complications. The heat patch maintains a temperature of about 40-45°C and is placed on the lower back (dermatome T10-L1), as the optimum temperature range for superficial heat therapy is between 40 and 45°C. Pain from uterine contractions is referred to the dermatomes that are supplied by T10 to L1, which was consistent with the

findings by Suthisuntornwong et al[8]. This randomized controlled trial validated the efficacy of the heat patch as an additional analgesic method post cesarean delivery without adverse events and maternal complications.

The strengths of this study included its randomized controlled design and the absence of participant dropout. A limitation of the present study was that we did not blind the intervention due to the nature of the heat patch, which might have influenced the outcomes.

Conclusion

A heat patch applied on the lower back resulted in significantly reduced pain 8 hours after cesarean delivery.

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Potential conflicts of interest

The author declares no conflicts of interest.

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OBSTETRICS

Efficacy of Preoperative Tranexamic Acid Administration for Intraoperative Blood Loss Reduction in High-risk Cesarean Delivery: A randomized controlled trial

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ABSTRACT

Objectives: To evaluate the efficacy of preoperative tranexamic acid (TXA) in reducing intraoperative blood loss in high-risk cesarean deliveries.

Materials and Methods: A randomized controlled trial was conducted with 50 pregnant women with gestational age over 34 weeks and a high risk of postpartum hemorrhage (PPH) (e.g., previous cesarean delivery, fetal macrosomia, and placenta previa) who underwent cesarean delivery using spinal anesthesia. The intervention group received one gram of TXA intravenously before skin incision, and 0.9% sodium chloride solution was used in the placebo group. The primary outcome was the measurement of intraoperative blood loss.

Results: The TXA group showed significantly lower intraoperative blood loss when compared to the placebo group (495.8 ± 294.6 ml vs 925.6 ± 448.9 ml, mean difference: -429.8 ml, 95% confidence interval (CI): -645.8 to -213.9, $p < 0.001$). The incidence of blood loss > 1,000 ml was also significantly lower in the TXA group (8% vs 36%, relative risk = 0.22, 95% CI: 0.05 to 0.92, $p = 0.039$), and fewer significantly decreased hemoglobin levels were observed in the TXA group in comparison with the placebo group (1.1 ± 7.0 g/dL vs 6.9 ± 9.6 g/dL, mean difference: -5.7 g/dL, 95% CI: -10.5 to -0.9, $p = 0.020$). There was no difference in the requirement for additional uterotonic drugs (8% vs 28%, $p = 0.065$). No serious adverse effects were observed in this study.

Conclusion: TXA effectively reduced intraoperative blood loss in women at high risk of PPH who underwent cesarean deliveries.

Keywords: tranexamic acid, cesarean delivery, postpartum hemorrhage.

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ประสิทธิภาพของยาทราเนซามิกเอซิดเพื่อลดการเสียเลือดหลังผ่าตัดคลอดในสตรีที่มีความเสี่ยงสูงต่อการตกเลือดหลังคลอด: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

ณิช วงศ์จริยกุล, อุษณีย์ สังคมกำแหง

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของยาทราเนซามิกเอซิดในการลดการสูญเสียเลือดระหว่างการผ่าตัดคลอดในกลุ่มเสี่ยงสูงต่อการตกเลือดหลังคลอด*

วัสดุและวิธีการ: *การศึกษานี้เป็นการทดลองแบบสุ่มที่มีกลุ่มควบคุมในสตรีตั้งครรภ์ 50 คน และได้รับการผ่าตัดคลอดร่วมกับการฉีดยาชาเข้าช่องน้ำไขสันหลัง มีอายุมากกว่า 18 ปี อายุครรภ์มากกว่า 34 สัปดาห์ และมีปัจจัยเสี่ยงสูงต่อการตกเลือดหลังคลอด (เช่น มีประวัติได้รับการผ่าตัดคลอดมาก่อน ทารกตัวโต ภาวะรกเกาะต่ำ) กลุ่มทดลองได้รับยาทราเนซามิกเอซิด ขนาด 1 กรัม ทางหลอดเลือดดำก่อนการผ่าตัด ส่วนกลุ่มควบคุมได้รับสารละลายน้ำเกลือ 0.9% ผลลัพธ์หลักคือการวัดปริมาณเลือดระหว่างการผ่าตัด*

ผลการศึกษา: *กลุ่มที่ได้รับยาทราเนซามิกเอซิด มีปริมาณเลือดระหว่างการผ่าตัดน้อยกว่ากลุ่มยาหลอกอย่างมีนัยสำคัญ (495.8 ± 294.6 กับ 925.6 ± 448.9 มิลลิลิตร, ความแตกต่างเฉลี่ย: -429.8 มิลลิลิตร, 95% confidence interval (CI): -645.8 ถึง -213.9, p < 0.001) การเสียเลือดมากกว่า 1,000 มิลลิลิตร พบน้อยกว่าในกลุ่มที่ได้รับยาทราเนซามิกเอซิด (8% กับ 36%, ค่าความเสี่ยงสัมพัทธ์ = 0.22, 95% CI: 0.05 ถึง 0.92, p = 0.039) กลุ่มที่ได้รับยาทราเนซามิกเอซิด มีการลดลงของระดับฮีโมโกลบินที่น้อยกว่า (1.1 ± 7.0 กับ 6.9 ± 9.6 กรัมต่อเดซิลิตร, ความแตกต่างเฉลี่ย: -5.7 กรัมต่อเดซิลิตร, 95% CI: -10.5 ถึง -0.9, p = 0.020) กลุ่มยาหลอกมีการใช้ยากระตุ้นการหดรัดตัวของมดลูกมากกว่า (8% กับ 28%, p = 0.065) และ ไม่พบผลข้างเคียงที่รุนแรงในการศึกษานี้*

สรุป: *ยาทราเนซามิกเอซิดช่วยลดปริมาณเลือดออกระหว่างการผ่าตัดคลอด ในสตรีที่มีความเสี่ยงสูงต่อการตกเลือดหลังคลอด*

คำสำคัญ: *ยาทราเนซามิกเอซิด, การผ่าตัดคลอด, การตกเลือดหลังคลอด*

Introduction

Cesarean delivery (CD) is the most frequently performed major surgery globally. CD rates have risen from under 10% prior to the 1980s to over 30% in a wide range of developed countries during the past decade[1]. In 2022, the CD rate at Khon Kaen Hospital was 49%. CD is associated with a 2- to 5-fold elevated maternal morbidity relative to vaginal delivery[2]. These conditions include postpartum hemorrhage (PPH), infection, thromboembolism, and adverse effects related to anesthesia[3]. Intraoperative and postoperative hemorrhage represent critical complications inherent to women at high risk of PPH who undergo CD. Conditions such as placenta previa, multiple gestation, and severe preeclampsia considerably increase the risk of severe PPH, frequently requiring prompt blood transfusion[1,4]. In 2022, high-risk CD in Khon Kaen Hospital accounted for 674 cases (32.5%) from a total of 2,074 CD cases. These high-risk CD cases included previous CD (21.6%), prenatal anemia (5.1%), multiple gestation (2.0%), placenta previa (1.5%), fetal macrosomia (1.5%) and transverse presentation (0.6%)[5].

Uterotonic agents are commonly used to prevent and treat PPH. Oxytocin is the first-line agent, while additional uterotonics include methylergonovine (Methergine) and prostaglandins such as misoprostol (Cytotec) and carboprost tromethamine[6,7]. Traditionally, uterotonics were the primary drugs used to treat PPH, as it was assumed that uterine atony was the main cause. However, it is now understood that PPH can also involve coagulopathy in its pathophysiology[8].

Tranexamic acid (TXA), a synthetic lysine derivative, functions as an antifibrinolytic agent that reversibly blocks plasminogen activation. By inhibiting fibrinolysis, it aids in reducing bleeding[9]. TXA has been shown to be effective in preventing bleeding complications across various conditions, with minimal side effects[10]. Tranexamic acid is known to cross the placenta and is found in cord blood at concentrations similar to those in maternal blood. The Australian Therapeutic Goods Administration (TGA) classifies it as category B for pregnancy, signifying that it has been administered to a limited number of pregnant women without demonstrating an increased risk of malformations or other direct or indirect detrimental effects on the fetus[11].

In obstetrics, TXA has been utilized to manage bleeding related to pregnancy complications[12,13]. Multiple studies have shown that TXA has proven efficacy in reducing blood loss in CD in various indications[12,14,15]. Many of these studies focused on women at low or general risk for PPH, and most reported reduced intraoperative blood loss. However, research on women at high risk for PPH is relatively limited. Systematic review is thus required to obtain new evidence of the efficacy of TXA in high-risk populations. Only two studies have focused on women at high risk for PPH[16,17]. Based on this information, the efficacy of preoperative TXA administration in high-risk PPH pregnancies undergoing CD remains uncertain due to insufficient evidence. Therefore, the objective of this study was to evaluate the efficacy of preoperative administration of TXA in reducing intraoperative blood loss during high-risk CD.

Materials and Methods

The aim of the study was to examine the efficacy of administering TXA preoperatively to reduce intraoperative blood loss in high-risk CD. The study was designed as a double-blind, randomized, placebo-controlled trial, conducted at Khon Kaen Hospital between September and December 2023.

The study included pregnant women who were 18 years or older, in their 34th week or later of pregnancy, scheduled for CD (either elective or emergency), and undergoing spinal anesthesia. In addition, they were required to present with one or more high-risk factors for PPH[18-23]. The factors that were considered included previous CD, transverse presentation, fetal macrosomia (estimated fetal weight exceeding 4.0 kg as determined by ultrasound), multiple gestation, placenta previa or low-lying placenta, prenatal anemia (hemoglobin levels below 9.9 g/dL), polyhydramnios (amniotic fluid index

exceeding 24 cm or a deep vertical pocket exceeding 8 cm), or a previous history of PPH. Women who had substantial medical conditions affecting the heart, liver, or kidneys, brain disorders, blood disorders, a known sensitivity to TXA, a history of or present venous or arterial thromboembolism, intrauterine fetal death, or major fetal anomalies were excluded from participating.

All participating women signed and dated an informed consent form after the study's risks and benefits were explained. All participants underwent a thorough evaluation, including a detailed medical history, general examination, and Leopold maneuvers to accurately assess risk factors and ensure compliance with the exclusion criteria. Upon admission, an obstetric ultrasound was conducted to assess fetal weight, detect anomalies, determine placental location, and measure amniotic fluid levels. Standard laboratory investigations, such as a complete blood count, were also performed.

On the day of surgery, participants were allocated to one of two groups through a process of randomization utilizing computer-generated random numbers by using block of 4. Allocation concealment was maintained by using sealed opaque envelopes. To ensure unbiased results, the participants, obstetricians, anesthesiologist, and outcome assessors were all blinded to the treatment allocation to ensure impartiality. All the ampules of TXA used throughout the study were produced by the same pharmaceutical company (T.P. Drug Laboratories (1969) Co., Ltd).

Nurses who were not involved in this study opened the envelopes, by which the participants were randomly assigned to one of the two groups. The nurses prepared the nameless solution (of both TXA and NSS) in the ward/labor room and sealed it within plastic containers when transferred to the operating room. TXA ampules were stored at a temperature of 25 °C in a dry container with clear colorless solution.

In the TXA group, participants received 1 gm TXA (1 gm/10 ml) (diluted with normal saline solution (NSS) 90 ml with intravenous administration 10-15 minutes before skin incision). In the placebo group, participants received 0.9% sodium chloride solution (NSS) (100 ml intravenous administration 10-15 minutes before skin incision). Both solutions were delivered by slow infusion over a period of 10 min via an infusion pump by an anesthesiologist.

All CD were performed under spinal anesthesia by a resident with at least one year of obstetric training or member of staff. The same surgical technique was consistently applied for all women, including a Pfannenstiel or low midline abdominal incision, an incision of the lower uterine segment, immediate umbilical cord occlusion after fetal extraction, repair of the uterine incision with one or two layers[24], and sequential closure of the abdominal wall. After fetal extraction, all participants received an intravenous bolus of 10 IU oxytocin, followed by an intravenous infusion of 20 IU of oxytocin, diluted in 1,000 ml of glucose 5% dextrose normal saline/2 at a rate of 120 ml/hr. If PPH occurred, one additional gram of tranexamic acid was administered by an anesthesiologist 30 minutes after the first dose[25]. The additional uterotonic agents were used when the uterus failed to contract adequately after delivery and there was an insufficient response to the first-line uterotonic agent (oxytocin)[6].

Intraoperative blood loss was measured by standardized operative nurses after completing the CD in the operating room. All participants received postoperative care following the standard protocol for CD under spinal anesthesia. Complete blood counts were collected at 24 hours after CD. Measurement of blood loss > 1,000 ml, operative time, additional uterotonic agents, blood transfusion, and adverse effects of TXA within 24 hours postpartum were recorded.

The primary outcome was measurement of intraoperative blood loss, which was measured from the time of placental delivery until skin closure by standardized operative nurses using the gravimetric method[26-28]. Total intraoperative blood loss was determined by weighing the blood-soaked materials

used during CD, subtracting the weight of the dry materials before the procedure, and adding the amount of blood collected in the suction bottle. One gram of weight increase in blood-soaked surgical gauze was considered equivalent to one milliliter of blood loss. Secondary outcomes included intraoperative blood loss > 1,000 ml, hemoglobin level change before and 24 hours after CD, operative time, intraoperative or postoperative blood transfusion within 24 hours, additional uterotonic agents within 24 hours, adverse effects of TXA, and the length of hospital stay (LOS).

$$n_1 = \frac{(z_{1-\frac{\alpha}{2}} + z_{1-\beta})^2 \left[\sigma_1^2 + \frac{\sigma_2^2}{r}\right]}{\Delta^2}$$
$$r = \frac{n_2}{n_1},\ \Delta = \mu_1 - \mu_2$$

The calculation of sample size for this study was based on a pilot study with 15 women per group. The average blood loss in the treatment group was 443.6 ml with a standard deviation (SD) of 160.7 ml, whereas the control group exhibited a mean blood loss of 933.9 ml with an SD of 469.9 ml. With a power of 90% and an alpha error of 5%, accounting for a 10% dropout rate, the study required a total population of 50 women, with 25 women per group. Continuous outcome data was reported as mean ± SD or median and interquartile length, as appropriate. Comparisons between groups at a single time point were conducted using the student t-test for normally distributed data or the Mann-Whitney U test for data that was not normally distributed. Dichotomous outcomes were analyzed using the chi-square test or Fisher's exact test if expected cell counts were less than 5. The treatment effect was reported as the mean difference (MD) along with a 95% confidence interval (CI), and p values below 0.05 were considered statistically significant. STATA version 18 was used for all analyses.

Based on the ethical principles of research on the basis of protecting the human rights, security and human dignity of each person, this proposal was submitted to Khon Kaen Hospital. Ethical approval was obtained from the Institutional Review Board for Human Research.

Results

Between September and December 2023, 50 eligible high risk PPH women who underwent CD under spinal anesthesia were enrolled in the study. None of them were excluded from the study. A total of 50 eligible women were randomly assigned into two groups: 25 to the TXA group and 25 to the placebo group. There were no dropouts (Fig. 1).

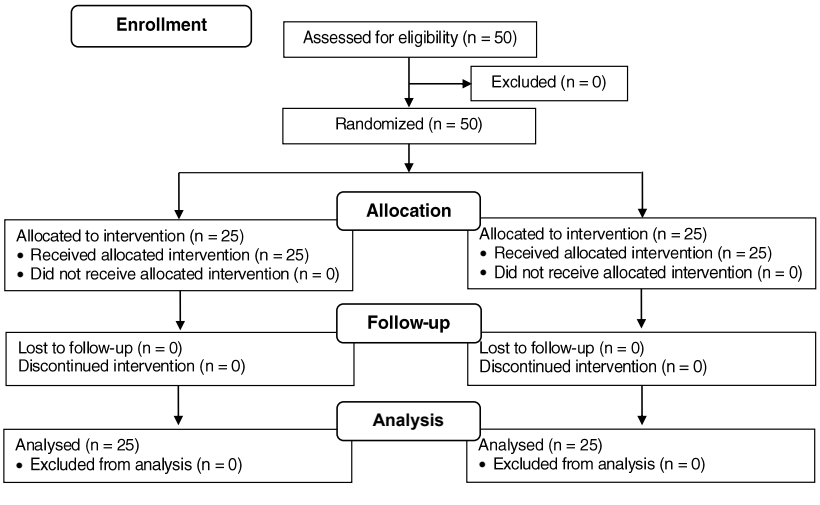

Fig. 1. Consort flow diagram.

No statistical difference was observed between women receiving TXA and those receiving the placebo in terms of maternal age, body mass index (BMI), mode of previous delivery, preoperative hemoglobin concentration, type of CD, skin incision, or surgeon, with all p values > 0.05. Previous CD was the most common risk factor in both groups, with fetal macrosomia and prenatal anemia following in frequency (Table 1).

Table 1. Demographic characteristics.

Characteristics	TXA group (n = 25)	Placebo group (n = 25)	p value
Age (years), mean ± SD	28.9 ± 5.0	29.9 ± 5.2	0.479
BMI (kg/m^2), mean ± SD	29.5 ± 5.4	28.6 ± 4.1	0.526
Mode of previous deliveries, n (%)			0.776
No previous delivery	3 (12)	1 (4)	
Vaginal delivery	4 (16)	5 (20)	
1 previous CD	17 (68)	19 (76)	
≥ 2 previous CD	1 (4)	0 (0)	
High risk identification, n (%)			0.945
Previous cesarean delivery	17 (68)	18 (72)	
Fetal macrosomia	3 (12)	2 (8)	
Prenatal anemia	2 (8)	1 (4)	
Previous history of PPH	1 (4)	2 (8)	
Multiple gestation	1 (4)	1 (4)	
Transverse presentation	0 (0)	1 (4)	
Placenta previa/low-lying	1 (4)	0 (0)	
Preoperative hemoglobin concentration (g/dL), mean ± SD	12.0 ± 1.2	12.1 ± 1.2	0.374
Type of cesarean delivery, n (%)			1.000
Elective	17 (68)	17 (68)	
Emergency	8 (32)	8 (32)	
Skin incision, n (%)			0.563
Pfannenstiel	14 (56)	16 (64)	
Low midline	11 (44)	9 (36)	
Surgeon, n (%)			0.390
Staff	12 (48)	9 (36)	
Resident	13 (52)	16 (64)	

TXA: tranexamic acid, SD: standard deviation, BMI: body mass index, CD: cesarean delivery, PPH: postpartum hemorrhage

The measurement of intraoperative blood loss was 495.8 ± 294.6 ml and 925.6 ± 448.9 ml in the TXA group and the placebo group, respectively. The MD was -429.8 ml (95%CI: -645.8 to -213.9). Measurement of intraoperative blood loss was statistically significantly lower in the TXA group compared to the placebo group (p < 0.001) (Table 2).

Table 2. Primary and secondary outcomes.

	TXA group (n = 25)	Placebo group (n = 25)	Mean Difference	95% CI	p value
Measurement of intraoperative blood loss (ml), mean ± SD	495.8 ± 294.6	925.6 ± 448.9	-429.8	-645.8 to -213.9	<0.001
Hemoglobin change (g/dL), mean ± SD	1.1 ± 7.0	6.9 ± 9.6	-5.7	-10.5 to -0.9	0.020
Operative time (min), mean ± SD	44.7 ± 12.9	61.5 ± 19.7	-26.3	-26.0 to -7.5	<0.001
Intraoperative/ postoperative blood transfusion, n (%)	0 (0)	2 (8)			0.148
Additional uterotonic agents, n (%)	2 (8)	7 (28)			0.065
Adverse effects of TXA, n (%)					0.570
None	16 (64)	14 (56)			
Dizziness	6 (24)	7 (28)			
Nausea/Vomit	1 (4)	4 (16)			
Headache	2 (8)	0 (0)			
LOS (days), mean ± SD	3.0 ± 0.7	3.1 ± 0.7			0.240

TXA: tranexamic acid, CI: confidence interval, SD: standard deviation, LOS: length of hospital stay

Excessive blood loss of more than 1,000 ml in the TXA and placebo group were 8% and 36%, respectively. The relative risk was 0.22, and 3.57 was the number needed to treat. Excessive blood loss of more than 1,000 ml was statistically significantly lower in the TXA group (95%CI -645.8 to -213.9, p = 0.039) (Table 3).

In addition, the operative time in the TXA group and the placebo group was 44.7 ± 12.9 min vs 61.5 ± 19.7 min, respectively. The respective hemoglobin level changes before and 24 hours after CD in the TXA group and the placebo group were 1.1 ± 7.0 g/dL and 6.9 ± 9.6 g/dL. The operative time and the hemoglobin level changes were significantly lower in the TXA group, with p <0.001 and 0.020 indicating statistical significance, respectively (Table 2).

The two study groups showed no significant differences in terms of blood transfusion requirements, or length of hospital stay. Although the need for additional uterotonic agents was greater in the placebo group compared to TXA group, this difference did not reach statistical significance (p = 0.065). Adverse effects associated with TXA included dizziness, nausea/vomiting and headache (Table 2). No serious adverse events were reported in this study.

Table 3. Blood loss >1,000 ml.

	TXA group (n = 25)	Placebo group (n = 25)	Relative risk	NNT	95% CI	p value
Measurement of blood loss > 1,000 ml, n (%)	2 (8)	9 (36)	0.22	3.57	0.05 to 0.92	0.039

TXA: tranexamic acid, NNT: number needed to treat, CI: confidence interval

Discussion

Our study aimed to evaluate the efficacy of preoperative TXA in reducing blood loss in women at high risk of PPH undergoing CD. The findings indicated that preoperative TXA administration significantly reduced measurement of intraoperative blood loss and the occurrence of PPH compared to the placebo.

No substantial differences were observed in the demographic characteristics, such as maternal age, BMI, mode of previous deliveries, preoperative hemoglobin concentration, type of CD, skin incision, and surgeon, between the TXA and placebo groups. This suggests that the initial features of the groups were similar, which guarantees the accuracy of the compared results. Previous CD, fetal macrosomia, and prenatal anemia were the most frequently seen high-risk factors, which aligned with earlier research studies that have emphasized these as notable risk factors for PPH[16-23]. Previous CD still remains the most common risk factor for PPH in Khon Kaen Hospital.

The primary outcome of the study showed that the TXA group had a considerably lower amount of intraoperative blood loss compared to the placebo group. This finding was consistent with prior research that has shown the effectiveness of TXA in reducing intraoperative blood loss during CD[16,17].

In the secondary outcomes, the TXA group experienced a shorter duration of surgery, indicating that the decreased blood loss potentially enhanced the efficiency of the surgical procedure. Moreover, in the TXA group, the occurrence of PPH (intraoperative blood loss > 1,000 ml) was effectively mitigated, which was the main result of this study. The need for additional uterotonic agents was greater in the placebo group compared to the TXA group with clinical significance but no statistical significance. This reduction in the use of additional uterotonic agents has important implications, as it may reduce the risk of the side effects associated with these drugs and simplify the management of hemorrhage in the operating room.

This parallels the findings of Ortuanya et al[29], which evaluated the use of prophylactic TXA for reducing intraoperative blood loss in CD among high-risk women. In their study, the TXA group experienced significantly lower mean blood loss compared to the placebo group (442.9 ± 200.9 ml vs 801.2 ± 258.6 ml; p = 0.001), reduced incidence of PPH (1.0% vs 19.0%; p = 0.001), and decreased need for additional uterotonic agents (39.0% vs 68.0%; p = 0.001). These findings and those of this current study demonstrated the effectiveness of TXA in minimizing both intraoperative blood loss and the risk of PPH in high-risk CD patients.

Our findings aligned with previous studies, such as the research conducted by Shalaby et al[16], which observed a notable disparity in intraoperative blood loss between the placebo group (896.8 ± 519.6 ml) and the TXA group (583.2 ± 379.6 ml) (p < 0.001) in women at high risk of PPH who underwent CD. In a related study, Abdel-Fatah et al[17] discovered a noteworthy decrease in intraoperative blood loss during CD when using preoperative TXA in pregnancies at high risk of PPH. The group that received TXA had an average blood loss of 484.8 ml, whereas the control group had 705 ml (p < 0.001).

In contrast, the research by Madar et al[30] examined the effect of preoperative TXA administration in women with multiple pregnancies undergoing CD. Their results showed that estimated blood loss exceeding 1,000 ml occurred in 62 of the 147 women (42.2%) in the TXA group and 67 of the 152 women (44.1%) in the placebo group (adjusted relative risk (RR) = 0.97; 95% CI 0.68 to 1.38; p = 0.86), indicating no significant difference between the two groups. This difference in outcomes could be attributed to variations in the populations studied. Our research focused on women with specific high-risk factors for PPH, in which TXA demonstrated clear effectiveness in reducing intraoperative blood loss and the occurrence of PPH.

Our study's findings also aligned with a comprehensive analysis conducted by Al-dardery et al[12], which involved 59 randomized controlled trials

(RCTs) and demonstrated that TXA effectively decreased overall blood loss in CD when compared to the placebo (standardized MD = -2.11, 95% CI -3.09 to -1.14, p < 0.001). This meta-analysis further confirmed the safety profile of TXA, demonstrating no substantial rise in side effects such as nausea or vomiting.

In research by Eyeberu et al[14], the effects of TXA on African women undergoing CD were explored. The study revealed that TXA had a substantial impact on mitigating blood loss both during and after the procedure (standardized MD = -1.93, 95% CI -2.40 to -1.47). This meta-analysis provides more evidence of the effectiveness of TXA in various groups and circumstances, reaffirming its importance in the management of blood loss during cesarean procedures.

The findings of Bellos et al[31] provided additional support for our results. Their meta-analysis encompassed 36 studies involving 10,659 women. The study revealed that the administration of TXA resulted in notable reductions in total blood loss (MD = -189.4 ml, 95% CI -218.6 to -160.2), hemoglobin drops, risk of blood loss over 1,000 ml, transfusion requirements, and the need for supplementary uterotonic agents.

In addition, research by Chatdoa et al[32] revealed a noteworthy decrease in intraoperative blood loss in the TXA group compared to the control group (740.5 ± 139.5 ml vs 853.5 ± 163.6 ml, p = 0.002). Their study focused on women who were undergoing elective CD and had a history of previous CD. This supports our research, in which the most common high-risk PPH factor was previous CD, and emphasizes the importance of TXA in addressing blood loss in previous CD populations, which is increasingly found as a high-risk PPH factor worldwide.

In a study by Sentilhes et al[33], women undergoing CD were given an intravenous prophylactic uterotonic agent along with either tranexamic acid (1 gm) or a placebo. The estimated blood loss exceeding 1,000 ml occurred in 556 out of the 2,086 women (26.7%) in the TXA group and in 653 out of the 2,067 women (31.6%) in the placebo group (adjusted RR = 0.84; 95% CI 0.75 to 0.94; p = 0.003). However, there were no significant differences between the two groups in terms of the mean blood loss measured using gravimetric methods. This contrast may be attributed to our stricter definition of high-risk factors, which included a higher prevalence of PPH. Furthermore, our research focused on the impact of TXA alone, allowing us to better assess its direct effects on intraoperative blood loss.

Oseni et al[34] also found that TXA had a significant impact on reducing intraoperative blood loss in emergency CD. In the TXA group, only 2 (1.6%) patients experienced blood loss over 1,000 ml, compared to 12 (9.8%) in the control group (p = 0.01). This discovery provides further evidence of the efficacy of TXA in various scenarios involving CD.

In contrast, the research conducted by Ruka et al[35] did not observe any notable variation in intraoperative blood loss in elective CD between the TXA (454.6 ml) and placebo groups (467 ml). There could be various reasons for this discrepancy, such as variations in the number of participants, the methodology used in the study, or the characteristics of the patients involved.

The study found that the negative impacts of TXA were mostly modest, such as dizziness, nausea/vomiting, and headache. The results aligned with the safety characteristics of TXA documented in prior research conducted by Shalaby et al and Abdel-Fatah et al[16,17], which similarly reported the safety record of TXA with rare occurrences of severe adverse effects. The minimal occurrence of negative outcomes in our study strengthened the assurance of the safety of TXA utilization in CD.

Preoperative administration of TXA has been shown to significantly reduce intraoperative blood loss, thereby potentially lowering the need for additional interventions such as blood transfusions. This reduction in blood loss not only leads to direct cost savings by decreasing the resources required for blood products but also minimizes the hospital

stay and recovery time for the patient. Moreover, patients who experience PPH often require additional medical interventions, which can further increase hospital costs and impact overall patient outcomes. By implementing a preoperative protocol for high-risk patients, healthcare providers may achieve better resource allocation and improved clinical outcomes, ultimately resulting in a more cost-effective approach to managing CD.

In contrast, intraoperative administration of TXA, while beneficial, may not provide the same level of efficacy as preoperative administration. Intraoperative TXA is administered after blood loss has already begun, which can result in less effective hemostatic control. The timing of administration is crucial, as preoperative TXA allows for optimal plasma levels of the drug before surgical intervention, enhancing its effectiveness in preventing excessive blood loss. Furthermore, preoperative TXA may mitigate the stress response to surgical trauma and enhance coagulation pathways before the onset of surgical bleeding.

The strengths of our study were that it was conducted as a randomized controlled trial with a double-blinded placebo control. The sample size was calculated accurately based on data from the pilot study, and there were no dropouts. Additionally, intraoperative blood loss was calculated using a measurement formula, resulting in minimal error.

On the contrary, the limitations of our study were that it used a single-center approach, which may limit the broader applicability of the findings. Moreover, there was a potential confounding factor, which was that the most common high-risk PPH factor was the previous CD. Due to the time constraints for data collection and the calculated sample size, the majority of the participants gathered at the time of the study consisted of individuals with previous CD.

Consequently, we suggested that preoperative TXA administration can be used in women at high risk of PPH undergoing CD to reduce intraoperative blood loss, without serious adverse effects. Further studies are needed to stratify women at high risk of PPH to cover other high-risk groups.

Conclusion

TXA effectively reduced intraoperative blood loss and the occurrence of PPH during high-risk CD under spinal anesthesia, without serious adverse effects.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Incidence of Chemotherapy-induced Severe Neutropenia in Nadir Period in Gynecologic Cancer Patients Receiving Carboplatin and Paclitaxel

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ABSTRACT

Objectives: This study aimed to determine the incidence of chemotherapy-induced severe neutropenia in the nadir period among gynecologic cancer patients receiving carboplatin and paclitaxel.

Materials and Methods: This prospective cohort study recruited 150 gynecologic cancer patients receiving carboplatin and paclitaxel. Complete blood counts were collected before receiving chemotherapy and during the nadir period of each cycle, followed until discontinuation of the regimen or completion of six cycles, to evaluate the incidence of severe neutropenia.

Results: A total of 793 cycles were analyzed in 150 patients. Severe neutropenia occurred in 366 cycles and 111 patients during the nadir periods, with 46.2% per cycle and 74.0% per patient, respectively. The incidence tended to increase in later cycles. The prior use of granulocyte-colony stimulating factor was 2.9%. The incidence of febrile neutropenia was 4.7%. No additional treatment for severe neutropenia was provided in 80.2%. Postmenopausal status and an initial white blood cell count below 7,000 cells/μL were significant risk factors for severe neutropenia. Additionally, an initial absolute neutrophil count (ANC) below 5,000 cells/μL was a significant risk factor for febrile neutropenia.

Conclusion: Despite severe neutropenia being relatively common during the nadir periods, the majority did not receive further management and subsequently recovered. Furthermore, the incidence of febrile neutropenia was low. Therefore, evaluation of ANC in nadir periods should be selectively performed in patients at risk for severe and febrile neutropenia.

Keywords: chemotherapy-induced neutropenia, nadir, gynecologic cancer, Carboplatin, Paclitaxel.

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อุบัติการณ์การลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรง ในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาว ในผู้ป่วยมะเร็งทางนรีเวชที่ได้รับยาเคมีบำบัดสูตร Carboplatin และ Paclitaxel

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์การลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรง ในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาว ในผู้ป่วยมะเร็งทางนรีเวชที่ได้รับยาเคมีบำบัดสูตร Carboplatin และ Paclitaxel*

วัสดุและวิธีการ: *การศึกษาไปข้างหน้า ด้วยการเก็บข้อมูลผู้ป่วยจำนวน 150 คน ที่วินิจฉัยเป็นมะเร็งนรีเวชและได้รับยาเคมีบำบัดสูตร Carboplatin และ Paclitaxel โดยเก็บข้อมูลผลเลือดการตรวจความสมบูรณ์ของเม็ดเลือด ก่อนให้ยาเคมีบำบัดและในสัปดาห์ที่ 2 หลังการให้ยาเคมีบำบัดที่จะมีการลดต่ำสุดของเม็ดเลือดขาวในแต่ละรอบ โดยเก็บข้อมูลตั้งแต่รอบที่ 1 จนถึงรอบที่ 6 ของการให้ยาเคมีบำบัดหรือจนถึงรอบที่มีการยกเลิกการให้ยาเคมีบำบัดสูตรนี้ เพื่อศึกษาอุบัติการณ์การลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาว*

ผลการศึกษา: *จากการเก็บข้อมูลทั้งหมด 793 รอบของการให้ยาเคมีบำบัดของผู้ป่วยจำนวน 150 คน พบว่าเกิดการลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรง ในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาวจำนวน 366 รอบของการให้ยาเคมีบำบัด และเกิดใน 111 คนของจำนวนผู้ป่วยทั้งหมด คิดเป็นอุบัติการณ์ ร้อยละ 46.2 ของจำนวนรอบและร้อยละ 74 ของจำนวนคน โดยอุบัติการณ์มีแนวโน้มเพิ่มขึ้นในการให้เคมีบำบัดรอบถัดมา โดยมีอัตราการใช้ยากระตุ้นเม็ดเลือดขาวร้อยละ 2.9 อุบัติการณ์การเกิดภาวะไข้จากเม็ดเลือดขาวต่ำจากการลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงร้อยละ 4.7 ในขณะเดียวกันร้อยละ 80.2 ของการเกิดภาวะเม็ดเลือดขาวชนิดนิวโทรฟิลต่ำระดับรุนแรงในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาว เม็ดเลือดขาวดีขึ้นได้เองก่อนการให้ยาครั้งถัดไปโดยไม่ต้องได้รับการรักษาเพิ่มเติม ปัจจัยเสี่ยงที่ทำให้เกิดการลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงคือ วัยหลังหมดระดูและการที่มีเม็ดเลือดขาวก่อนให้ยาเคมีบำบัดน้อยกว่า 7,000 เซลล์ต่อลูกบาศก์เมตร ปัจจัยเสี่ยงในการเกิดภาวะไข้จากเม็ดเลือดขาวต่ำคือ การที่มีระดับเม็ดเลือดขาวชนิดนิวโทรฟิล ก่อนให้ยาเคมีบำบัดน้อยกว่า 5,000 เซลล์ต่อลูกบาศก์เมตร*

สรุป: *ถึงแม้อุบัติการณ์การลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงในช่วงที่มีการลดลงต่ำสุดของเม็ดเลือดขาวในผู้ป่วยมะเร็งทางนรีเวชที่ได้รับยาเคมีบำบัดสูตร Carboplatin และ Paclitaxel จะพบได้บ่อย แต่ผู้ป่วยกลุ่มนี้ส่วนมากเม็ดเลือดขาวสามารถเพิ่มขึ้นเองได้โดยไม่ต้องได้รับการรักษาเพิ่มเติม และการเกิดภาวะไข้จากเม็ดเลือดขาวต่ำพบได้น้อย ดังนั้นการเจาะเลือดในช่วงที่มีการลดต่ำสุดของเม็ดเลือดขาวหลังได้ยาเคมีบำบัดอาจพิจารณาทำในเฉพาะผู้ป่วยที่มีความเสี่ยงต่อการเกิดการลดลงของเม็ดเลือดขาวชนิดนิวโทรฟิลระดับรุนแรงและการเกิดภาวะไข้จากเม็ดเลือดขาวต่ำ*

คำสำคัญ: *นิวโทรฟิล, ยาเคมีบำบัด, มะเร็งนรีเวช, คาร์โบพลาติน, แพ็คลิแท็กเซล*

Introduction

Gynecologic cancer is essential and common in female cancers. Among women's cancers, gynecological cancer is frequently encountered, second only to breast cancer. The most commonly encountered gynecological cancer in Thai women is cervical cancer, followed by endometrial cancer and ovarian cancer, respectively[1, 2].

Currently, gynecologic cancer treatment has undergone continuous study and development to achieve the best treatment outcomes and minimize side effects. The standard chemotherapy regimen commonly used is carboplatin/paclitaxel because of its effectiveness[3], minimal side effects[4], and flexibility for administration. This regimen is suitable for both outpatient and inpatient settings. The typical dosage includes carboplatin at an area under the concentration (AUC) versus time of 5 mg/ml/min and paclitaxel at 175 mg/m^2, administered intravenously every three weeks for at least six cycles[5]. Then, the response to chemotherapy will be examined by per vaginal examination (PV) or imaging such as ultrasound or computed tomography (CT) scan.

Carboplatin has side effects such as nausea, vomiting, nephrotoxicity, and neurotoxicity less than other chemotherapy drugs. However, it has another severe side effect: bone marrow suppression that induces neutropenia[6].

Chemotherapy-induced neutropenia has a significant impact on prognosis and overall survival. Some patients who have neutropenia will increase their risk for febrile neutropenia (FN) or secondary infections, which can lead to mortality. Therefore, detecting and treating neutropenia before severe complications are important. According to the National Cancer Institute's common terminology criteria for adverse events (CTCAE version 5.0), the severity of chemotherapy-induced neutropenia has four grades: grade 1 absolute neutrophil count (ANC): 1,500-2,000 cells/mm^3, grade 2 ANC: 1,000-1,500 cells/mm^3, grade 3 ANC: 500-1,000 cells/mm^3, and grade 4: ANC < 500 cells/mm^3. The grade 3 and 4 neutropenia are graded as severe neutropenia, requiring close monitoring for complications.

Chemotherapy-induced neutropenia often occurs 10-14 days after receiving chemotherapy (the nadir phase) and typically resolves within 21-28 days[7]. Therefore, at the Division of Gynaecologic Oncology, Faculty of Medicine, Siriraj Hospital, all patients who receive carboplatin/paclitaxel will have to be examined for the ANC to evaluate chemotherapy-induced neutropenia in the nadir phase (2 weeks after receiving chemotherapy) and before receiving the next cycle (3 weeks after receiving the last chemotherapy). Although severe neutropenia is detected during each cycle of chemotherapy, it is usually managed through subsequent monitoring before receiving the next cycle without additional treatment when there are no complications. Therefore, this study aimed to determine the incidence of chemotherapy-induced severe neutropenia at the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel at Siriraj Hospital. Additionally, the incidences of management and complication were also reported to evaluate the necessity of routinely examining the ANC in the nadir period in all patients.

Materials and Methods

This was a prospective cohort study. After approval from the Siriraj Institutional Review Board (SIRB), the patients who matched the inclusion criteria and had gynecologic cancers, including cervical cancer, corpus uteri cancer, ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, and were receiving carboplatin/paclitaxel (initial dose carboplatin AUC 5 mg/ml/min/paclitaxel 175 mg/m^2) at Siriraj Hospital and could be evaluated for ANC in the nadir period and also before receiving the subsequent chemotherapy in each cycle, were recruited and informed consent had been obtained.

The researchers collected baseline blood test results, including CBC, blood urea nitrogen (BUN), creatinine, and liver function tests, before administering the first cycle of chemotherapy, as well as CBC results in the second week (nadir period) and the third week after receiving chemotherapy (before receiving the subsequent chemotherapy) of each cycle. Data has been collected from the first cycle until discontinuation of the regimen or completion of six cycles. The number of cycles that occurred in severe neutropenia and FN (complications from severe neutropenia) and the management of severe neutropenia had been collected. There was no routine use of granulocyte-colony stimulating factor (G-CSF) in this study; the use depended on the physician's decision on the severity of neutropenia. However, in all cases of febrile neutropenia, the G-CSF was used. The number of cycles using G-CSF was collected. In addition, the basic characteristics of the patients were gathered, including age, underlying disease, menopausal status, parity, Eastern Cooperative Oncology Group (ECOG) performance status scale, body mass index (BMI), episode, type, staging, and histology of cancer, history of prior surgery, radiation, and chemotherapy to evaluate the risk factors of severe neutropenia and FN. The data were recorded in case record forms.

The sample size was calculated based on the previous study of the incidence of chemotherapy-induced severe neutropenia at the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel, which was 0.29[8]. In this study, an estimation error of less than 7.5% was allowed at a 95% confidence level (type I error = 0.05, 2-sided), requiring a sample size of 140 participants. To account for 5% of data incompleteness, the total sample size for this study was 150 participants.

The data had been analyzed by the SPSS program (PASW Statistic 18) to determine, as the primary objective, the incidence of chemotherapy-induced severe neutropenia in the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel at Siriraj Hospital and reported in number, percent, and 95% confidence interval (CI). Further, the secondary objectives were evaluated: the incidence of FN, the incidence of effects on management in the next cycle of severe neutropenia in nadir periods (including no management, delayed cycle, received G-CSF, and decreased dose chemotherapy) was reported in number, percent, and 95% CI. The risk factors associated with chemotherapy-induced severe neutropenia and FN were analyzed by univariable analysis. The significant variables (p value < 0.05) from univariable analysis had been analyzed by multivariable analysis with multiple logistic regressions and backward method and were reported in odds ratio, 95% CI, and p value.

Results

During the study, there were a total of 793 cycles among 150 gynecological cancer patients receiving carboplatin and paclitaxel at Siriraj Hospital. The baseline characteristics of patients are shown in Table 1. The age ranges were 33 to 87 years. The median age was 61. 78% of the patients were in postmenopausal status. The majority of patients were ECOG 0 (76%); the others were ECOG 1 (20%), ECOG 2 (1.3%), and ECOG 3 (2%). The new case was 82%. The gynecologic cancers included cervical cancer at 8%, corpus uteri cancer at 34%, ovarian cancer, fallopian tube cancer and primary peritoneal cancer at 54%, and synchronous cancer (corpus, ovary) at 3.3%.

Table 1. Patient characteristics (Total n = 150).

Characteristics	n	%
Age		
Median 61 years (range 33-87)		
Underlying disease		
None	52	34.7
Metabolic disease	67	44.7
Other cancer	10	6.7
Other	46	30.7
Cardiac disease (IHD, VHD, AF, DCM)	6	4.0
Pulmonary disease (Asthma)	3	2.0
Thromboembolic disease (PE, DVT)	10	6.7
Renal disease (CKD)	9	6.0
Hepatic disease (Chronic HBV, Fatty liver)	2	1.3
(Chronic HBV, Fatty liver)		
Thyroid disease	6	4.0
(Hyperthyroid, Hypothyroid)		
Neurological disease	3	2.0
(Parkinson, Dementia, Alzheimer)		
Psychiatric disease	4	2.7
(MDD, OCD, schizophrenia)		
Autoimmune disease (RA, Scleroderma)	5	3.3
HIV disease	1	0.7
Genetic disease (Achondroplasia)	1	0.7
Menopause status		
Premenopausal	32	21.3
Postmenopausal	118	78.7
Parity		
0	61	40.7
≥1	89	59.3
ECOG		
0	115	76.7
1	30	20.0
2	2	1.3
3	3	2.0
BMI		
Underweight (<18.5 kg/m2)	16	10.7
Normal (18.5-22.9 kg/m2)	75	50.0
Overweight (23-24.9 kg/m2)	22	14.7
Obese (25-29.9 kg/m2)	22	14.7
Extremely obese (>30 kg/m2)	15	10.0
Episode		
New case	124	82.7
Recurrence	26	17.3

Characteristics	n	%
Cancer		
Cervix	12	8.0
Corpus	51	34.0
Ovary, Fallopian tubes, Peritoneum	82	54.7
Synchronous cancer (Corpus, Ovary)	5	3.3
Stage		
Cervix		
1		
2	52	34.7
3	67	44.7
4	10	6.7
Corpus	46	30.7
1	6	4.0
2	3	2.0
3	10	6.7
4	9	6.0
Ovary, Fallopian tubes, Peritoneum	2	1.3
1	6	4.0
2	3	2.0
3		
4	4	2.7
Synchronous cancer (Corpus, Ovary)		
1	5	3.3
2	1	0.7
3	1	0.7
Histology		
Squamous cell carcinoma	32	21.3
Adenocarcinoma	118	78.7
Other		
Disease confined in primary organ	61	40.7
No	89	59.3
Yes		
Radiation	115	76.7
No radiation	30	20.0
Before chemotherapy	2	1.3
During chemotherapy	3	2.0
Prior surgery		
No	16	10.7
Yes	75	50.0
Prior chemotherapy	22	14.7
No	22	14.7
Yes	15	10.0

IHD: ischemic heart disease, VHD: valvular heart disease, AF: atrial fibrillation, DCM: dilated cardiomyopathy, PE: pulmonary embolism, DVT: deep vein thrombosis, CKD: chronic kidney disease, HBV: hepatitis B virus, MDD: major depressive disorder, OCD: obsessive compulsive disorder, RA: Rheumatoid arthritis, HIV: Human Immunodeficiency Virus

There were 366 cycles, and 111 patients had severe neutropenia in the nadir periods. The incidence of severe neutropenia at the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel was 74% (95%CI, 66-80%) of patients and 46.15% (95%CI, 43-50%) of all cycles. 2.9% of cycles had previously used G-CSF, which could have affected the incidence. During the chemotherapy cycle, the incidence tended to rise. The incidence of severe neutropenia in each cycle is shown in Table 2.

Table 2. Incidence of severe neutropenia in nadir periods (total cycle = 793).

	n	%	95% CI	Number of prior using G-CSF		Total cycle
				n	%	
Nadir C1	45	30.00	(0.23,0.38)	2	1.33	150
Nadir C2	65	45.14	(0.37,0.53)	4	2.78	144
Nadir C3	66	48.18	(0.39,0.56)	3	2.19	137
Nadir C4	59	46.83	(0.38,0.56)	4	3.17	126
Nadir C5	68	55.74	(0.47,0.64)	6	4.92	122
Nadir C6	63	55.26	(0.46,0.64)	4	3.51	114
Total	**366**	**46.15**	**(0.43,0.50)**	**23**	**2.90**	**793**

CI: confidence interval, G-CSF: granulocyte-colony stimulating factor

The febrile neutropenia (severe neutropenia complication) was occurring in 7 patients. The incidence of febrile neutropenia from severe neutropenia was 4.7% (95%CI, 0.4-0.5%).

The effects of severe neutropenia on management in the next cycle of chemotherapy were that no additional treatment for severe neutropenia was provided at 80.2%, the delayed cycle was 13.53%, the received GCSF in the next cycle was 2.46%, and the decreased dose of chemotherapy was 1.32%. The details of management in each cycle are shown in Table 3.

Table 3. Incidence of effect to management in next cycle of severe neutropenia in nadir periods.

	No management		Delayed cycle		G-CSF		Decreased dose CMT		Total number of severe neutropenia
	n	%	n	%	n	%	n	%	
Nadir C1	35	77.78	6	13.33	2	4.44	2	4.44	45
Nadir C2	52	80.00	8	12.31	2	3.08	1	1.54	65
Nadir C3	56	84.85	5	7.58	3	4.55	0	0.00	66
Nadir C4	45	76.27	10	16.95	2	3.39	0	0.00	59
Nadir C5	55	80.88	12	17.65	0	0.00	1	1.47	68
Total	**243**	**80.20**	**41**	**13.53**	**9**	**2.46**	**4**	**1.32**	**303**

G-CSF: granulocyte-colony stimulating factor, CMT: combined modality treatment

The significant risk factors for severe neutropenia from the univariable analysis were age ≥ 50 years (OR 2.6, p = 0.038), postmenopausal status (OR 2.42, p = 0.033), initial white blood cell (WBC) below 7000 cells/ul (OR 3.88, p = 0.001), and initial ANC below 5000 cells/ul (OR 3.05, p = 0.004). The significant risk factors for severe neutropenia from multivariable analysis (multiple logistic regression, backward method) were postmenopausal status (OR 2.83, p = 0.02) and initial WBC below 7000 cells/ul (OR 4.61, p < 0.001). The significant risk factor for febrile

neutropenia from univariable and multivariable analysis was initial ANC below 5000 cells/ul (OR 2.68, p = 0.02) (Table 4).

Table 5 demonstrated the incidence of other hematotoxicity from carboplatin/ paclitaxel in the nadir period, as graded by CTCAE version 5.0.

Table 4. Risk factor for severe neutropenia and febrile neutropenia in multivariate analysis (multiple logistic regression, backward method).

	OR	95%CI	Sig. (p value)
Severe neutropenia			
Postmenopausal	2.83	1.15,6.99	0.02
WBC < 7000	4.61	1.99,10.70	< 0.001
Febrile neutropenia			
Age 70-89	3.64	0.93,14.24	0.06
ECOG 1-3	0.42	0.17,1.02	0.06
ANC < 5000	2.68	1.21,5.95	0.02

OR: odds ratio, CI: confidence interval, WBC: white blood cell count, ECOG: Eastern Cooperative Oncology Group, ANC: antenatal care

Table 5. Incidence of hematotoxicity in nadir periods (total cycles = 793).

	Grading									
	0		1		2		3		4	
	n	%	n	%	n	%	n	%	n	%
Anemia	50	6.31	347	43.76	340	42.88	55	6.94	1	0.13
Leukopenia	218	27.49	216	27.24	265	33.42	93	11.73	1	0.13
Neutropenia	182	22.95	88	11.10	157	19.80	254	32.03	112	14.12
Thrombocytopenia	766	96.60	15	1.89	6	0.76	6	0.76	0	0.00

Discussion

This study revealed that most patients (74% of patients and 46.15% of all cycles) experienced severe neutropenia in the nadir period. Although only 4.6% had the complication of severe neutropenia, FN. The use of G-CSF was 2.9%. Compared to the previous study, the incidence of severe neutropenia was in a wide range between 29-79% of patients[8-11] and 53% of the cycles[10]. The study that reported the low incidence of severe neutropenia for 29-36%[8, 9] had G-CSF support for 26%[9], and another study had the general policy of reducing the dose of chemotherapy in subsequent cycles in the presence of severe neutropenia[8]. In contrast, the study that documented the high incidence, which was approximately equal to our study for 75-79% of patients[10, 11], and 53% of the cycles[10] that administered G-CSF during the study was only 6% and did not have active management for severe neutropenia. The factors that may interfere with the incidence are the different management strategies for severe neutropenia in other studies, such as criteria for G-CSF and reduced-dose chemotherapy. The study that used more G-CSF or had an intensive policy for severe neutropenia had a lesser incidence of severe neutropenia. There was a similar incidence in the study that used G-CSF equivalent to ours. For febrile neutropenia, the incidence was low, only 1.4-6% from the prior study[8-11], and the incidence in our study was in this range. The incidence of febrile neutropenia did not appear to be impacted by the administration of G-CSF or reduced-dose chemotherapy.

The effects of severe neutropenia in the nadir period on management in the subsequence cycle of chemotherapy have not been evaluated in previous

studies. This point will be beneficial for plan management in asymptomatic severe neutropenia. In 80.2% of severe neutropenia, the ANC can improve for the next cycle of chemotherapy with no further management.

The effects of severe neutropenia in the nadir period on management in the subsequence cycle of chemotherapy have not been evaluated in previous studies. This point will be beneficial for plan management in asymptomatic severe neutropenia. In 80.2% of severe neutropenia, the ANC can improve for the next cycle of chemotherapy with no further management.

The significant risk factors for severe neutropenia in gynecologic patients receiving carboplatin/paclitaxel from multivariable analysis (multiple logistic regression, backward method) were postmenopausal status and initial WBC below 7,000 cells/ul. The significant risk factors for febrile neutropenia from the multivariable analysis were initial ANC below 5,000 cells/ul. Compared with previous studies, the significant risk factors in each study differed due to the different factors that were considered for the study and the different definitions of severe neutropenia. Some studies defined severe neutropenia as ANC less than 500/mm^3 [12, 13]; others defined it as ANC less than 1,000/mm^3 [14], similar to our study. The other significant risk factors for severe neutropenia that were similar in our study were older age (over 70 years) ($p < 0.0001$)[12]. Our study found that age ≥ 50 years and postmenopausal status were significant risk factors in univariable analysis. Although, in multivariable analysis, only postmenopausal status was the significant risk factor, it was also related to age. Our study's other significant risk factor was an initial WBC below 7,000 cells/ul, which was not the factor that previous studies considered.

For the significant risk factor of febrile neutropenia, older age was also a risk factor that has been similar in most studies. Robin et al[13] reported that the significant risk factor was age > 60 (hazard ratio 2.84; $p = 0.05$), and guidelines NCCN Clinical Practice Guidelines in Oncology 2017[15] and European Organisation for Research and Treatment of Cancer 2010[16] reported age > 65 years, in our study, older age (70-89 years) was a risk factor for febrile neutropenia (OR 3.64; $p = 0.06$), but not significant, the small sample size could be the cause.

However, preexisting neutropenia was the risk factor in our study that was compatible with the guidelines of NCCN 2017(15) and EORTC 2010[16]. Our study identified initial ANC below 5,000 cells/ul as the significant risk factor for febrile neutropenia. Although it is not within the range of neutropenia, it implies that the lower initial ANC tends to have a greater risk of febrile neutropenia.

The limitations of this study were the small sample size and the unavoidable factors that may interfere with the incidence of severe neutropenia, such as giving G-CSF or reducing the dose of chemotherapy. However, the strengths of this study were the prospective study, in which the data was almost complete and reliable, and the study of the effects of severe neutropenia in nadir on management in the next cycle of chemotherapy. No previous studies evaluated this subject, which will guide the management of asymptomatic severe neutropenia in the nadir period. Another strength was the study of various risk factors for severe neutropenia and febrile neutropenia, but due to the small sample size, some factors could not evaluate the OR.

The clinical implication of our study is the guided evaluation for ANC in nadir periods for the most safety, value, and benefit for the patients. Although severe neutropenia was relatively common during the nadir periods, the majority did not receive further management and subsequently recovered. Additionally, the incidence of febrile neutropenia was low. Thus, evaluation for ANC in nadir periods should be performed only in patients who have the risk for severe neutropenia and febrile neutropenia that are postmenopausal status, initial WBC below 7,000 cells/ul, and initial ANC below 5,000 cells/ul.

Further evaluation of the large sample size for significant risk factors for severe neutropenia and febrile neutropenia and the design for the study of the

incidence of severe neutropenia that decreased the unavoidable factor that may interfere with severe neutropenia should be considered.

Conclusion

The incidence of severe neutropenia during the nadir period in gynecologic cancer patients receiving carboplatin and paclitaxel was high, affecting 74% of patients and 46.15% of cycles, while febrile neutropenia was rare (4.7%). Most cases of severe neutropenia (80.2%) resolved without intervention. Postmenopausal status and an initial WBC < 7,000 cells/μL were significant predictors of severe neutropenia, and an initial ANC < 5,000 cells/μL predicted febrile neutropenia. These findings supported selective ANC monitoring during the nadir period for high-risk patients, optimizing resource use while maintaining patient safety.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

Lidocaine-Prilocaine Cream versus Placebo in Conjunction with Lidocaine Injection for Pain Relief during Episiotomy Repair after Normal Vaginal Delivery

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ABSTRACT

Objectives: To study the efficacy of lidocaine-prilocaine cream versus placebo in conjunction with lidocaine injection in relieving pain during episiotomy repair.

Materials and Methods: Postpartum women who underwent restrictive episiotomy with second-degree perineal tears from August 2023 to February 2024 were randomly allocated into two groups. In the intervention group, lidocaine-prilocaine cream was applied around the episiotomy wound in conjunction with lidocaine injection, while in the control group, placebo cream was applied instead. The primary outcome was pain intensity during episiotomy repair using a 10-cm visual analogue scale (VAS).

Results: Ninety women were randomly assigned into two groups (45 in each group). Pain score during lidocaine injection in the lidocaine-prilocaine cream group was significantly lower compared to the control group (2.45 ± 2.49 vs 3.71 ± 2.73; mean difference (MD) -1.26, 95% confidence interval (CI) -2.07 to -0.46, p = 0.002). Pain scores during perineal muscle repair and perineal skin repair in the lidocaine-prilocaine cream group were significantly lower than the control group (1.95 ± 2.13 vs 3.13 ± 2.34; MD -1.19, 95%CI -2.11 to -0.27, p = 0.012 and 1.87 ± 2.12 vs 3.82 ± 2.86; MD -1.95, 95%CI -2.95 to -0.95, p < 0.001, respectively). Perineal wound complications were not significantly different between groups (p = 0.556). No adverse reactions were found.

Conclusion: Lidocaine-prilocaine cream in conjunction with lidocaine injection effectively reduced pain during lidocaine injection, perineal muscle repair, and perineal skin repair without adverse reaction.

Keywords: Episiotomy, lidocaine-prilocaine cream, pain intensity, perineal repair.

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การศึกษาเปรียบเทียบประสิทธิภาพของครีมยาชาไลโดเคน-พริโลเคนกับยาหลอกที่ให้ร่วมกับการฉีดยาชาไลโดเคนในการลดความเจ็บปวดขณะเย็บแผลฝีเย็บหลังคลอด

ลลิตา วงศ์วิวัฒนาการ, ทุมวดี ตั้งศิริวัฒนา

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของครีมยาชาไลโดเคน-พริโลเคนเทียบกับยาหลอกที่ให้ร่วมกับการฉีดยาชาไลโดเคนในการลดความเจ็บปวดขณะเย็บแผลฝีเย็บหลังคลอด*

วัสดุและวิธีการ: *สตรีหลังคลอดที่ได้รับการตัดฝีเย็บร่วมกับมีการฉีกขาดของแผลฝีเย็บระดับสอง ระหว่างเดือนสิงหาคม พ.ศ. 2566 ถึงเดือนกุมภาพันธ์ พ.ศ. 2567 ได้ถูกสุ่มแบ่งออกเป็นสองกลุ่ม คือ กลุ่มทดลองซึ่งได้รับการทาครีมยาชาไลโดเคน-พริโลเคนรอบแผลฝีเย็บและกลุ่มควบคุมซึ่งได้รับการทาครีมยาหลอก ร่วมกับการฉีดยาชาไลโดเคน และวัดผลความเจ็บปวดขณะเย็บแผลฝีเย็บโดยใช้มาตรวัดความเจ็บปวดด้วยสายตาความยาว 10 เซนติเมตร*

ผลการศึกษา: *สตรีหลังคลอดจำนวน 90 คนถูกสุ่มออกเป็นสองกลุ่ม กลุ่มละ 45 คน คะแนนความเจ็บปวดขณะฉีดยาชาไลโดเคนในกลุ่มทดลองต่ำกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (2.45 ± 2.49 vs 3.71 ± 2.73; mean difference (MD) -1.26, 95% confidence interval (CI) -2.07 ถึง -0.46, p = 0.002) คะแนนความเจ็บปวดขณะเย็บกล้ามเนื้อฝีเย็บและเย็บผิวหนังฝีเย็บในกลุ่มทดลองต่ำกว่ากลุ่มควบคุมอย่างมีนัยสำคัญทางสถิติ (1.95 ± 2.13 vs 3.13 ± 2.34; MD -1.19, 95%CI -2.11 ถึง -0.27, p = 0.012 และ 1.87 ± 2.12 vs 3.82 ± 2.86; MD -1.95, 95%CI -2.95 ถึง -0.95, p < 0.001 ตามลำดับ) ภาวะแทรกซ้อนของแผลฝีเย็บในทั้งสองกลุ่มไม่แตกต่างกันและไม่พบผลข้างเคียงที่สัมพันธ์กับการใช้ครีมยาชาไลโดเคน-พริโลเคน*

สรุป: *การใช้ครีมยาชาไลโดเคน-พริโลเคนร่วมกับการฉีดยาชาไลโดเคน มีประสิทธิภาพในการลดความเจ็บปวดขณะฉีดยาชา ขณะเย็บกล้ามเนื้อฝีเย็บและขณะเย็บผิวหนังฝีเย็บ โดยไม่มีผลข้างเคียง*

คำสำคัญ: *การตัดฝีเย็บ, ครีมยาชาไลโดเคน-พริโลเคน, ระดับความเจ็บปวด, การเย็บแผลฝีเย็บ*

Introduction

Perineal trauma is a common consequence of vaginal delivery, occurring in about 85% of postpartum women after vaginal birth[1]. It can result from either spontaneous perineal tears or intentional episiotomy[2]. Episiotomy is an intended incision of the perineum performed to enlarge the vaginal opening for birth and prevent severe perineal trauma in selective use[3]. Today, numerous methods exist to provide anesthesia during episiotomy repair. These methods comprise non-pharmacological methods, such as warm or cold compression and perineal massage, and pharmacological methods such as local or topical anesthetics[4,5]. The most common technique performed is perineal infiltration with local anesthetic. However, the injection itself can cause pain and tissue edema[6]. Moreover, based on the literature review, the pain intensity during perineal repair under lidocaine injection alone is still moderate pain[7–9].

Nowadays, sprays, gels, and creams are topical alternatives to injectable anesthetics[10,11]. The superior advantages of topical anesthesia over local infiltration anesthesia are achievement of local effect without significant systemic absorption, painless application, and avoidance of swelling at surgical sites which can distort wound margins in perineal repair[12].

Lidocaine-prilocaine cream is a widely used topical anesthetic agent, consisting of 5% eutectic mixture with 25 mg/ml of lidocaine and 25 mg/ml of prilocaine in emulsion cream[13]. After application, lidocaine-prilocaine cream acts by releasing lidocaine and prilocaine into the epidermis and dermis, where it blocks pain receptors and nerve conduction. On intact skin, the onset duration of lidocaine-prilocaine cream is 1–2 hours for adequate anesthesia. However, the onset is much shorter when applied to the genital mucosa (5–10 minutes) with a maximum duration of effective anesthesia of about 45 minutes[14,15]. The systemic absorption of lidocaine and prilocaine depends on the duration and the size of the application area. Nevertheless, lidocaine-prilocaine cream has few adverse reactions, such as redness, burning sensation, and edema, and rare complications include allergic and systemic reactions[15,16]. Lidocaine-prilocaine cream is frequently used in various minor procedures in the pediatric, skin, and plastic fields[17–19]. It is also applied in minor gynecological procedures including genital warts removal, vulvar biopsy, minor surgery of genital mucosa, laser therapy for cervical intraepithelial neoplasia (CIN), and hysteroscopy[20].

Many studies have aimed to compare the efficacy of lidocaine-prilocaine cream to lidocaine injection for pain relief during perineal repair. However, they evaluated each method of anesthesia separately, and the pain intensity during perineal repair was still moderate pain[7–9]. We hypothesized that the conjunction of lidocaine-prilocaine cream with lidocaine injection may increase the analgesic effect. Therefore, the objective of this study was to evaluate the efficacy of lidocaine-prilocaine cream versus placebo in conjunction with lidocaine injection for pain relief during episiotomy repair.

Materials and Methods

This randomized control trial was conducted at the Department of Obstetrics and Gynecology, Khon Kaen Hospital between August 2023 and February 2024. The study was started after being approved by the Khon Kaen Hospital Institute Review Board in Human Research (KEF66013).

The eligibility criteria were term singleton pregnant women aged ≥ 18 years old with cephalic presentation who underwent vaginal delivery with restrictive episiotomy with second-degree perineal tears. The exclusion criteria were pregnant women with (a) operative vaginal delivery (forceps or vacuum extraction); (b) manual removal of placenta; (c) perineal wound hematoma; (d) postpartum hemorrhage; (e) previous adverse reaction to local anesthesia; (f) glucose-6-phosphate dehydrogenase deficiency; (g) compromised cardiac and pulmonary systems; (h) hepatic diseases; (i) congenital or idiopathic methemoglobinemia; and (j) difficulty communicating in Thai language.

All eligible pregnant women were informed about the study, and their consent was obtained by

the research assistants before enrollment. During vaginal delivery, the restrictive episiotomy was performed among those with fetal indication (shoulder dystocia, fetal distress) or when the operator considered that episiotomy might prevent birth canal trauma. Before performing the episiotomy, 1% lidocaine with epinephrine 10 ml was injected at the incision site via a 23-gauge needle. After vaginal delivery and examination of the perineal wound, participants who met the eligibility criteria were randomly allocated into two groups (the lidocaine-prilocaine cream group and the placebo cream group) by computer-generated randomization using a block of four with sealed opaque envelopes. The unaware nurse opened the envelopes which contained a 5 g container of lidocaine-prilocaine cream or the placebo cream (made from cream base) identical in appearance as prepared by a pharmacist. Then, the 5 g of cream was applied around the perineal wound edge by the blinded operator who performed the episiotomy repair. After 5 minutes of application, the cream was removed, and 1% lidocaine with epinephrine 10 ml was injected into the wound. In the case of active bleeding, gauze packing was applied to control the bleeding. All episiotomy repairs were performed by an experienced doctor or nurse using plain catgut 2-0 with a 30 mm needle starting at 2 minutes after the lidocaine injection. An anchor stitch was placed above the wound apex to begin continuous with lock suture to close the vaginal epithelium and deeper tissues and reapproximate the hymenal ring. A transition stitch redirected suturing from vagina to perineum. The superficial transverse perineal and bulbospongiosus muscles were reapproximated using a continuous, non-locking technique. After that, the continuous suture was carried upward as a subcuticular stitch. The final knot was tied proximal to the hymenal ring.

During lidocaine injection before repairing the perineal wound and at each step of perineal repair, the participants were asked by another unaware doctor or nurse to report their pain intensity at the perineal wound using a 10-centimeter visual analogue scale (VAS), in which 0 points represents “no pain” and 10 points represents “the greatest pain possible.” Vertical lines across the VAS were marked by participants in order to indicate their pain levels at each step (during lidocaine injection, vaginal mucosa repair, perineal muscle repair, perineal skin repair, and 1 hour after perineal repair). When patients had moderate pain (VAS > 4) or requested additional anesthesia, 1% lidocaine with epinephrine 5 ml was provided and recorded.

Before being transferred from the delivery room, the patients were asked to rate their satisfaction with the application on a 5-point Likert scale offering the following options: completely satisfied, satisfied, neutral, dissatisfied, and completely dissatisfied. All participants received the same postpartum care including observation of uterine contraction, vaginal bleeding and voiding, promotion of breastfeeding and ambulation, and pain control. Adverse reactions to the lidocaine-prilocaine cream, such as rash, erythema, itching, allergy, and anaphylactic reactions (urticaria, angioedema, bronchospasm, and shock), or methemoglobinemia (cyanotic skin discoloration and/or abnormal coloration of the blood) were recorded if present.

At discharge, the symptoms checklist of perineal wound infection including pain, fever, abnormal discharge, and perineal edema was provided and explained to the participants. They were advised to report and return to the hospital before their postpartum appointment if abnormal symptoms were experienced. In addition, all participants were asked by phone about the symptoms of perineal wound infection at 1 week after delivery. Baseline characteristics were recorded: age, gestational age, body mass index (BMI), parity, duration of second stage of labor, duration of perineal repair, neonatal birth weight, operators, estimated blood loss, and length of stay after delivery.

The primary outcome of the study was the pain score during perineal skin repair. The sample size calculation was based on a pilot study with a power of 80%, at a 5% level of significance, and a dropout rate of 10%. Ninety participants (45 in each group)

were thus required. The secondary outcomes were (a) pain score during lidocaine injection, (b) pain score during vaginal mucosa repair, (c) pain score during perineal muscle repair, (d) pain score 1 hour after perineal repair, (e) additional anesthesia, (f) patient satisfaction, and (g) perineal wound complications. Data were analyzed using STATA version 17 based on intention-to-treat analysis. The student t-test and the Mann-Whitney U test were used to analyze continuous data, while the chi-squared test and Fisher's exact test were used to analyze categorical data. A p value of < 0.05 was considered statistically significant.

Results

Between August 2023 and February 2024, 128 eligible term singleton pregnant women with cephalic presentation who planned vaginal delivery were enrolled. Thirty-eight were excluded due to delivery without episiotomy (n = 17), indicated cesarean delivery (n = 14), vacuum extraction (n = 4), third-degree perineal tear (n = 1), postpartum hemorrhage (n = 1), and manual removal of placenta (n = 1). Therefore, a total of 90 eligible women were randomly assigned into two groups: 45 to the lidocaine-prilocaine cream group and 45 to the placebo group. There was no dropout, and the data of the 90 participants were analyzed. Fig. 1 presents the consort flow diagram. Baseline characteristics were similar between groups, which included maternal age, gestational age, current BMI, parity, duration of second stage of labor, duration of perineal repair, neonatal birth weight, operators, estimated blood loss and length of stay after delivery (Table 1).

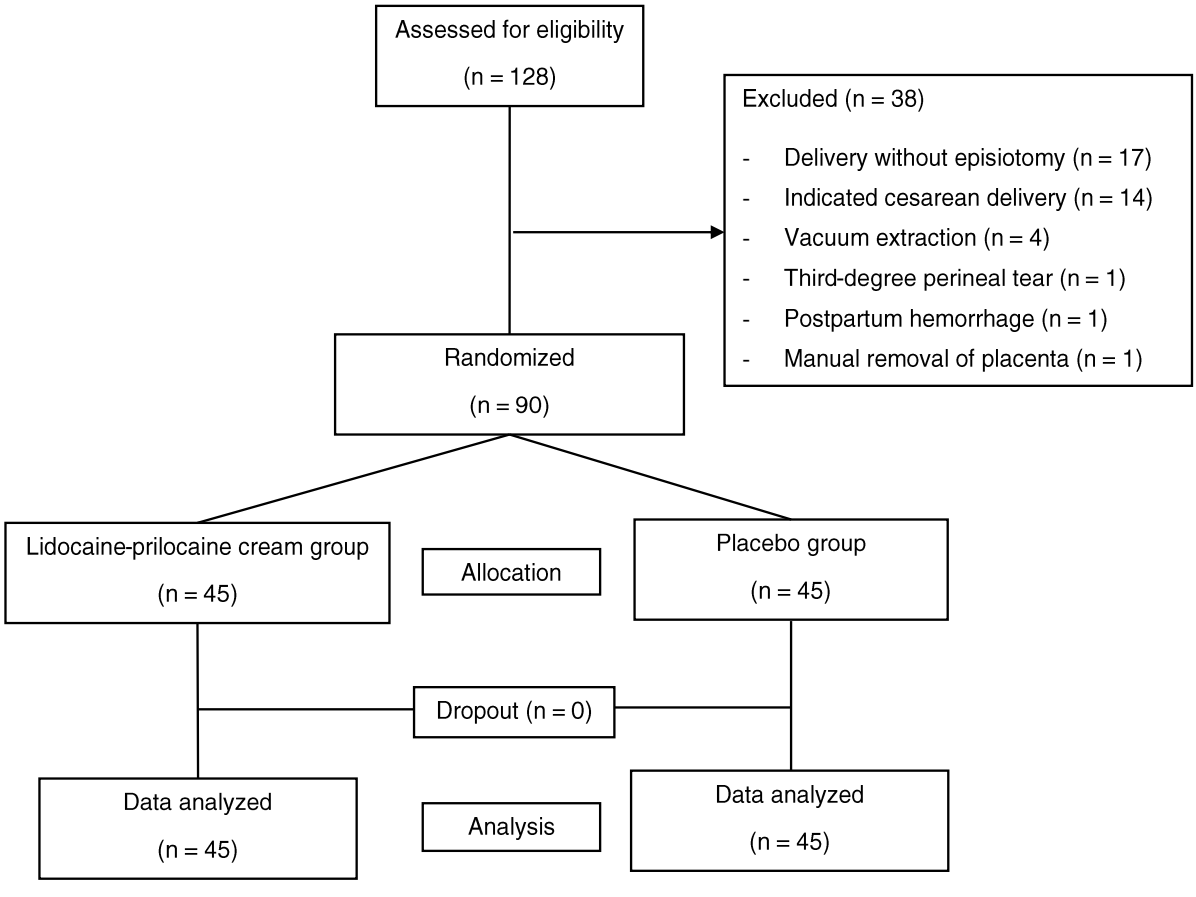

Fig. 1. Consort flow diagram.

Table 1. Baseline characteristics of participants.

Baseline characteristics	Lidocaine-prilocaine cream (n = 45)	Placebo (n = 45)	p value
Maternal age (years), mean ± SD	26.62 ± 5.41	27.13 ± 5.51	0.658[a]
Gestational age (weeks), mean ± SD	38.78 ± 1.13	38.56 ± 0.92	0.308[a]
Body mass index (kg/m²), mean ± SD	26.55 ± 3.81	27.84 ± 4.42	0.144[a]
Parity, n (%)			0.202[b]
Nulliparous	29 (64.4)	22 (48.9)	
Multiparous	16 (35.6)	23 (51.1)	
Duration of second stage of labor (min), mean ± SD	14.82 ± 11.13	15.02 ± 14.11	0.941[a]
Duration of perineal repair (min), mean ± SD	22.24 ± 11.83	21.22 ± 8.13	0.633[a]
Neonatal birth weight (kg), mean ± SD	3.00 ± 0.26	3.10 ± 0.33	0.105[a]
Operators, n (%)			0.962[c]
Staff	5 (11.1)	6 (13.3)	
Resident 3	4 (8.9)	2 (4.4)	
Resident 2	9 (20.0)	10 (22.2)	
Resident 1	21 (46.7)	22 (49.0)	
Nurses	6 (13.3)	5 (11.1)	
Estimated blood loss (ml), median (IQR)	100 (100 - 150)	100 (100 - 130)	0.529[d]
Maternal length of stay (hours), mean ± SD	56.76 ± 9.51	58.13 ± 14.47	0.595[a]

[a] student t-test, [b] chi-square test, [c] Fisher's Exact test, [d] Mann-Whitney U test
SD: standard deviation, IQR: interquartile range

The primary and secondary outcomes are presented in Table 2. The mean pain scores in the lidocaine-prilocaine cream group were significantly lower compared to those of the placebo group during lidocaine injection (2.45 ± 2.49 vs 3.71 ± 2.73; 95% confidence interval (CI) -2.07 to -0.46, p = 0.002), perineal muscle repair (1.95 ± 2.13 vs 3.13 ± 2.34; 95%CI -2.11 to -0.27, p = 0.012) and perineal skin repair (1.87 ± 2.12 vs 3.82 ± 2.86; 95%CI -2.95 to -0.95, p < 0.001). The mean pain scores during vaginal mucosa repair (p = 0.064) and at 1 hour after episiotomy repair (p = 0.176) were not significantly different between groups.

The need for additional anesthesia was not significantly different between groups (13.3% vs 11.1%; p = 0.747). According to the data, 97.8% of patients in the lidocaine-prilocaine cream group were satisfied or completely satisfied with pain control compared to 93.4% of patients in the placebo group. To sum up, the patient satisfaction was not different between groups. Two participants in the lidocaine-prilocaine cream group were diagnosed with episiotomy wound infection, and one participant in the placebo group had episiotomy wound infection and dehiscence. However, perineal wound complications between groups were not significantly different (4.4% vs 2.2%; p = 0.556). No adverse reactions related to lidocaine-prilocaine cream were found.

Table 2. Outcomes.

Outcomes	Lidocaine-prilocaine cream (n = 45)	Placebo (n = 45)	mean difference (95% CI)	p value
Pain scores, mean ± SD				
Lidocaine injection	2.45 ± 2.49	3.71 ± 2.73	-1.26 (-2.07, -0.46)	0.002 [a]
Vaginal mucosa repair	2.26 ± 2.10	3.07 ± 2.51	-0.81 (-1.66, 0.05)	0.064 [a]
Perineal muscle repair	1.95 ± 2.13	3.13 ± 2.34	-1.19 (-2.11, -0.27)	0.012 [a]
Perineal skin repair	1.87 ± 2.12	3.82 ± 2.86	-1.95 (-2.95, -0.95)	< 0.001 [a]
1 hour after perineal repair	1.54 ± 1.68	2.29 ± 1.73	-0.75 (-1.84, 0.34)	0.176 [a]
Need for additional anesthesia, n (%)	6 (13.3)	5 (11.1)		0.747 [b]
Patient satisfaction, n (%)				0.745 [c]
Completely satisfied	25 (55.6)	26 (57.8)		
Satisfied	19 (42.2)	16 (35.6)		
Neutral	1 (2.2)	2 (4.4)		
Dissatisfied	0 (0.0)	1 (2.2)		
Completely dissatisfied	0 (0.0)	0 (0.0)		
Perineal wound complications, n (%)	2 (4.4)	1 (2.2)		0.556 [c]
Infection	2 (4.4)	1 (2.2)		
Dehiscence	0 (0.0)	1 (2.2)		

[a] student t-test, [b] chi-square test, [c] Fisher's Exact test, [d] Mann-Whitney U test
SD: standard deviation, CI: confidence interval

Discussion

The results of the current study found that lidocaine-prilocaine cream in conjunction with lidocaine injection was more effective than placebo for pain relief during episiotomy repair. The pain score during lidocaine injection in the lidocaine-prilocaine cream group was significantly lower when compared to that of the control group (2.45 ± 2.49 vs 3.71 ± 2.73; mean difference (MD) -1.26, 95%CI -2.07 to -0.46, p = 0.002). It could be explained that the lidocaine-prilocaine cream numbed the tissues at the injection site before the lidocaine injection. Additionally, pain scores during perineal muscle repair and perineal skin repair in the lidocaine-prilocaine cream group were significantly lower than those in the control group (1.95 ± 2.13 vs 3.13 ± 2.34; MD -1.19, 95%CI -2.11 to -0.27, p = 0.012 and 1.87 ± 2.12 vs 3.82 ± 2.86; MD -1.95, 95%CI -2.95 to -0.95, p < 0.001, respectively). This might be due to the synergistic effect of anesthesia of the lidocaine-prilocaine cream and lidocaine injection. However, although the pain score was statistically significant between groups, the difference was 1-2 points of the VAS. Therefore, the difference in pain scores might not be clinically significant. The pain score during vaginal mucosa repair in the study group was not different from that of the placebo group (2.26 ± 2.10 vs 3.07 ± 2.51; MD -0.81, 95%CI -1.66 to 0.05, p = 0.064), which might be due to fewer free nerve endings supply at the vaginal mucosa, especially at the posterior wall, resulting in less pain[21].

There has been no previous study about lidocaine-prilocaine cream in conjunction with

lidocaine injection in pain relief during episiotomy repair. Mostly, many studies compared lidocaine-prilocaine cream versus local infiltration anesthesia. Kargar et al conducted a study on primiparous women comparing the efficacy of lidocaine-prilocaine cream applied at the episiotomy area for an hour before estimated delivery time and before repair of episiotomy wounds with conventional lidocaine injection for pain reduction during episiotomy repair. The mean pain score was 4.1 in the lidocaine-prilocaine cream group and 4.3 in the lidocaine infiltration group with 15% and 22% of participants in each group needing further anesthesia[7]. Duhan et al also evaluated the efficacy in pain relief of lidocaine-prilocaine cream compared with lidocaine injection during episiotomy repair in primiparous women. Based on the results, the mean pain score and need for additional anesthesia in both groups were comparable (4.30 vs 4.14 and 26% vs 18%, respectively)[8]. Similarly, Moradi et al assessed the lidocaine-prilocaine cream and lidocaine injection effectiveness during episiotomy repair in primiparous and multiparous women. The mean pain score was 4.06 in the first group and 4.19 in the latter group[9]. Consistently, the authors of these three studies mentioned all concluded that the pain intensity difference between the lidocaine-prilocaine cream group and the lidocaine injection group was insignificant. Furthermore, the need for additional anesthesia was not significantly different between groups. However, according to the study of Abbas et al, the analgesic effect of lidocaine-prilocaine cream was significantly lower than that of the lidocaine infiltration group during the repair of spontaneous perineal tears after vaginal birth (3.86 ± 1.59 vs 5.99 ± 1.47; p = 0.001)[22]. Moreover, the mean pain intensity in the study was higher than that found in the studies of Kargar et al, Moradi et al, and Duhan et al. This might have resulted from different amounts of anesthesia, as in the study on episiotomy repair, patients were given lidocaine infiltration or lidocaine-prilocaine cream application before undergoing episiotomy, and before perineal repair, patients were given another repeated dose of anesthesia.

In our study, the mean pain score during perineal skin repair in the placebo group, in which patients received 1% lidocaine with epinephrine 10 ml before episiotomy and then another 10 ml before episiotomy repair was performed, was 3.82, correlating with the mean pain scores during episiotomy repair of previous studies. The mean pain score during perineal skin repair in the lidocaine-prilocaine cream group was 1.87, significantly lower than that of the placebo group. Moreover, the pain score during lidocaine injection was significantly lower in the study group. Lidocaine-prilocaine cream alone provided maximal duration of analgesia for 45 minutes[15,16]. In conjunction with lidocaine injection, the pain scores at 1 hour after episiotomy repair were not significantly different between groups, as mild intensity pain persisted in both groups. This might be explained by the diminishing effect of lidocaine-prilocaine cream. The need for additional anesthesia in our study was 11.1% in the lidocaine-prilocaine cream group and 13.3% in the control group without statistical significance. Nevertheless, when compared to Kargar et al and Duhan et al, the need for additional anesthesia in the patients who received lidocaine-prilocaine cream in conjunction with lidocaine injection was lower than that found in the use of conventional lidocaine injection alone[7, 8].

In our study, 97.8% of patients in the lidocaine-prilocaine cream group were satisfied or completely satisfied with the pain control compared to 93.4% of patients in the control group. Thus, patient satisfaction was not different between groups. The perineal wound complication was also not significantly different between groups. In addition, even though the combination of lidocaine-prilocaine cream and lidocaine injection increased the dose of lidocaine given to the patients, there were no adverse effects such as allergy, erythema, itching, rash, or systemic reaction found in the study. Therefore, lidocaine-prilocaine cream can be safely used in conjunction with lidocaine injection for pain relief during the repair of second-degree perineal tears after normal vaginal delivery with restrictive episiotomy.

There were several previous research studies that examined the pain control of postpartum perineal pain, using both non-pharmacological and pharmacological methods. Harasai et al investigated the efficacy of single-dose administration of ibuprofen and acetaminophen in comparison with acetaminophen for postpartum perineal pain relief given immediately after episiotomy repair and found that the ibuprofen plus acetaminophen combination was more effective for perineal pain relief than acetaminophen alone at 1 and 2 hours after treatment. The median pain score at 1 hour after perineal repair was 3 vs 4, respectively[23]. Chaichanalap et al evaluated the efficacy of music therapy in alleviating postpartum episiotomy pain. They concluded that the pain score was significantly lower in the music group at 2 hours (24.0 vs 36.5 millimeters, $p < 0.001$) and 6 hours (12.0 vs 22.0 millimeters, $p < 0.001$) after episiotomy repair[24]. Abbas et al compared the analgesic effect of topical lidocaine-prilocaine cream and rectal meloxicam suppository given once immediately after episiotomy repair on postpartum episiotomy pain in primiparous women. The study found no immediate differences in mean pain scores (8.54 ± 1.35 vs 8.33 ± 1.50, $p = 0.419$) nor at 6 hours post-episiotomy (1.24 ± 0.56 vs 1.23 ± 0.55, $p = 0.859$) but lower mean pain scores in the lidocaine-prilocaine cream group were found at 12 hours (1.20 ± 0.50 vs 5.65 ± 1.65, $p < 0.001$) and 5 days post-episiotomy (1.19 ± 0.49 vs 2.64 ± 1.73, $p < 0.001$)[25]. In our study, the mean pain scores at 1 hour after perineal repair in the lidocaine-prilocaine cream group and placebo group were 1.54 and 2.29, respectively. In comparison, it seemed like patients who received lidocaine-prilocaine cream had lower pain scores immediately after perineal repair than those who received other methods of pain relief in those previous studies.

The strengths of the current study were first, it was a double-blind, randomized, placebo-controlled trial. Second, no patients dropped out. Finally, this was the first study that compared lidocaine-prilocaine cream in conjunction with conventional lidocaine injection. The limitations of this study were that we included only patients who have undergone episiotomy with second-degree perineal tears and in the current study, the cost-effectiveness of conjunctional lidocaine-prilocaine cream was not analyzed. Further research should focus on patients who tend to have more pain intensity, such as postpartum women with operative delivery, third- or fourth-degree perineal tears, or spontaneous perineal tears because they would not be given anesthesia at perineum before delivery as in the case of those with episiotomy. This would allow more benefits from the use of conjunctional lidocaine-prilocaine cream to be revealed. Moreover, research on the effectiveness of lidocaine-prilocaine cream compared with other oral analgesics such as non-steroidal anti-inflammatory drugs should be considered in the future.

Conclusion

Lidocaine-prilocaine cream in conjunction with lidocaine injection more effectively reduced pain during lidocaine injection, perineal muscle repair, and perineal skin repair than placebo without adverse reaction.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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Prevalence and Associated Factors of Sexually Transmitted Infection among Female Sexual Assault Victims attending the Police General Hospital

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ABSTRACT

Objectives: To assess the prevalence of sexually transmitted infections (STIs) and identify factors associated with STIs among female sexual assault victims.

Materials and Methods: A retrospective analysis of medical records for sexual assault victims at the Police General Hospital was conducted over the period from January 2018 to December 2022.

Results: Among 1,006 female victims, 12.33% tested positive for at least one STI, with Chlamydia trachomatis (6.66%) and Neisseria gonorrhoeae (2.88%) being the most common. Notably, chlamydia positivity dramatically increased in 2022, while other infections, including syphilis, hepatitis B & C, human immunodeficiency virus have shown minor variations over the years. The 10–19 age group, the largest demographic, had the highest STI prevalence (14.54%). Multivariate analysis identified pyuria as a strong independent predictor of STIs (adjusted odds ratio 4.85, $p < 0.001$)

Conclusion: STIs are prevalent among younger female victims, with Chlamydia trachomatis being the most common. Pyuria were strongly associated with STI risk, with routine urinalysis serving as a valuable diagnostic clue.

Keywords: sexual assault victims, sexually transmitted infections, associated factors.

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ความชุกและปัจจัยเสี่ยงที่เกี่ยวข้องกับโรคติดต่อทางเพศสัมพันธ์ในหญิงผู้ถูกล่วงละเมิดทางเพศที่มารับบริการที่โรงพยาบาลตำรวจ

ปาริชาติ นามเพ็ง, สุธรรม สุธาพร

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาแนวโน้มความชุกของโรคติดต่อทางเพศสัมพันธ์และปัจจัยเสี่ยงที่เกี่ยวข้องกับโรคติดต่อทางเพศสัมพันธ์ในหญิงผู้ถูกล่วงละเมิดทางเพศที่เข้ารับบริการที่โรงพยาบาลตำรวจ*

วัสดุและวิธีการ: *การศึกษาย้อนหลังโดยเก็บข้อมูลจากเวชระเบียนหญิงผู้ถูกล่วงละเมิดทางเพศที่เข้ารับบริการที่โรงพยาบาลตำรวจ ระหว่างวันที่ 1 มกราคม พ.ศ. 2561 ถึงวันที่ 31 ธันวาคม 2565*

ผลการศึกษา: *หญิงผู้ถูกล่วงละเมิดทางเพศจำนวน 1,006 ราย พบว่าร้อยละ 12.33 มีการติดเชื้อโรคติดต่อทางเพศสัมพันธ์อย่างน้อยหนึ่งชนิด โดยโรคหนองในเทียม พบได้มากที่สุดที่ร้อยละ 6.66 รองลงมาคือโรคหนองใน ร้อยละ 2.88 ทั้งนี้ในปี พ.ศ. 2565 มีอัตราการติดเชื้อโรคหนองในเทียมเพิ่มขึ้นเป็นอย่างมาก ขณะที่โรคติดต่อทางเพศสัมพันธ์ชนิดอื่นๆ เช่น ซิฟิลิส ไวรัสตับอักเสบบี ไวรัสตับอักเสบซี และเอชไอวี มีการเปลี่ยนแปลงเพียงเล็กน้อยเมื่อเปรียบเทียบในช่วงระยะเวลาการศึกษา หญิงผู้ถูกล่วงละเมิดทางเพศส่วนใหญ่ช่วงอายุระหว่าง 10-19 ปี มีอัตราการติดเชื้อโรคติดต่อทางเพศสัมพันธ์มากที่สุด (ร้อยละ 14.54) การวิเคราะห์ถดถอยโลจิสติคเชิงพหุพบว่าการตรวจพบเม็ดเลือดขาวในปัสสาวะ เป็นปัจจัยที่มีความสัมพันธ์อย่างมีนัยสำคัญกับการติดเชื้อโรคติดต่อทางเพศสัมพันธ์ (adjusted odds ratio 4.85, $p < 0.001$)*

สรุป: *โรคติดต่อทางเพศสัมพันธ์พบได้บ่อยในหญิงผู้ถูกล่วงละเมิดทางเพศ โดยเฉพาะในกลุ่มอายุน้อย โดยเชื้อโรคหนองในเทียม เป็นเชื้อที่พบมากที่สุด การตรวจพบเม็ดเลือดขาวในปัสสาวะเป็นปัจจัยสำคัญที่สัมพันธ์กับการติดเชื้อโรคติดต่อทางเพศสัมพันธ์ ซึ่งการตรวจปัสสาวะเป็นเครื่องช่วยชี้วัดสำคัญในการวินิจฉัยโรคติดต่อทางเพศสัมพันธ์*

คำสำคัญ: *ผู้ถูกล่วงละเมิดทางเพศ, โรคติดต่อทางเพศสัมพันธ์, ปัจจัยสัมพันธ์*

Introduction

Sexual assault are critical global public health issues that disproportionately affect women, leading to profound physical and psychological harm. Globally, almost 1 in 3 women have experienced sexual assault at some point in their lives[1]. In the U.S., 43.6% of women experienced sexual violence in their life, which was almost double compared to men (24.8%)[2]. These abusive acts frequently result in an elevated risk of sexually transmitted infections (STIs) due to their often coercive and unprotected nature. According to the World Health Organization (WHO), in 2021, the prevalence of women experiencing physical and sexual violence between 2000 and 2018 was particularly high in regions such as the Pacific Islands (37%), South Asia (35%), and South-Eastern Asia (21%)[1]. The 1,465 cases of sexual assault reported by the Royal Thai Police in Thailand between October 2020 and August 2021 display alarming prevalence of sexual assault, rooted in entrenched sociocultural and systemic challenges. This statistic highlights the urgent need for coordinated interventions to prevent sexual assault and mitigate its health consequences, particularly the heightened risk of STIs among survivors[3]. Additionally, STI incidence continues to rise globally, with over 1 million new infections occurring daily, primarily through unprotected sexual contact[4]. In Thailand, incidence of major STIs, including syphilis, gonorrhea, chlamydia, chancroid, and lymphogranuloma venereum, was at 29.2 per 100,000 people in 2021, with syphilis being the most prevalent[5]. Given the strong association between sexual violence and STI transmission, this study aimed to assess the prevalence of STIs, including human immunodeficiency virus (HIV), gonorrhea, chlamydia, syphilis, hepatitis B, and hepatitis C, among sexual assault victims attending the Police General Hospital over the past five years. Furthermore, this study aimed to examine the prevalence of STIs and the factors associated with STIs among female sexual assault victims, offering critical insights to enhance prevention and treatment strategies.

Sexual assault generally refers to non-consensual or coerced actions such as vaginal or anal penetration by an object, finger, or penis, oral sex, fondling of the breasts or genital area, or forced contact with another individual's genitalia. This also encompasses situations where the victim is unable to provide consent due to intoxication, cognitive impairment, misperception because of age, or other forms of incapacitation[6, 7].

Materials and Methods

A retrospective review of medical records of female sexual assault victims who sought consultation at the Police General Hospital between January 2018 and December 2022 was conducted, with cases selected based on specific inclusion criteria. Sexual assault was defined as non-consensual sexual intercourse. At the Police General Hospital, all cases of suspected sexual assault are managed using a standardized protocol. This protocol includes a comprehensive clinical evaluation, consisting of a detailed history of the incident, physical examination, and forensic assessment. Evidence collection is performed using a sexual assault forensic examination kit, which includes swabs for biological samples, documentation of injuries, and other relevant forensic materials. This multidisciplinary approach ensures systematic documentation of both medical and forensic evidence to support diagnosis and subsequent management. The study was approved by the Ethics Committee of the Police General Hospital. Data were anonymized to ensure participant confidentiality, and all findings were meticulously documented in adherence to ethical standards.

Female sexual assault victims assessed using the standardized clinical and forensic protocols of the Police General Hospital for incidents reported between January 1, 2018, and December 31, 2022, were included in the study. Exclusion criteria were 1. Female victims of statutory rape, 2. Female sexual assault victims who denied sexual intercourse with vaginal penetration, 3. Female sexual assault victims with incomplete medical records, 4. Deceased female sexual assault victims, 5. Female sexual assault victims who refused medical evaluation, 6. Female sexual assault victims with a pre-existing history of HIV, hepatitis B, or hepatitis C infection.

Laboratory testing was conducted at the Police General Hospital's certified diagnostic laboratory, adhering to strict quality control measures and standardized protocols. Blood tests for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (anti-HCV) were performed using chemiluminescent microparticle immunoassays (CMIA), both demonstrating 100% sensitivity and specificity exceeding 99% (Abbott Diagnostics Division, Ireland;[8] Abbott Diagnostics GmbH, Germany[9]). HIV was diagnosed using a rapid immunochromatographic assay for HIV-1/2 antibodies and p24 antigen, with 100% sensitivity and specificity of 99.96% and 99.76%, respectively (Abbott Diagnostics Medical Co., Ltd., Japan)[10]. Syphilis was identified using the venereal disease research laboratory test (Biorex Diagnostics Limited, United Kingdom)[11]. Pyuria was assessed through urinalysis and defined as ≥ 10 white blood cells/ high power field on microscopy. Vaginal swabs for Neisseria gonorrhoeae were analyzed using Gram staining to detect gram-negative diplococci, with culture for confirmation. Chlamydia trachomatis was diagnosed using the Chlamydia Rapid Test Cassette (CITEST Diagnostics Inc., Vancouver, Canada), with 96.6% accuracy, 93.3% sensitivity, and 97.5% specificity[12]. All test results were interpreted by licensed medical technologists and reviewed by experienced clinical microbiologists, ensuring high diagnostic accuracy and reliability.

Statistical analysis

Baseline characteristics were summarized as mean (standard deviation) for continuous variables and frequency (%) for categorical variables. Associations between sexually transmitted diseases and categorical variables among female sexual assault victims were assessed using the chi square test, and significant risk factors were identified through univariate and multivariate logistic regression using the forward stepwise method. All analyses were conducted using STATA software, version 16.0 (StataCorp, College Station, TX, USA), with statistical significance defined as $p < 0.05$.

Results

A total of 2,420 female sexual assault victims were initially included in the study. Following the exclusion of 1,414 cases of statutory rape, 161 without evidence of vaginal penetration, 334 with incomplete records, 98 who declined evaluation, and 13 with pre-existing STIs, the final analysis comprised 1,006 victims. Most female sexual assault victims (89.97%) involved a single assailant. Repeated assault occurred in 33.20% of cases. In 62.03% of the cases, the assailants ejaculated, while in 7.46% of cases, they did not; in 30.52% of cases, this information was unclear. Oral copulation of the victim's genitals was less common, occurring in 7.75% of cases. Only 6.26% of sexual assault victims involved anal penetration (Tables 1, 2).

Table 1. Basic information of female sexual assault victims (n = 1,006).

Characteristics	n	%
Age (year) of the victim	1,006	100%
≤ 9	72	7.16%
10-19	509	50.60%
20-29	261	25.94%
30-39	101	10.04%
40-49	42	4.17%
≥ 50	21	2.09%
Current/Highest Education	1,006	100%
No education/Less than primary school level	56	5.57%
Primary school	210	20.87%
High school	533	52.98%
Bachelor's degree	185	18.39%
Postgraduate level	17	1.69%
Unclear	5	0.50%
Occupations	1,006	100%
Unemployed	141	14.02%
Student	467	46.42%
General employee	167	16.60%
Government official	16	1.59%
Company employee	125	12.43%
Sex worker	39	3.88%
Private business	51	5.07%
Marital status	934	100%
Single	862	92.29%
Married	45	4.82%
Widow	27	2.89%
History of sexual Intercourse	1,006	100%
No	419	41.65%
Yes	569	56.56%
Unclear	18	1.79%
Pior Sexual Intercourse	569	100%
< 1 month	298	52.37%
1 - 3 months	73	12.83%
> 3 months	198	34.80%
Time to Medical Attention (days)	1,006	100%
< 3 days	505	50.20%
3 - 7 days	144	14.31%
> 7 days	357	35.49%

Table 2. Characteristics of female aexual assault victims (n = 1,006).

Characteristics	n	%
Number of Assailants	1,006	100%
1	911	90.56%
> 2	89	8.85%
Unclear	6	0.60%
Ejaculation	1,006	100%
No	75	7.46%
Yes	624	62.03%
Unclear	307	30.52%
Repeated Assault		
No	652	64.81%
es	334	33.20%
Unclear	20	1.99%
Oral copulation of victim's genitals	1,006	100%
No	869	86.38%
Yes	78	7.75%
Unclear	58	5.77%
Tried	1	0.10%
Anal penetration	1,006	100%
No	894	88.87%
Yes	63	6.26%
Unclear	48	4.77%
Tried	1	0.10%
Penetration of Vagina by finger	1,006	100%
No	823	81.81%
Yes	115	11.43%
Unclear	63	6.26%
Tried	5	0.50%
Vaginal douching after the incident by victim	1,006	100%
No	692	68.79%
Yes	299	29.72%
Unclear	15	1.49%
Condom use of assailant	1,006	100%
No	731	72.66%
Yes	125	12.23%
Unclear	150	14.91%

Among the 1,006 female sexual assault victims, 12.33% tested positive for at least one STI. Chlamydia trachomatis was the most prevalent (6.66%), followed by Neisseria gonorrhoeae (2.88%), syphilis (1.89%), hepatitis B (1.09%), HIV (0.99%), and hepatitis C (0.40%). Although STI prevalence fluctuated from 2018 to 2022, these changes were not statistically significant ($p > 0.05$). Overall, chlamydia positivity dramatically increased in 2022, while other infections, including syphilis, hepatitis B, HIV, and hepatitis C, showed minor variations over the years (Fig. 1).

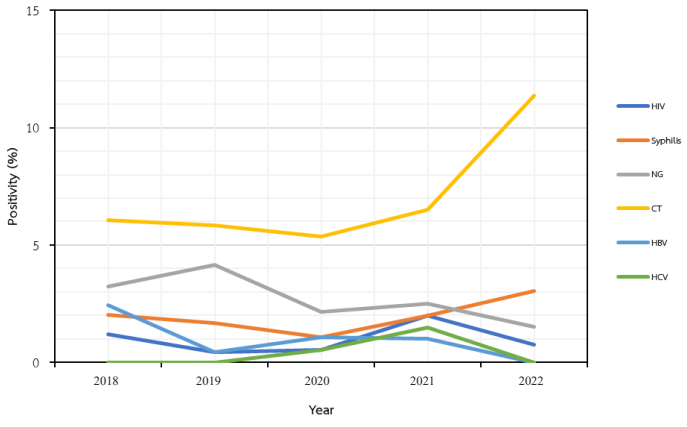

Fig. 1. Annual positivity rate of sexually transmitted infections in female sexual assault victims.

STI prevalence varied across age groups. Among the less than 9 years old age group, 2.78% tested positive for STIs, with Neisseria gonorrhoeae (1.39%) being the most common; no cases of HIV or syphilis were recorded. The 10–19 age group, the largest demographic, had the highest STI prevalence (14.54%), with Chlamydia trachomatis (8.45%) and Neisseria gonorrhoeae (4.52%) being the most frequent infections. In the 20–29 age group, 13.03% tested positive for STIs, with higher rates of HIV (1.92%) and syphilis (2.68%) compared to younger groups. The prevalence of STIs generally decreased with age, except in those aged 50 years and above, where the prevalence was 14.29%, with hepatitis B (9.52%) being the most common. No cases of Chlamydia trachomatis or HIV were found in this group, but syphilis (4.76%) and Neisseria gonorrhoeae (4.76%) were present (Fig. 2).

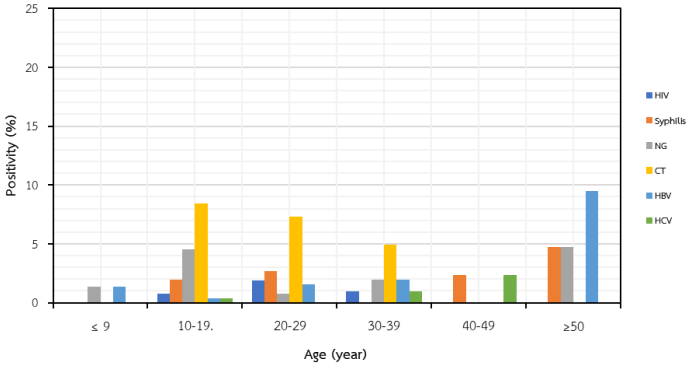

Fig. 2. Prevalence of sexually transmitted infections in female sexual assault victims by age.

Multivariate analysis identified pyuria as a strong predictor of sexually transmitted infections (STIs) (adjusted odds ratio 4.85, 95% confidence interval: 2.92–8.07, $p < 0.001$). In contrast, associations observed in univariate analysis, such as prior sexual intercourse and repeated sexual assault, were attenuated after adjustment. Other factors, including age, substance use, alcohol consumption, and sexual behaviors, were not significantly associated with STI risk (Table 3).

Table 3. Factors correlated with clinically Important sexually transmitted infections by multivariate logistic regression analysis (n = 1,006).

Factors	Univariate regression			Multivariate regression		
	OR	95%CI	p value	aOR	95%CI	p value
Age (ref.: ≥ 40)						
≤ 19	1.75	0.68-4.49	0.248			
20-39	1.56	0.59-4.11	0.365			
Substance abused (ref.: no)	0.94	0.33-2.71	0.907			
Alcohol consumption (ref.: no)	1.12	0.69-1.81	0.659			
Ejaculation (ref.: no)	2.15	0.84-5.48	0.110			
Pyuria (ref.: negative)	4.85	2.92-8.07	< 0.001*	4.74	2.84-7.91	< 0.001*
Prior sexual intercourse (ref.: no)	1.53	1.03-2.28	0.037*	1.37	0.90-2.09	0.138
Time to medical attention (ref.: < 7 day)	1.04	0.70-1.54	0.842			
Number of assailants (ref.: < 2)	1.36	0.74-2.49	0.320			
Condom use of assailant (ref.: yes)	0.62	0.32-1.20	0.157			
Repeated assault (ref.: no)	0.62	0.40-0.96	0.031*	0.69	0.44-1.09	0.110
Oral copulation of victim's genitals (ref.: no)	0.76	0.36-1.63	0.488			
Anal penetration (ref.: no)	0.72	0.30-1.71	0.456			
Penetration of vagina by finger (ref.: no)	0.87	0.47-1.61	0.660			
Vaginal douching after the incident (ref.: yes)	1.23	0.83-1.84	0.305			

* p value <0.05

OR: odds ratio, CI: confidence interval, aOR: adjusted odds ratio.

Discussion

Sexual assault is a critical public health issue that disproportionately affects women and significantly increases their risk of STIs. This study highlighted the vulnerability of younger females to sexual assault, with over half (50.60%) of the 1,006 female victims aged 10–19 years. The majority of them were students (46.42%). Repeated assault (33.20%) and lack of condom use (72.66%) were common, potentially leading to STIs. Chlamydia trachomatis (6.66%) and Neisseria gonorrhoeae (2.88%) were the most prevalent infections. The notable rise in Chlamydia positivity in 2022 was consistent with national data from the United Kingdom, which reported a 22.2% increase in Chlamydia diagnoses from 2021 to 2022[13]. According to Thailand's Department of Disease Control, there was an increase in STI incidence from 2.7 per 100,000 in 2021 to 5.1 per 100,000 in 2023. This trend may be attributed to inconsistent condom use. Behavioral surveillance data indicates that only 40.4% of male vocational students consistently utilized condoms with romantic partners. Although the usage rate was slightly higher with sex workers and casual partners, it remains insufficient and reflects a significant gap in preventive practices[14]. These findings illustrate the urgent need to address systemic barriers to sexual health education and expand access to preventive services. Moreover, the increased prevalence of STIs emphasizes the critical importance of early detection and effective treatment to prevent severe health complications, including pelvic inflammatory disease and infertility.

The overall prevalence of STIs in this study was 12.33%, indicating a substantial burden of infection within the examined population. These findings aligned with data from the Netherlands (11.2%), where Chlamydia trachomatis and Neisseria gonorrhoeae were tested using the gold standard polymerase chain

reaction (PCR). Although different laboratory tests, including Chlamydia rapid test for Chlamydia trachomatis and Gram staining/culture for Neisseria gonorrhoeae, were used in this study, the prevalence rates were similar[15]. In contrast, South Korea reported a significantly higher overall STI prevalence of 60.2%, largely attributed to integrated care models and aggressive screening techniques, particularly those using PCR for Chlamydia trachomatis, Neisseria gonorrhoeae, Mycoplasma genitalium, Mycoplasma hominis, Ureaplasma urealyticum, Trichomonas vaginalis, and cytomegalovirus[16]. Chlamydia trachomatis (6.66%) and Neisseria gonorrhoeae (2.88%) were the most common STIs in this study. These findings were comparable to data from France, where the prevalence of Chlamydia trachomatis and Neisseria gonorrhoeae were 8.2% and 2.3%, respectively[17]. In South Korea, Ureaplasma urealyticum was the most detected STI, while Chlamydia trachomatis ranked third at 17.4%, and Neisseria gonorrhoeae had a prevalence of 2.8%[16]. This disparity could be caused by regional differences and testing methods; thus, standardized testing methods are important to improve detection rates. The presence of pyuria as a significant predictor of STI risk, with an adjusted odds ratio (aOR) of 4.85 (95% CI: 2.92–8.07, $p < 0.001$), was consistent with studies from South Korea[16,18]. Pyuria is a non-invasive and early indicator; its routine use in post-assault care could suggest the presence of STIs, leading to earlier detection and serving as a valuable diagnostic clue.

Adolescents were the most vulnerable group in this study, with an STI prevalence of 14.54% among those aged 10–19 years. This finding was consistent with other national data, such as in South Korea (48.19%–68% of STIs at the age of 15–19 years[16,18] and Brazil (32.6% of STIs at the age of 10–19 years[19]. However, in Thailand, Suthaporn et al (2014) reported a 25.6% risk of STIs among victims aged 18–39, which was higher than the 20.9% risk observed among those aged 13–17. The higher prevalence of STIs in the 18–39 age group may be attributed to the broader age range[20]. The 20–29 age group exhibited a notable STI prevalence of 13.03% in this study. This finding was consistent with data from the United Kingdom (2021), which reported a 26.5% increase in STI diagnoses among individuals aged 20–24. Although condom use was not found to be a significant clinical factor in this study, its absence remains a plausible risk factor, particularly given the rising trend in condomless sexual activity, which is widely associated with an increased risk of STIs[13]. The age group 50 years and above, though smaller, showed high prevalence (14.29%), likely due to age-related physiological changes, such as reduced mucosal integrity, and barriers to healthcare access. Targeted interventions for adolescents should include early medical intervention and sexual harassment prevention training to empower them to recognize inappropriate behaviors, identify early warning signs, and report incidents confidently. Strengthening online safety measures and fostering open communication with trusted adults are essential strategies to mitigate risks and improve health outcomes. For older adults, interventions should focus on addressing their unique vulnerabilities by enhancing access to care through mobile clinics, telemedicine, and provider awareness campaigns.

Timely access to medical care is critical for forensic evidence collection, prevention of STIs, and pregnancy. Only 50.20% of victims in this study received treatment within the 72-hour window. These findings were comparable to those of Suthaporn et al (2014)[20], where only 49.4% of individuals aged 13–17 years sought medical consultation within 72 hours, compared to 76.8% of those aged 18–39 years. Delayed medical care reduces the effectiveness of post-exposure prophylaxis for STIs and emergency contraception. In Thailand, barriers to timely care may result from sociocultural factors, stigma, and inadequate support systems. By comparison, South

Korea has reported a substantially higher rate of early intervention, with 77.2% of individuals seeking care within the first 24 hours[16]. Efficient healthcare system, strong legal support, and public awareness campaigns are considered key factors contributing to timely post-sexual assault consultations in South Korea.

This study's strengths included data collection from the Police General Hospital, a primary referral center for sexual assault victims in Thailand, which provided a large and diverse five-year dataset. The substantial sample size enhanced the reliability of the findings and supports their applicability to similar urban contexts.

However, the retrospective design may have resulted in incomplete data. The absence of baseline pyuria data limits the ability to determine whether observed pyuria was pre-existing or assault-related, potentially confounding its association with STIs. The Chlamydia rapid test, while practical, may have underestimated Chlamydia trachomatis prevalence compared to PCR testing[12, 21]. Additionally, the use of vaginal swabs for detecting Neisseria gonorrhoeae via Gram staining, rather than endocervical swabs, may have reduced sensitivity and led to underestimation of prevalence, despite confirmatory culture. Infections with long latency periods, such as hepatitis B, hepatitis C, and HIV, may have been underreported due to the lack of follow-up testing. Findings from a single urban hospital may also not generalize to rural or more diverse populations. Future research should employ prospective designs, utilize gold-standard diagnostics, and include broader sampling to enhance accuracy and generalizability.

The Centers for Disease Control and Prevention (CDC) emphasize the critical need for early medical intervention and comprehensive care for sexual assault victims. CDC guidelines recommend empiric treatment for common STIs, along with hepatitis B and human papilloma virus vaccinations[22, 23]. In Thailand, although these international guidelines are widely applied, providing practical care remains challenging, particularly in rural areas with limited resources. Adapting international clinical guidelines to local protocols is essential for effective care. A holistic approach should encompass not only medical treatment but also psychological, social, and preventive care. Immediate STI screening, vaccination, and follow-up care are necessary to monitor the health of victims. Psychosocial support is required to address the emotional trauma following sexual assault. Expanding educational outreach should be endorsed to raise awareness about STI prevention. Promoting early intervention is also necessary. The high rate of repeated assault observed in this study (33.20%) emphasizes the urgent need for safe and supportive spaces to protect victims from further harm. These spaces, whether situated within communities, hospitals, or specialized care facilities should be staffed by professionals trained in victim-centered care to prioritize safety, foster recovery, and empower survivors. Additionally, implementing a comprehensive, multidisciplinary care framework that integrates medical treatment, legal advocacy, and social support is essential to address the multifaceted and intersecting needs of sexual assault survivors effectively.

Conclusion

Sexually transmitted infections were notably prevalent among female sexual assault victims, particularly those aged 10–19 years, with Chlamydia trachomatis and Neisseria gonorrhoeae being the most commonly identified infections. Pyuria was significant risk factors for STIs. Delays in accessing healthcare, reported in nearly half of cases, highlight critical shortcomings in post-assault medical services. These findings emphasized the urgent need for targeted prevention strategies, timely medical interventions, and standardized care protocols to improve health outcomes in this vulnerable population.

Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

The Effectiveness of Cryotherapy in Reducing Postoperative Pain in Cesarean Delivery, Pfannenstiel Skin Incision: A randomized controlled trial

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ABSTRACT

Objectives: To evaluate the effectiveness of cold pack gel in reducing postoperative pain after cesarean delivery, Pfannenstiel skin incision.

Materials and Methods: This study was a randomized controlled trial. There were 48 post-cesarean patients who were divided into two groups; group 1 (n = 24) received cold pack gel and group 2 (n = 24) received no treatment. The standard postoperative analgesic medicine and care were used in both groups. The primary outcome was to compare the postoperative pain score using the numerical rating scale (NRS) at 6, 12 and 24 hours after operation. The secondary outcomes were to compare the amount of opioid used, length of hospital stay and side effects in both groups.

Results: The cold pack gel significantly decreased the amount of postoperative opioid consumption (mean opioid used 8.33 ± 19.03 mg vs 25.00 ± 32.97 mg, mean difference was 16.67 mg (95% confidence interval 8.56-24.76). However, the cold pack gel insignificantly decreased pain after cesarean delivery which mean NRS of intervention and control group at 6 hours, 12 hours, 24 hours postoperation were 3.96 ± 1.71 vs 4.92 ± 2.06, 2.62 ± 1.47 vs 3.29 ± 1.46 and 2.17 ± 1.24 vs 2.67 ± 1.66, respectively. There was no significant side effect from cold pack gel use.

Conclusion: The cold pack gel could reduce postoperative opioid use without any serious side effects. However, the postoperative pain scores were not decreased. It can be used as an additional multimodality care in post-cesarean delivery care.

Keywords: postoperative, cryotherapy, cold pack gel, cesarean delivery.

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ประสิทธิผลของการบำบัดด้วยความเย็นเพื่อลดความปวดหลังการผ่าตัดคลอดทางหน้าท้องชนิดแผลผ่าตัดแบบ Pfannenstiel: การทดลองแบบสุ่ม

ภูริณัฐ ใจธรรม, โชคชัย โชติบูรณ์, เมธา ทรงธรรมวัฒน์, เอื้อมพร สุ่มมาตย์, เมธา ทรงธรรมวัฒน์

บทคัดย่อ

วัตถุประสงค์*: เพื่อประเมินประสิทธิผลของเจลเย็น (cold pack gel) ในการลดความเจ็บปวดหลังผ่าตัดคลอดแบบแผลผ่าตัด Pfannenstiel*

วัสดุและวิธีการ*: การศึกษานี้เป็นการศึกษาทดลองแบบสุ่ม ในผู้ป่วยหลังผ่าตัดคลอด 48 คน แบ่งเป็นสองกลุ่ม โดยกลุ่มที่ 1 (n = 24) ได้รับเจลเย็น และกลุ่มที่ 2 ไม่ได้รับเจลเย็น โดยได้รับการดูแลรักษาหลังผ่าตัดและยาแก้ปวดตามมาตรฐานเหมือนกันทั้งสองกลุ่ม วัตถุประสงค์หลักของการศึกษาเพื่อเปรียบเทียบค่าคะแนนความเจ็บปวด (Numerical rating scale) หลังผ่าตัดที่ 6, 12 และ 24 ชั่วโมงหลังผ่าตัด และวัตถุประสงค์รองเพื่อเปรียบเทียบ จำนวนการใช้ยาแก้ปวดชนิด Opioid ที่ใช้หลังผ่าตัด ระยะเวลาการนอนโรงพยาบาล และ ผลข้างเคียงของการใช้เจลเย็นระหว่างกลุ่ม*

ผลการศึกษา*: การใช้เจลเย็นหลังผ่าตัดคลอดสามารถลดการใช้ยา Opioid อย่างมีนัยสำคัญทางสถิติ (ค่าเฉลี่ยการใช้ยา 8.33 ± 19.03 มก. vs 25.00 ± 32.97 มก., ผลต่างค่าเฉลี่ย 16.67 มก. (95% confidence interval 8.56-24.76) โดยการใช้เจลเย็นมีผลลดความเจ็บปวดหลังผ่าตัดคลอดแต่ไม่มีนัยสำคัญทางสถิติ ที่ 6, 12, 24 ชั่วโมง 3.96 ± 1.71 ต่อ 4.92 ± 2.06, 2.62 ± 1.47 ต่อ 3.29 ± 1.46 และ 2.17 ± 1.24 ต่อ 2.67 ± 1.66 ตามลำดับ ไม่พบผลข้างเคียงร้ายแรงที่เกิดจากการใช้เจลเย็นประคบ*

สรุป*: การใช้เจลเย็นประคบมีประสิทธิผลในการลดการใช้ยา opioid หลังผ่าตัดคลอดและไม่มีผลข้างเคียงที่ร้ายแรง อย่างไรก็ตามไม่พบการลดลงของค่าคะแนนความปวดหลังผ่าตัด เจลเย็นสามารถเป็นการรักษาอีกทางเลือกเพิ่มเติมในการลดความเจ็บปวดแบบหลากหลายวิธีหลังการผ่าตัดคลอด*

คำสำคัญ*: ความเจ็บปวดหลังผ่าตัด, การบำบัดด้วยความเย็น, เจลเย็น, ผ่าตัดคลอด*

Introduction

Cesarean delivery is a one of the most common operations around the world and postoperative pain is an area of great concern to the patients[1]. A previous study in our center reported that 57.0% of the post-cesarean patients had moderate to severe pain with the pain score > 4 within 24 hours after the operation despite the use of intravenous opioid drugs[2]. Multimodal postoperative care was recommended to decrease pain after the procedure to facilitate the patient's wellbeing as well as to promote the important movement such as early breast feeding[3].

There are various pharmacological and non-pharmacological methods employed to decrease postoperative pain. Cryotherapy by cold pack gel is one of the effective methods used in gynecologic surgery and obstetrics procedure from the previous reports[4-6]. The mechanism of action is anti-inflammation by decreasing proinflammatory cytokine (Interleukin (IL) -1, tumor necrosis factor-α, IL-6, IL-12 and IL-17), reduced nerve conduction velocity and decreased oxidative stress[7, 8]. However, it has not been studied in the Pfannenstiel incision cesarean delivery which is a common operation in daily clinical practice. Therefore, this study aimed to study the effectiveness of the additional cryotherapy (cold pack gel) as one of the multimodalities

Materials and Methods

The present study was a randomized controlled trial which was conducted in the Department of Obstetrics and Gynecology, UdonThani Hospital, Udonthani, Thailand, from April to September 2024. The study protocol was approved by the Udonthani Hospital Ethical Committee in Human subject Research: No.74/2567 and was registered in thaiclinicaltrials.org (clinical trial number: TCTR20240812001).

There were 48 pregnant women included in this study, the inclusion criteria were term singleton pregnant women aged 18 years old or older who underwent cesarean section with Pfannenstiel skin incision. The exclusion criteria were those patients who had serious underlying diseases such as severe renal disease, valvular heart disease, having allergy to cold or cold pack gel or those who needed intensive care unit admission or ventilator use after surgery.

The study details were explained to all participants during their labor room admission and their written informed consents were received before participation. The randomization was performed using computer-generated numbers, prepared in sealed, opaque envelopes by the research assistants. The eligible patients were assigned into one of two groups, the first group was the cold pack gel group (n = 24), the second group was the no treatment group (n = 24). The cesarean delivery was done by both obstetricians and residents. The intraoperative anesthesia was conducted by anesthesiologist using both spinal and general anesthesia. The standard postoperative analgesics care, using intravenous opioid and paracetamol as the patient's requested every six hours, were used in both groups, In the cold pack gel group, the cold pack gel was a 3M company cold pack gel size 10x25 cm, and was frozen at zero degree Celsius in the freezer for two hours, covered by a 3M bag (in the box set), then placed on top of the Pfannenstiel incision cesarean wound dressing for two hours, after two hours postoperation[4].

Numerical rating scale (NRS)[9] with a score of 0-10 was used to evaluate postoperative pain after the cesarean section at 6, 12 and 24 hours. 0 reflected no pain and 10 reflected maximum pain. The postpartum ward nurses explained the meaning of the score to the patients, then asked them to verbally reflect their pain using that numerical scale. The pain score of less than 4 was classified as mild intensity pain, NRS score of 4 or more was moderate to severe pain[10]. The side effects of cold pack gel were evaluated by nurses at 24 hours after operation. The amount of opioid consumption and length of hospital stay were also recorded.

Sample size was calculated using the N4studies

application. Using the formula for comparing continuous outcomes in randomized controlled trial. The mean pain score postoperative pain at 6 hours of the treatment and control groups for calculation were 3.2 ± 2.4 and 5.3 ± 2.2[11], respectively. Power 80% with alpha error 0.05 were used, dropout rate was estimated to be 10%. The calculated sample size was 24 for each group[12-14].

Statistical analysis

STATA statistical program version 13 was used for analysis. Continuous data were reported as mean and standard deviation. Categorical data were shown as the number and percentage. Unpaired t-test was used for the comparison of continuous data, mean difference and 95% confidence interval (CI) and binary regression with relative risk and 95%CI, Pearson chi square and Fisher's exact test were used for categorical data. P value < 0.05 was considered statistically significant.

Results

Forty-eight pregnant women were assessed for eligibility, and all were accepted to participate with this study without anyone excluded. The randomization was done and all participants continued their participation without any dropout. The consort diagram is shown in Fig. 1.

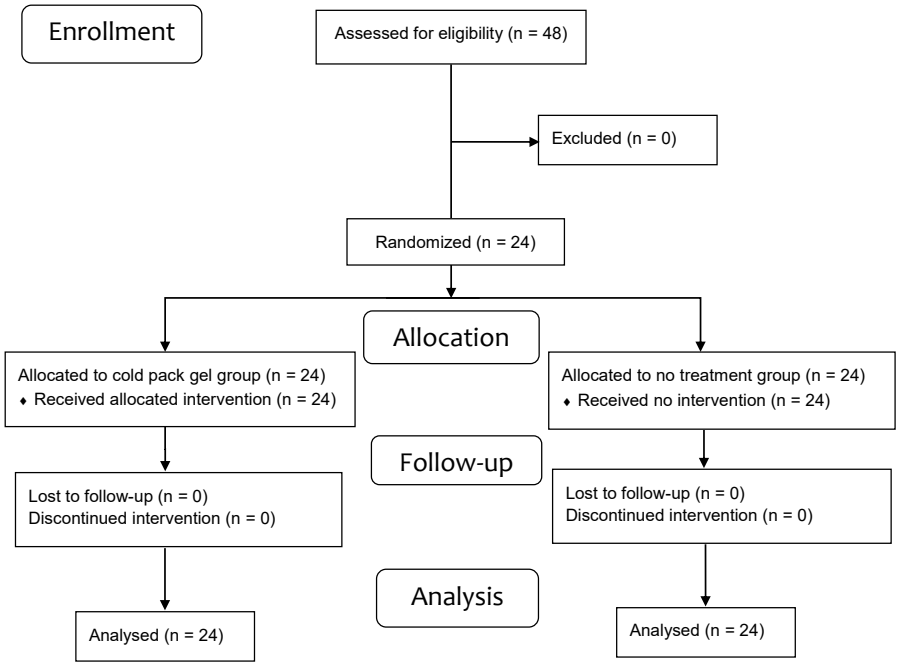

Fig. 1. The consort flow diagram.

The demographic characteristics between both groups including age, body mass index, gestational age, operative time, nulliparity, indication for cesarean section, tubal resection, types of anesthesia, estimated blood loss, baby sex and birthweight were not statistically different

in either group, the details are shown in Table1.

The postoperative pain scores at 6, 12 and 24 hours were insignificantly decreased in the cold pack gel group with the mean pain scores at 6 hours were 3.96 ± 1.71 in the cold pack gel group and 4.92 ± 2.06 in the placebo group, the mean difference was 0.95 (95%CI -0.14, 2.06), at 12 hours were 2.62 ± 1.47 in the cold pack gel group and 3.29 ± 1.46 in the placebo group, the mean difference was 0.67(95%CI -0.18, 1.52) and 24 hour were 2.17 ± 1.24 in the cold pack gel group and 2.67±1.66 in the placebo group, the mean difference was 0.5(95%CI -0.35, 1.35)

The opioid consumptions were decreased significantly in the cold pack gel group with the mean difference was 16.67 (95% CI 1.03, 32.31). The length of hospital stay was not significantly different between the groups. The details of primary and secondary outcomes are shown in Table 2.

Table 1. Baseline clinical characteristic.

Characteristics	Cold pack gel group (n = 24)	No treatment group (n = 24)	p value
Age (years), mean ± SD	27.83 ± 7.29	30.04 ± 7.81	0.317*
Body mass index (kg/m^2), mean ± SD	24.71 ± 4.20	25.59 ± 4.60	0.491*
Gestational age (weeks), mean ± SD	38.45 ± 1.10	38.33 ± 1.09	0.695*
Operative time (min), mean ± SD	43.96 ± 10.41	42.00 ± 9.92	0.508*
Nulliparity, n (%)	10 (41.67)	11 (45.83)	0.771**
Indication for cesarean delivery			
prior cesarean delivery, n (%)	8 (33.33)	11 (45.83)	0.376**
CPD, n (%)	7 (29.17)	5 (20.83)	0.505***
Other, n (%)	9 (37.50)	8 (33.33)	0.763**
Tubal resection, n (%)	10 (41.67)	9 (37.50)	0.768**
Types of anesthesia			
General anesthesia	4 (16.67)	5 (20.83)	0.712***
Spinal anesthesia	20 (83.33)	19 (79.17)	
Estimated blood loss (ml), mean ± SD	245.83 ± 58.82	258.33 ± 77.55	0.532*
Baby sex			
male, n (%)	14 (58.33)	13 (54.17)	0.771**
female, n (%)	10 (41.67)	11 (45.83)	
Birth weight (grams), mean ± SD	2,991.88 ± 297.02	3,083.13 ± 384.01	0.362*

SD: standard deviation, CPD: cephalopelvic disproportion.

*calculated by unpaired t-test, **calculated by Pearson chi square, ***calculated by Fisher's exact test

Table 2. Study outcomes.

Outcomes	Cold pack gel group (n = 24)	No treatment group (n = 24)	mean difference (95%CI) p value
Postoperative pain at 6 hour			
NRS, mean ± SD	3.96 ± 1.71	4.92 ± 2.06	0.95 (-0.14, 2.06) 0.086*
Moderate to severe pain, n (%)	15 (62.50)	19 (79.17)	RR 0.79 (95%CI 0.54-1.15) 0.213**
Postoperative pain at 12 hour			
NRS, mean ± SD	2.62 ± 1.47	3.29 ± 1.46	0.67 (-0.18, 1.52) 0.122*
Moderate to severe pain, n (%)	7 (29.17)	11 (45.83)	RR 0.63 (95%CI 0.30-1.36) 0.244**
Postoperative pain at 24 hour			
NRS, mean ± SD	2.17 ± 1.24	2.67 ± 1.66	0.5 (-0.35, 1.35) 0.243*
Moderate to severe pain, n (%)	3 (12.50)	7 (29.17)	RR 0.43 (95%CI 0.13-1.46) 0.176**
Opioid consumption (mg), mean ± SD	8.33 ± 19.03	25.00 ± 32.97	16.67 (1.03, 32.31) 0.037*
Length of hospital stay (days), mean ± SD	3.33 ± 0.48	3.42 ± 0.50	0.08 (-0.20, 0.36) 0.561*

NRS: numerical rating scale, SD: standard deviation, RR: relative risk, CI: confidence interval
*calculated by unpaired t-test, ** calculated by binary regression analysis

Discussion

The present study demonstrated that the cold pack gel could decrease the opioid consumption in the post-cesarean delivery patients without side effects. However, the mean pain score at 6, 12 and 24 hours after cesarean section were insignificantly decreased in the cold pack gel group. The proportion of moderate to severe pain and length of hospital stay were also insignificantly decreased.

The decremental of opioid consumption from cold pack gel were also reported in Nuangpho et al[5] and Suwannalert et al's studies[11] which reported postoperative opioid use decrement from cold pack gel use. However, the cold pack gel was reported to decrease postoperative pain in Chumkam et al[4], Nuangpho et al[5] and Srirussamee et al's[15] studies which studied in post gynecologic operation and Siripanthong et al's[16] study which studied in post-cesarean midline incision operation. The difference of result from this study might be due to the difference of the patient's setting, operation types and different cold pack technique.

The mean NRS of post-cesarean pain at 6 hours postoperation in the control group was 4.92 ± 2.06 with 79.17% having moderate to severe pain which was higher than the 57.0% reported in a previous study conducted in our center[2] that reflected the inadequate pain control even if the opioid was used. The adding of multimodality treatment is needed for proper pain management.

The clinical application of cold pack gel in post-cesarean delivery is recommended from the findings of this study. However, even though the cold pack gel was added, 62.50% still had moderate to severe pain postoperation. Therefore, other pain control methods should be added and the most appropriate method for pain control still needs further studies.

The strength of this study was the prospective randomized control trial study design together with an adequate sample size. However, the limitation of this study was the unblinding in the control group due to the nature of intervention.

Conclusion

Cold pack gel could reduce postoperative opioid use without any serious side effect in post-cesarean delivery, Pfannenstiel skin incision. However, the postoperative pain scores were not significantly decreased. It can be used as an additional multimodality treatment in post-cesarean delivery care.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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OBSTETRICS

The Efficacy of Antenatal Perineal Massage in Reducing Postpartum Anal Incontinence: A randomized controlled trial

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ABSTRACT

Objectives: This study evaluated the efficacy of antenatal perineal massage (APM) in reducing postpartum morbidities, particularly anal incontinence (AI).

Materials and Methods: A randomized controlled trial was conducted at Rajavithi Hospital, Bangkok, from October 2023 to April 2024. Nulliparous women with singleton pregnancies were randomly assigned to the APM or control group using block randomization. Participants in the APM group performed a daily 5-minute perineal massage on themselves from 34–36 weeks of gestation until delivery. Both groups received standard prenatal, intrapartum, and postpartum care. The primary outcome was AI incidence at 3 months postpartum, assessed using the Pelvic Floor Distress Inventory-20 (PFDI-20). Secondary outcomes included intrapartum variables, urinary incontinence, and dyspareunia.

Results: 106 women were randomized into two groups of 53 each. After exclusions, 37 participants per group were analyzed. At 3 months postpartum, AI incidence was lower in the APM group (32.43%) compared to the control group (56.76%), though not statistically significant ($p = 0.061$). The APM group showed significantly reduced AI severity ($p = 0.017$) and fecal incontinence incidence ($p = 0.030$).

Conclusion: Although the reduction in AI incidence was not statistically significant, the findings suggested potential clinical benefits that warrant further investigation. APM significantly reduced fecal incontinence incidence and AI severity without increasing maternal or neonatal complications. These findings support incorporating APM into routine prenatal care to reduce postpartum morbidities.

Keywords: antenatal perineal massage, perineal injuries, anal incontinence, postpartum morbidities.

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ประสิทธิภาพของการนวดฝีเย็บในระยะฝากครรภ์ในการลดภาวะอุจจาระหรือผายลมเล็ดจากการคลอดบุตร การทดลองแบบสุ่มและมีกลุ่มควบคุม

มงคล เกิดแปลงทอง, บุษรัญญา พุทธธนะพิทักษ์

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการนวดฝีเย็บในระหว่างฝากครรภ์ ในการลดภาวะแทรกซ้อนหลังคลอดโดยเฉพาะภาวะอุจจาระหรือผายลมเล็ด*

วัสดุและวิธีการ: *การทดลองแบบสุ่มและมีกลุ่มควบคุมดำเนินการที่โรงพยาบาลราชวิถี กรุงเทพมหานคร ระหว่างเดือนตุลาคม 2566 ถึงเดือนเมษายน 2567 สตรีตั้งครรภ์ที่ไม่เคยคลอดบุตรและมีครรภ์เดี่ยวถูกสุ่มจัดกลุ่มโดยวิธีการสุ่มแบบ ไปยังกลุ่มทดลองหรือกลุ่มควบคุม กลุ่มทดลองทำการนวดฝีเย็บด้วยตนเองวันละ 5 นาที ตั้งแต่อายุครรภ์ 34-36 สัปดาห์จนถึงคลอด ทั้งสองกลุ่มได้รับการดูแลก่อนคลอด ระยะคลอด และหลังคลอดตามมาตรฐาน ผลลัพธ์หลักคือการเกิดภาวะอุจจาระหรือผายลมเล็ดภายใน 3 เดือนหลังคลอด โดยใช้แบบสอบถาม Pelvic Floor Distress Inventory-20 ผลลัพธ์รองที่ประเมินได้แก่ ผลลัพธ์ระหว่างการคลอด ภาวะกลั้นปัสสาวะไม่อยู่ และอาการเจ็บขณะมีเพศสัมพันธ์*

ผลการศึกษา: *จากผู้เข้าร่วมวิจัย 106 คน มีการคัดออก 32 คน ทำให้เหลือผู้เข้าร่วมวิจัยกลุ่มละ 37 คน ในช่วง 3 เดือนหลังคลอด อัตราการเกิดภาวะอุจจาระหรือผายลมเล็ดในกลุ่มทดลองลดลง (ร้อยละ 32.43) เมื่อเทียบกับกลุ่มควบคุม (ร้อยละ 56.76) อย่างไม่มีนัยสำคัญทางสถิติ ($p = 0.061$) อย่างไรก็ตามความรุนแรงของภาวะอุจจาระหรือผายลมเล็ดในกลุ่มทดลอง ลดลงอย่างมีนัยสำคัญทางสถิติ ($p = 0.017$) และภาวะอุจจาระเล็ดลดลงอย่างมีนัยสำคัญในกลุ่มทดลอง ($p = 0.030$)*

สรุป: *แม้อัตราการเกิดภาวะอุจจาระหรือผายลมเล็ดจะไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ แต่ผลการศึกษาบ่งชี้ถึงประโยชน์ทางคลินิกที่ควรศึกษาต่อยอด การนวดฝีเย็บในระหว่างฝากครรภ์ช่วยลดความรุนแรงของภาวะอุจจาระหรือผายลมเล็ด โดยเฉพาะภาวะอุจจาระเล็ด โดยไม่เพิ่มภาวะแทรกซ้อนต่อมารดาหรือทารก การศึกษานี้สนับสนุนให้รวมการนวดฝีเย็บไว้ในแนวทางการดูแลในระยะฝากครรภ์ เพื่อช่วยลดภาวะแทรกซ้อนหลังคลอด*

คำสำคัญ: *การนวดฝีเย็บในระหว่างฝากครรภ์, การบาดเจ็บของฝีเย็บ, ภาวะอุจจาระหรือผายลมเล็ด, ภาวะแทรกซ้อนจากการคลอดบุตร*

Introduction

Perineal tears during childbirth are a common occurrence[1], either spontaneously or due to an episiotomy. These tears can result in both short-term and long-term complications. Short-term complications include postpartum hemorrhage, wound dehiscence, infection[2], and postpartum pain[3], which can disrupt the bonding between mother and child[4] and cause dyspareunia (painful intercourse)[5]. Long-term complications may include pelvic floor dysfunctions, such as anal incontinence (AI), pelvic organ prolapse (POP), and urinary incontinence (UI), even after surgical repair[6, 7]. The long-term complications impact both physical and mental health, causing embarrassment and social withdrawal[8]. Factors that increase the risk of perineal injury include nulliparity, Asian ethnicity, median episiotomy, fetal macrosomia, precipitous labor, maternal obesity, and instrumental delivery[2].

Antenatal perineal massage (APM) has traditionally been used to improve blood circulation and relax the perineal muscles, promoting increased elasticity, expanding the birth canal, and facilitating a smoother delivery process. The massage may be performed by the pregnant individual or their partner, generally beginning 4 to 6 weeks prior to delivery. A systematic review from 2020[3] found that APM decreases the need for episiotomy, mitigates the occurrence and severity of perineal tears, shortens the duration of the second stage of labor, and improves Apgar scores at 1 and 5 minutes after birth. Additionally, it has been shown to decrease the risk of AI[3].

Due to the elevated risk of perineal tears among the Asian population and the lack of definitive research on Southeast Asian women, this study was conducted to evaluate the efficacy of APM in reducing postpartum morbidities, both short- and long-term, among pregnant women at Rajavithi Hospital. The hospital provides care to a diverse population from Southeast Asia, encompassing Thai, Myanmar, Cambodian, and Lao women.

Materials and Methods

A prospective randomized controlled trial was conducted among pregnant women attending the antenatal care clinic at Rajavithi Hospital from October 2023 to April 2024. Both healthcare workers and the investigator were blinded to the intervention. Ethical approval for the study was obtained from the Office of the Research Ethics Committee of Rajavithi Hospital. The trial was registered on ClinicalTrials.gov (ID: NCT06162312), and all participants provided written informed consent after receiving a thorough explanation of the study's objectives.

For the primary outcome, the sample size was calculated by comparing the proportion of patients experiencing postpartum AI between the two groups, with an α-error set at 0.05 and a power of 80%. Previous study[9] indicated an AI rate of 12.5% in the control group and 42% in the APM group. To account for these differences, the optimal sample size was determined to be at least 35 participants per group, with an additional 50% dropout rate due to the high cesarean section rate in the study setting. As a result, a total of 106 pregnant women were recruited for the study, with 53 participants in each group.

The statistical study was performed using SPSS Statistics version 26 developed by IBM Corp. in Armonk, NY, USA. In the case of normally distributed variables, the results were displayed as means and standard deviations (SD), while for non-normally distributed data, they were described as medians and ranges. Statistical analysis of categorical variables was conducted using the chi square test, whereas normally distributed data was analyzed using the unpaired t test. The Mann Whitney U test was used for data that did not follow a normal frequency distribution. Statistical significance was defined as a p value less than 0.05.

The inclusion criteria were nulliparous pregnant women with singleton pregnancies, aged 18 years or older, and with gestational ages ranging from 34 to 36 weeks. The fetus must be in a cephalic position. Participants were required to be proficient in the Thai

language to understand the study materials and instructions. Among the exclusion criteria were vaginal infections such as herpes or candida vulvovaginitis, mothers who had undergone cesarean sections or instrumental birth, pregnant women who have a medical history of persistent cough, present or previous problems with UI or AI, POP, or connective tissue diseases. Additionally, conditions prohibiting vaginal delivery, such as placenta previa or placenta accreta spectrum, were also considered important factors for exclusion.

Participants in the research were divided into two groups in a 1:1 ratio through block randomization, resulting in an APM group and a control group. Both groups provided personal information, including maternal age, ethnicity, body mass index (BMI), educational level, and underlying health conditions.

The APM group received instructions on perineal massage from a physician and via educational video. The participants were instructed to perform digital perineal massage, which involved lubricating their fingers with a water-based lubricant and gently inserting one or two fingers, or the thumb, 3–5 cm into the vagina to perform a 5-minute daily perineal massage. The massage consisted of three techniques: steady pressing of the perineum towards the anus for 1 minute, pressing in an up-and-down motion towards the anus for 1 minute, and pressing massage of the perineum in a U-shape motion for 3 minutes. This regimen began at 34–36 weeks of gestational age and continued until delivery. Participants practiced perineal massage under physician supervision during the first session to ensure proper technique. Participants were required to document their perineal massage sessions in a dedicated log. The research team conducted follow-up phone calls twice (after the first and third weeks) to assess the consistency of the massage, any side effects, and to encourage continuation if there were no contraindications, such as bleeding, wounds, or genital infections. Partners were also encouraged to assist with the massage at home.

Both groups underwent standard antenatal, intrapartum, and postpartum care at Rajavithi Hospital, which included labor induction, episiotomy, and cesarean section as clinically indicated. All participants were delivered by obstetrics and gynecology residents following standardized delivery and episiotomy repair protocols. The collected data included mode of delivery, degree of perineal tear, episiotomy status, duration of the second stage of labor, blood loss, newborn birth weight, Apgar scores at 1 and 5 minutes, and perineal pain evaluated 24 hours postpartum using the verbal numerical rating scale (NRS).

AI and pelvic floor health were assessed at three months postpartum using the Pelvic Floor Distress Inventory-20 (PFDI-20) via a structured phone interview. The PFDI-20 comprises three subscales: the Pelvic Organ Prolapse Distress Inventory-6 (POPDI-6) for prolapse symptoms, the Colorectal-Anal Distress Inventory-8 (CRADI-8) for bowel symptoms, and the Urinary Distress Inventory-6 (UDI-6) for urinary symptoms. Higher PFDI-20 scores reflect greater distress and more severe symptoms. AI was identified based on positive responses to questions 8, 9, or 10, while UI was determined by positive responses to questions 16, 17, or 18. The Thai translation and validation of the PFDI-20 demonstrated excellent reliability, with a Cronbach's alpha coefficient of 0.93[10].

Results

A total of 106 pregnant women were recruited (Fig. 1), with 53 assigned to the APM group and 53 to the control group. However, 32 women were excluded for the following reasons: 29 underwent cesarean section, 2 delivered at other hospitals, and 1 delivered underwent instrumental delivery.

Table 1 summarizes the demographic characteristics of the study groups, showing similarities between the APM and control groups in age, BMI, ethnicity, education, and gestational age at recruitment.

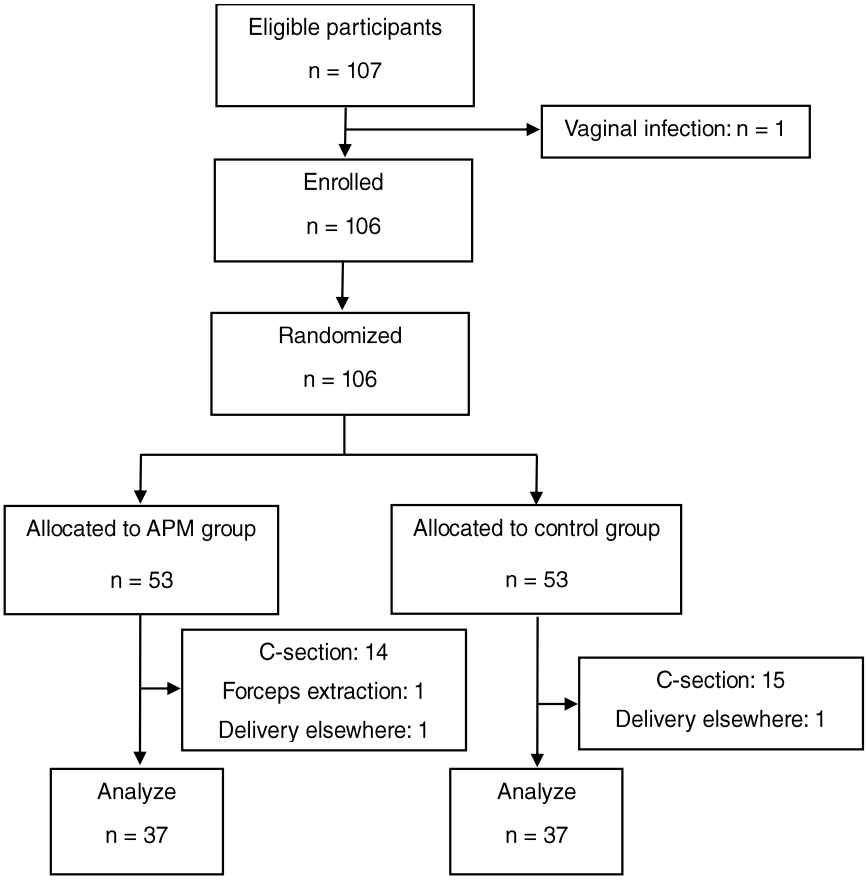

Fig. 1. Study flow diagram.

Table 1. Demographic characteristics of the studied groups.

	APM group (n = 37)	**Control group (n = 37)**
Age (years), mean ± SD	26.24 ± 5.06	25.73 ± 3.65
Body mass index (kg/m^2), mean ± SD	24.83 ± 4.12	25.06 ± 4.05
Ethnicity, n (%)		
Thai	21 (56.76)	17 (45.95)
Non-Thai Southeast Asia	16 (43.24)	20 (54.05)
Education, n (%)		
Illiterate/Primary	20 (54.05)	17 (45.95)
Secondary/College	17 (45.95)	20 (54.01)
GA at Recruitment, mean ± SD	34.84 ± 0.67	34.76 ± 0.48

† Unpaired t-test, †† Chi-square test

SD: standard deviation, APM: antenatal perineal massage.

Table 2 presents variables during labor and newborn outcomes. Gestational age at delivery, mode of delivery, second-stage duration, fetal birth weight, episiotomy rates, and blood loss were comparable between the groups, with no statistically significant differences observed. All participants experienced second-degree perineal tears, with no third- or fourth-degree tears reported. Preterm birth rates and Apgar scores at 1 and 5 minutes were similar, with no significant differences between the groups. Pain scores within the first 24 hours postpartum also showed no statistically significant difference.

Table 2. Variables during labor and newborns.

	APM group (n = 37)	Control group (n = 37)	p value
GA at delivery, mean ± SD	38.49 ± 1.47	38.65 ± 1.25	0.610†
Preterm delivery, n (%)	4 (10.81)	3 (8.11)	1.000††
Mode of delivery, n (%)			1.000††
Spontaneous labor	32 (86.49)	33 (89.19)	
Induction	5 (13.51)	4 (12.11)	
2nd stage duration (min), median (IQR)	16 (7.5-30.5)	15 (8-20)	0.495‡
Birth weight (g), mean ± SD	3,003.70 ± 352.64	2,959.46 ± 609.37	0.703†
Episiotomy, n (%)	35 (94.59)	35 (94.59)	1.000††
Degree of perineal tear, n (%) Second-degree tear	37 (100.00)	37 (100.00)	
Blood loss (ml), median (min-max)	100 (50-600)	100 (50-400)	0.771‡
Apgar score, mean ± SD			
At 1 min	8.73 ± 0.65	8.86 ± 0.54	0.333†
At 5 min	9.7 ± 0.52	9.86 ± 0.42	0.144†
Numeric rating score for pain at 24 hours, mean ± SD	4.22 ± 1.34	4.76 ±1.86	0.156†

† Unpaired *t*-test, †† Chi-square test, ‡ Mann–Whitney U test

GA: gestational age, SD: standard deviation, IQR: interquartile range, APM: antenatal perineal massage.

Table 3 presents the primary outcomes at 3 months postpartum. AI incidence was 32.43% in the APM group and 56.76% in the control group (p = 0.061). Fecal incontinence occurred in 24.32% of the APM group compared to 51.35% in the control group (p = 0.030). Flatus incontinence was reported at similar rates in both groups (13.51%, p = 1.000).

UI was reported in 24.32% of participants in the APM group and 35.14% in the control group, with no statistically significant difference (p = 0.446). Total PFDI-20 scores were lower in the APM group (median 4, IQR 2-7) compared to the control group (median 10, IQR 4.5-14, p = 0.001). Significant differences were observed in the POPDI-6 (p = 0.002) and CRADI-8 (p = 0.007) subscale, while the UDI-6 subscale showed no significant difference (p = 0.745). The AI severity subscale was significantly lower in the APM group (p = 0.017).

Both groups had a similar rate of return to

sexual intercourse at 3 months postpartum (56.76%). Additionally, pain during intercourse, assessed by a numeric rating scale, showed no statistically significant difference between groups (mean 2.62 ± 2.48 in the APM group vs 2.14 ± 2.01 in the control group; p = 0.498).

Table 3. Variables at 3 months postpartum.

	APM group (n = 37)	Control group (n = 37)	p value
Primary outcome			
Anal incontinent, n (%)	12 (32.43)	21 (56.76)	0.061††
Fecal incontinent, n (%)	9 (24.32)	19 (51.35)	0.030††
Flatus incontinent, n (%)	5 (13.51)	5 (13.51)	1.000††
Secondary outcome			
Urinary incontinent, n (%)	9 (24.32)	13 (35.14)	0.446††
PFDI-20, median (IQR)			
AI severity	0 (0-2)	2 (0-3)	0.017‡
POPDI-6	0 (0-2)	2 (0-4)	0.002‡
CRADI-8	2 (0-3)	4 (1-6.5)	0.007‡
UDI-6	2 (0-3.5)	3 (0-6)	0.309‡
Total score	4 (2-7)	10 (4.5-14)	0.001‡
Return of sexual intercourse, n (%)	21 (56.76)	21 (56.76)	1.000††
Numeric rating score for pain during sexual intercourse, mean ± SD	2.62 ± 2.48	2.14 ± 2.007	0.498†

† Unpaired t-test, †† Chi-square test, ‡ Mann–Whitney U test

SD: standard deviation, IQR: interquartile range, APM: antenatal perineal massage, PFDI-20: pelvic floor distress inventory-20, AI: Anal incontinent, POPDI-6: Pelvic Organ Prolapse Distress Inventory-6, CRADI-8: Colorectal-Anal Distress Inventory 8, UDI-6: Urinary Distress Inventory-6

Discussion

This study evaluated the efficacy of APM in reducing AI and postpartum morbidity. Although the reduction in AI incidence was not statistically significant (32.43% vs 56.76%, p = 0.061), the findings suggested potential clinical benefits, as the p value indicates a trend toward significance that may reflect a true effect of APM and warrants further investigation. Fecal incontinence was significantly lower in the APM group (24.32% vs 51.35%, p = 0.030), and the severity of AI was also significantly reduced (p = 0.017). These results aligned with Abdelhakim et al[3], who reported that APM significantly reduced AI incidence. While the relatively small sample size may have limited the ability to detect statistical significance for AI incidence, the observed improvements in fecal incontinence and symptom severity supported APM as a valuable addition to prenatal care. Further studies with larger sample sizes are needed to confirm these findings.

Both groups received episiotomies, which likely explained the lack of significant differences in intrapartum and newborn variables, such as second stage duration, and neonatal outcomes. The routine use of episiotomy may have minimized differences in

perineal trauma between the groups. Similarly, the study by Mei-Dan et al[11] found that antenatal perineal massage did not significantly reduce perineal trauma or episiotomy rates.

Regarding secondary outcomes, urinary incontinence was slightly lower in the APM group (24.32% vs 35.14%), though this was not statistically significant (p = 0.446). However, APM significantly improved overall pelvic floor health, as reflected by lower PFDI-20 scores (p = 0.001), particularly in reducing pelvic organ prolapse and colorectal-anal distress (p = 0.002 and p = 0.007, respectively). These findings suggested that APM may reduce postpartum morbidity by improving pelvic floor function among nulliparous women.

Sexual function, measured by the rate of return to intercourse and pain during intercourse, was similar between groups, with no significant differences in pain levels (p = 0.498). This suggested that APM may not have a strong influence on postpartum sexual recovery. These findings aligned with those of Manresa et al[5], which found that dyspareunia was linked to the degree of perineal trauma. However, the routine use of episiotomy in both groups likely minimized differences in perineal trauma, contributing to similar dyspareunia rates.

This study had limitations. The involvement of multiple physicians in delivering participants may have introduced confounding factors, despite adherence to standardized protocols. Additionally, the follow-up period of three months postpartum may not be sufficient to fully evaluate the long-term efficacy of APM. Future research should examine the impact of APM beyond three months to assess its prolonged benefits and effectiveness.

Conclusion

Although the reduction in the incidence of AI was not statistically significant, it demonstrated potential clinical benefits that warrant further investigation. APM significantly reduced fecal incontinence and the severity of AI, improving overall pelvic floor health and reducing postpartum morbidity among nulliparous women. These findings supported the integration of APM into routine antenatal care. Further research with larger sample sizes in settings without routine episiotomy is needed to validate these findings.

Potential conflicts of interest

The authors declare no conflicts of interest.

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GYNAECOLOGY

The Efficacy of Oral Ginger Powder in Prevention of Postoperative Ileus after Benign Gynecologic Hysterectomy: A Randomized Controlled Trial

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ABSTRACT

Objectives: To assess the efficacy of oral ginger powder for prevention of postoperative bowel ileus in benign gynecologic abdominal hysterectomy.

Materials and Methods: A randomized, double-blind, placebo-controlled trial was conducted. Benign gynecologic patients who underwent abdominal hysterectomy were allocated into two groups: the experimental group received oral ginger capsules, and the control group received placebo capsules. Postoperative bowel ileus was measured by using time to first flatus as a primary outcome.

Results: Fifty-six patients were randomized to the ginger group (n = 28) and the placebo group (n = 28). The ginger group had significantly less time to first flatus than the control group (29.5 ±10.0 vs 38.9 ±8.6 hours, mean difference (MD) 9.31 hours, 95% confidence interval (CI) 4.2-14.3, p < 0.001). The ginger group also had significantly less time to first defecation than the control group (45.8 ±9.1 vs 58.5 ±14.7 hours, MD 12.6 hours, 95%CI 4.5-20.8, p = 0.003). According to the Kaplan-Meier graph, the median time to first flatus (50%) of the ginger group was 26.5 hours (95%CI 21.1-32.5) and that of the control group was 39.33 hours (95%CI 31.7- 44.7) (p = 0.007). Median time to defecation (50%) of the ginger group was 44.7 hours (95%CI 42.0-47.6) and that of the control group was 59.7 hours (95%CI 51.7-64.7) (p = 0.012). No serious adverse effects were reported.

Conclusion: Oral ginger powder could reduce postoperative bowel ileus in benign gynecologic abdominal hysterectomy.

Keywords: ginger, benign gynecologic surgery, postoperative bowel ileus

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การศึกษาประสิทธิภาพของการรับประทานขิงชนิดผงเพื่อป้องกันอาการท้องอืดหลังการผ่าตัดเอามดลูกออกทางหน้าท้อง: การทดลองแบบสุ่มที่มีกลุ่มควบคุม

วิชชุดา ล้อศิริรัตน์, สุกัญญา ศรีนิล

บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการรับประทานขิงชนิดผงในการป้องกันอาการท้องอืดหลังการผ่าตัดเอามดลูกออกทางหน้าท้องในกลุ่มโรคทางนรีเวชที่ไม่ใช่มะเร็ง*

วัสดุและวิธีการ: *เป็นการทดลองแบบสุ่มที่มีกลุ่มควบคุม โดยแบ่งกลุ่มอาสาสมัครที่เป็นผู้ป่วยทางนรีเวชที่ไม่ใช่มะเร็งและต้องได้รับการรักษาด้วยการผ่าตัดเอามดลูกออกทางหน้าท้องเป็นสองกลุ่ม คือ กลุ่มที่รับประทานขิงชนิดผง และกลุ่มได้รับยาหลอกภายหลังการผ่าตัด เพื่อศึกษาประสิทธิภาพของการรับประทานขิงชนิดผงป้องกันอาการท้องอืดด้วยการเปรียบเทียบระยะเวลาการผายลมครั้งแรกหลังการผ่าตัด*

ผลการศึกษา: *จำนวนอาสาสมัครในการวิจัยนี้มีทั้งสิ้น 56 ราย แบ่งเป็นกลุ่มที่รับประทานขิงชนิดผงจำนวน 28 ราย และกลุ่มได้รับยาหลอกจำนวน 28 ราย พบว่าอาสาสมัครกลุ่มที่รับประทานขิงชนิดผง มีระยะห่างของเวลาระหว่างการผายลมครั้งแรกและหลังการผ่าตัดเสร็จน้อยกว่ากลุ่มได้รับยาหลอก (29.5 ± 10.0 vs 38.9 ± 8.6 ชั่วโมง, mean difference (MD) 9.3 ชั่วโมง, 95% confidence interval (CI) 4.2-14.3, p < 0.001) รวมถึงระยะห่างของเวลาระหว่างการถ่ายอุจจาระครั้งแรกและหลังการผ่าตัดเสร็จมีระยะเวลาน้อยกว่ากลุ่มได้รับยาหลอกอย่างมีนัยสำคัญทางสถิติเช่นกัน (45.8 ± 9.1 vs 58.5 ± 14.7 ชั่วโมง, MD 12.6 ชั่วโมง, 95% CI 4.5-20.8, p = 0.003) นอกจากนี้ไม่พบผลข้างเคียงที่สัมพันธ์กับการรับประทานขิงชนิดผง*

สรุป: *การรับประทานขิงชนิดผงช่วยลดอาการท้องอืดในผู้ป่วยที่ได้รับการผ่าตัดเอามดลูกออกทางหน้าท้อง จากโรคทางนรีเวชที่ไม่ใช่มะเร็งได้*

คำสำคัญ: ขิง, การผ่าตัดโรคทางนรีเวชที่ไม่ใช่มะเร็ง, ภาวะลำไส้อืดหลังการผ่าตัด

Introduction

Hysterectomy is one of the most commonly performed procedures by gynecologists, second only to cesarean section[1]. It can be performed through three main approaches: vaginally, laparoscopically, or abdominally.

Globally, approximately 6.1 to 8.6 per 1,000 women undergo a hysterectomy[2]. Postoperative ileus (POI) is a common complication among patients undergoing abdominal surgeries. Postoperative ileus occurs in up to 25% of patients following elective abdominal surgery[3]. Symptoms of postoperative ileus (POI) include nausea, vomiting, delayed passage of flatus and stool, abdominal distention and abdominal tenderness[3]. The hallmark of postoperative ileus is a delayed bowel movement or passage of flatus[4]. Findings from physical examination are generally non-specific, but patients often present with a distended, tympanic abdomen and absent bowel sounds[4]. The diagnosis of postoperative ileus is based on clinical assessment[4]. Postoperative bowel ileus can result in prolonged hospital stays, increased postoperative pain, and impaired wound healing, potentially delaying mobilization. Several methods can help prevent POI, including early postoperative feeding, correcting electrolyte imbalances, prophylactic nasogastric tube insertion, bowel preparation, analgesia, prokinetics, and gum chewing[5–7]. However, no agent has been proven effective in preventing this condition[3]. In addition to early ambulation, laxatives, and antiflatulent drugs, in order to relieve abdominal distention, some patients try alternative treatments such as ginger[8].

Ginger, the rhizome of Zingiber officinale, belongs to the Zingiberaceae family and has long been used as a spice worldwide[9]. Previous studies have reported the anti-inflammatory, antioxidative and antitumor properties of ginger[7]. Ginger, as a dietary agent, has a carminative effect that reduces pressure on the lower esophageal sphincter, decreases intestinal cramping, and prevents flatulence, bloating and dyspepsia[10–12]. Ginger is used to relieve abdominal distention, nausea and vomiting[9,13]. Ginger can also alleviate flatulence and constipation by enhancing gastrointestinal motility[14,15].

Ginger is classified as “generally recognized as safe” by the U.S. Food and Drug Administration, and the German Commission E Monographs indicate that ginger has no known adverse side effects or interactions with drugs or herbs[16].

To date, no clinical trials have investigated the use of oral ginger powder for preventing postoperative ileus after benign gynecologic hysterectomy. Therefore, the primary aim of this study was to evaluate the time to first flatus in patients after hysterectomy. Secondary aims included assessing the time to first defecation, length of hospital stay, postoperative vomiting, and any adverse events related to oral ginger powder administration.

Materials and Methods

This randomized, double-blinded, placebo-controlled trial was performed at the Department of Obstetrics and Gynecology, Khon Kaen Hospital between July 2023 and May 2024. This study received approval from the Khon Kaen Hospital Institutional Review Board for Human Research (reference: KEF66016).

Recruited patients included those diagnosed with benign gynecological conditions and scheduled for abdominal hysterectomy with or without adnexal surgery. Patients were excluded if they had (a) a history of carminative drug use, (b) allergy to ginger, (c) reoperation within 24 hours, (d) immobility such as being on a ventilator, unconsciousness, or in shock, (e) intraoperative complications involving the gastrointestinal organs, kidneys, ureters or urinary bladder system, (f) underlying gastrointestinal disease such as gastroesophageal reflux disease and dyspepsia, (g) underlying chronic kidney disease

(glomerular filtration rate < 30 ml/min/ 1.73 m^2), (h) use of anticoagulants such as warfarin, (i) postoperative flatus before the start of the intervention, (j) underlying respiratory disease such as chronic obstructive pulmonary disease, asthma, or lung cancer, (k) peripheral arterial occlusion disease, (l) an operative time > 3 hours, (m) a low albumin level (< 3.5 g/dL), or (n) intraabdominal infection. The patients were informed about the study by the research assistant at the gynecological out-patient department before recruitment. Written informed consent was obtained from each participant in the gynecological ward prior to enrollment at the gynecological ward after recruitment.

Post-hysterectomy women who met the eligibility criteria were randomly assigned to one of two groups: the ginger group or the control group. A randomization scheme was generated using a random number table with a block of four technique and allocation concealment using sequentially opaque envelopes. Baseline characteristics were recorded: age, body mass index (BMI), underlying disease, prior abdominal surgery, type of skin incision, operative procedure, postoperative diagnosis, operative time, estimated blood loss, length of skin incision, perioperative blood transfusion and time to ginger administration. All patients were managed using the same postoperative protocols, in which laxative and antiflatulent medications were not routinely prescribed. The postoperative feeding regimen was standardized, starting with a liquid or soft diet on the first postoperative day (within 24 hours after surgery), followed by a solid or regular diet within the next 24 hours, as tolerated.

Ginger (Zingiber officinale Roscoe, 500 mg per capsule) (KMP, Thailand) was assigned to the treatment group, while a corresponding placebo was given to the control group. The drugs and placebo, which were identical in color, shape and size were prepared by a pharmacist not involved in the study. As soon as the inclusion criteria were met by a study subject, the nurses proceeded to select an opaque envelope that was sequentially numbered. To ensure randomization, each opaque envelope contained 18 capsules of either ginger or placebo and was sequentially labeled. The envelopes were distributed in numerical order, and both the study participants and health care providers were blinded to the treatment assignment.

The treatment began once the participants started drinking water. The drug dose was two capsules taken three times daily after meals and continued for three days[17]. Treatment assignments remained concealed until the data collection was complete. All participants were admitted to the gynecological ward, and if there were no postoperative complications, they were discharged three days after the operation.

The primary outcome was the time to first flatus (hours) defined as the interval from the end of the operation to the first observed passage of flatus.

The secondary outcomes were assessment of (a) time to first defecation (hours) defined as the interval from the end of the operation to the first observed passage of defecation; (b) length of hospital stay (hours) calculated from the end of the surgery to the time of discharge; (c) postoperative vomiting measured by the number of episodes per day and evaluated once daily from postoperative days 1 to 3, with vomiting occurring more than 5 minutes apart considered as an independent event and recorded separately; (d) adverse events, including heartburn, diarrhea, etc.; and (e) additional antiflatulent/laxative drug requirements.

The sample size, which was calculated based on a pilot study of 30 patients, required 56 participants (28 in each group) to achieve an alpha level of 0.05 and a power of 90%, and to account for a 10% dropout rate.

Statistical analysis was conducted using SPSS version 29. Categorical variables were analyzed with the Fisher's exact test or chi square test, while

continuous variables were assessed using the student's t-test. The primary outcome was presented as mean ± standard deviation with a 95% confidence interval. The Kaplan-Meier survival analysis was used to analyze the time to first flatus and defecation after surgery. A p value of less than 0.05 was considered statistically significant, and the trial analysis was performed using intent-to-treat (ITT) analysis.

Results

There were 106 eligible women scheduled for abdominal hysterectomy with or without adnexal surgery who were enrolled into the study. Fifty of them were excluded from the study: 23 because of postoperative flatus before the start of the intervention, 10 because they had underlying dyspepsia, 7 because they had a history of carminative drug use within one month, 5 due to having a serum albumin level < 3.5 g/dL, 2 because of underlying chronic kidney disease (CKD), 2 because of use of warfarin, and 1 because of underlying asthma.

A total of 56 eligible women were randomly assigned to two groups: 28 received ginger and 28 received the placebo. There were no dropouts (Fig. 1). For the baseline characteristics, no significant differences were found between the two groups (Table 1).

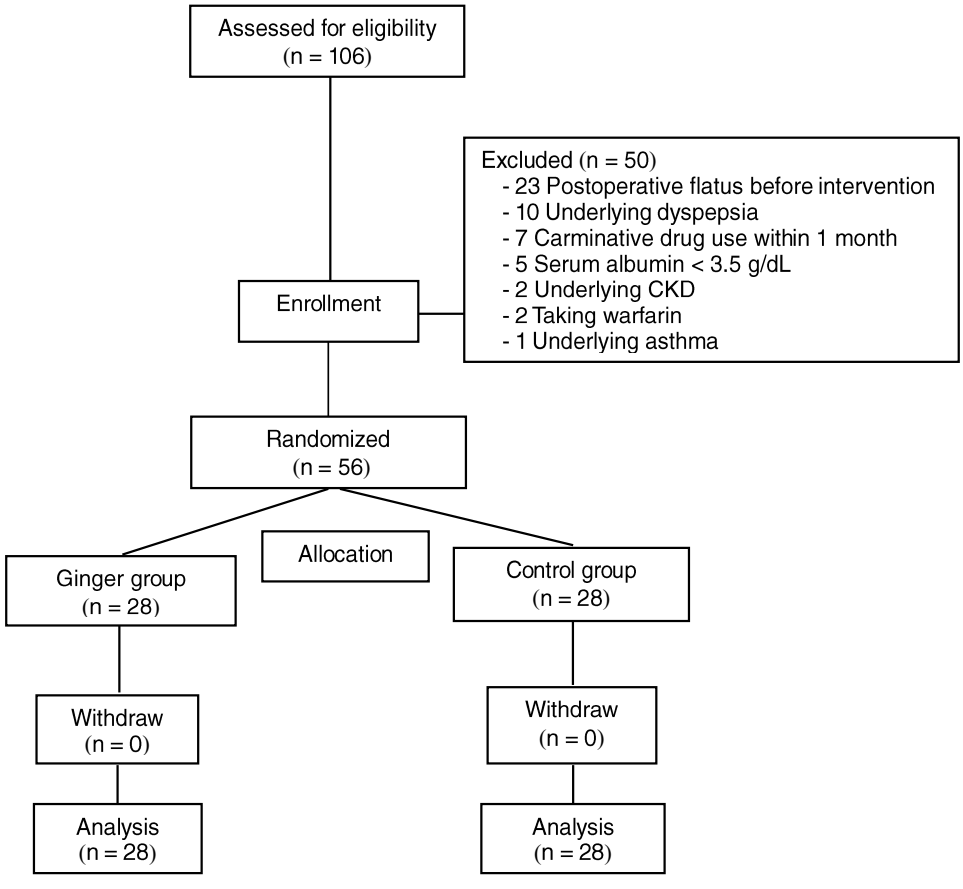

Fig. 1. Study flow diagram.

Table 1. Baseline characteristics of participants undergoing total abdominal hysterectomy for benign gynecologic conditions.

Baseline characteristics	Ginger group (n = 28)	Control group (n = 28)	p value
Age (years), mean ± SD	45.8 ± 4.6	48.3 ± 8.2	0.166 [a]
BMI (kg/m^2), mean ± SD	25.43 ± 4.8	24.43 ± 4.6	0.438 [a]
Underlying diseases, n (%)			
Diabetes mellitus	3 (10.7)	2 (7.1)	0.639 [b]
Hypertension	2 (7.1)	3 (10.7)	0.639 [b]
Others	4 (14.3)	4 (14.3)	1.000 [b]
Prior abdominal surgery, n (%)			
Yes	12 (42.9)	9 (32.1)	0.408 [b]
No	16 (57.2)	19 (67.9)	
Type of skin incision, n (%)			0.342 [b]
Low midline	8 (28.6)	5 (17.9)	
Pfannenstiel	20 (71.4)	23 (82.1)	
Operative procedure, n (%)			0.365 [b]
TAH with BS	6 (21.4)	9 (32.1)	
TAH with BSO	22 (78.6)	19 (67.9)	
Postoperative diagnosis, n (%)			0.135 [c]
Uterine myoma	16 (57.2)	20 (71.4)	
Adenomyosis	10 (35.6)	4 (14.4)	
CIN III	0 (0.0)	2 (7.1)	
Endometrial hyperplasia	1 (3.6)	0 (0.0)	
Ovarian tumor	1 (3.6)	2 (7.1)	
Operative time (min), mean ± SD	103.7 ± 21.9	90.6 ± 22.0	0.300 [a]
Estimated blood loss (ml), mean ± SD	191.4 ± 41.8	129.4 ± 21.3	0.193 [a]
Length of incision (cm), mean ± SD	12.5 ± 1.0	12.8 ± 1.2	0.353 [a]
Perioperative blood transfusion, n (%)	1 (3.6)	2 (7.1)	0.352 [c]
Time to ginger/placebo administration (hours)*, mean ± SD	18.7 ± 2.3	19.1 ± 1.9	0.498 [a]

[a] Two sample t test, [b] chi square test, [c] Fisher's exact test
SD: standard deviation, BMI: body mass index, TAH: total abdominal hysterectomy, BS: bilateral salpingectomy, BSO: bilateral salpingo-oophorectomy, CIN: cervical intraepithelial neoplasia
* Time from end of operation to start of intervention (hours)

Time to first flatus was significantly lower in the ginger group than in the control group (29.5 ± 10.0 vs 38.9 ± 8.6 hours, mean difference (MD) 9.31 hours, 95% confidence interval (CI) 4.2-14.3, p < 0.001) (Table 2), and time to first defecation was significantly lower in the ginger group than in the control group (45.8 ± 9.1 vs 58.5 ± 14.7 hours, MD 12.6 hours, 95%CI 4.5-20.8, p = 0.003) (Table 2).

Table 2. Primary and secondary outcomes.

Results	Ginger group (n = 28)	Control group (n = 28)	Mean difference 95%CI	p value
Time to first flatus (hours), mean ± SD	29.5 ± 10.0	38.9 ± 8.6	9.31 (4.2-14.3)	< 0.001[a]
Time to first defecation (hours), mean ± SD	45.8 ± 9.1	58.5 ± 14.7	12.6 (4.5-20.8)	0.003 [a]
Length of hospital stay (hours), mean ± SD	70.3 ± 5.5	76.8 ± 21.3	6.6 (1.8-14.9)	0.120 [a]
Postoperative vomiting, n (%)				
Day 1	1 (3.6)	3 (10.7)		0.611 [c]
Day 2	0 (0.0)	1 (3.6)		0.500 [c]
Day 3	-	-		-
Adverse events, n (%)	0 (0.0)	3 (10.7)		0.236 [c]
Diarrhea	4 (14.3)	7 (25.0)		0.313 [b]
Additional antiflatulent drug requirements, n (%)	0 (0.0)	2 (7.1)		0.491 [c]
Additional laxative drug requirements, n (%)				
Lactulose	0 (0.0)	2 (7.1)		0.491[c]
Milk of magnesia	0 (0.0)	1 (3.6)		0.500 [c]

[a] two sample t test, [b] chi square test, [c] Fisher's exact test
CI: confidence interval, SD: standard deviation

The Kaplan-Meier survival analysis of time to first flatus between groups is presented in Fig. 2. The respective median survival time to first flatus after surgery (50%) in the ginger group and control group was 26.5 hours (95%CI 21.1-32.5) vs 39.33 hours (95%CI 31.7-44.7, p = 0.007) and time to first defecation between groups is presented in Fig. 3, in which the respective median survival time to first defecation after surgery (50%) in the ginger group and control group was 44.7 hours (95%CI 42.0 to 47.6) vs 59.7 hours (95%CI 51.7 to 64.7, p = 0.012). There were no statistically significant differences between the ginger group compared to the control group regarding (a) length of hospital stay, (b) postoperative vomiting, (c) adverse events, and (d) additional antiflatulent/laxative drug requirements. Moreover, we found no serious adverse effects related to the use of ginger.

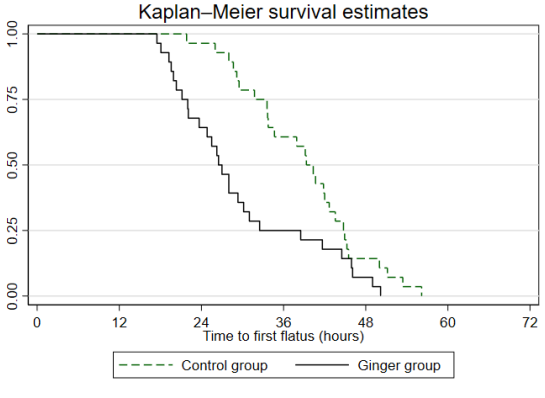

Fig. 2. The Kaplan-Meier survival analysis of time to first flatus.

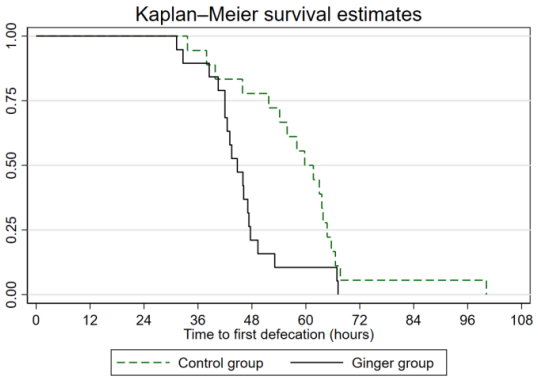

Fig. 3. The Kaplan-Meier survival analysis of time to first defecation.

Discussion

This study was a randomized, double blinded, placebo-controlled trial to evaluate the efficacy of oral ginger powder for prevention of postoperative bowel ileus in benign gynecologic abdominal hysterectomy. The study demonstrated that ginger enhanced the recovery of gastrointestinal function following surgery by significantly shortening the time to first flatus compared to that of the placebo group (29.5 ± 10.0 vs 38.9 ± 8.6 hours) and significantly reduced the time to first defecation in the ginger group more than in the placebo group (45.8 ± 9.1 vs 58.5 ± 14.7 hours). The average time to first flatus and defecation in the ginger group were shorter than those in the placebo group, which supports the hypothesis that oral ginger powder can effectively reduce postoperative bowel ileus in benign gynecologic hysterectomy. Based on the results of reducing POI, a possible explanation can be that the ginger increases gastrointestinal motility.

In contrast, Pongsupanimit et al[20] demonstrated that ginger supplementation did not significantly reduce the incidence of postoperative ileus (POI) or enhance bowel function recovery following hysterectomy under the Enhanced Recovery After Surgery (ERAS) protocol[20]. These differences may be attributed to several factors. First, early initiation of feeding and intervention differed between 3–4 hours after surgery in Pongsupanimit et al's study and 18–19 hours postoperation in our study. Early postoperative oral feeding has been shown to reduce POI by accelerating intestinal motility[19]. Second, the target population in our study was focused solely on patients with benign gynecological conditions undergoing total abdominal hysterectomy (TAH). At the same time, Pongsupanimit et al[20] included patients with benign or malignant gynecological conditions undergoing TAH or total laparoscopic hysterectomy (TLH). Malignant conditions often involve greater intestinal manipulation than benign conditions during surgery, which can affect bowel recovery. Third, anesthetic methods in Pongsupanimit et al[20] included patients receiving general anesthesia and/or spinal block with morphine, whereas our study included patients under general anesthesia. Indicating that various anesthetic methods can impact gastrointestinal recovery, leading to differing outcomes. However, the results of our study indicated a longer time to the first flatus compared to Pongsupanimit et al[20] findings, likely due to their use of the ERAS protocol, which has been shown to promote a rapid return of bowel function[21].

Our research findings were similar to those of Tianthong et al[17]. Their previous study showed that oral ginger powder can relieve abdominal distention after cesarean sections under spinal anesthesia. Despite these differences in types of surgery and anesthesia, both studies found that ginger effectively reduced postoperative abdominal distention.

A systematic review and meta-analysis18 of fourteen clinical trials showed the beneficial effects of ginger on postoperative nausea and vomiting, which

is one symptom of POI, and ginger is widely used as an antiemetic and is effective in reducing postoperative nausea and vomiting and relieving nausea and vomiting in pregnancy. Our study showed that postoperative vomiting tended to be less in the ginger group, even though not statistically significant. These results differed from another meta-analysis[19] that reported ginger significantly preventing postoperative nausea and vomiting, perhaps explained by differences in types of operation, dosage of ginger administration and time to start diet. The difference in the dosage and schedule of this study and the systematic review and meta-analysis Chaiyakunapruk et al[19] was that the administration of at least 1 gm of ginger one hour before the induction of anesthesia was found to prevent postoperative vomiting (POV). Therefore, the administration schedule before an operation can be a crucial factor for the most potent efficiency of ginger in preventing POV. Additionally, there was a low incidence of vomiting in this study, and the optimal sample size was calculated according to the primary outcome, the time of the first flatus. Therefore, further research on the effectiveness of postoperative administration of ginger on POV in patients who undergo TAH may be required.

However, the length of hospital stay was not significantly different between the two groups. The explanation may be that the POI symptoms in these patients did not induce serious events. All the patients presented mild discomfort symptoms of bloating and flatulence, which can be relieved by ginger and additional antiflatulence medicine. Moreover, the objective of this research was to study patients with benign gynecologic conditions who underwent TAH without serious intraoperative events, including bowel injury. Therefore, the effect of ginger on these POI symptoms did not directly impact the length of hospital stays.

The strength of this study was that it is the first randomized, double blinded, placebo-controlled trial of time to first flatus and defecation, which are two clinical symptoms of POI.

There were some limitations of this study. First, it was carried out at a single center. Second, the study was conducted within a group with benign gynecologic conditions.

However, we suggest that further research on the use of ginger powder should be conducted in relation to other POI symptoms and under other gynecologic conditions in order to generalize its efficacy.

Conclusion

The administration of postoperative oral ginger powder, at a dose of 500 milligrams per capsule, two capsules after meals three times a day, continued for three days after surgery, could prevent POI by enhancing bowel motility, which decreased the time to first flatus and defecation. Thus, oral ginger powder can be used a treatment to prevent POI in benign gynecologic abdominal hysterectomy that has no serious adverse events. Ginger may therefore be used as an alternative method in the prevention of POI in post-hysterectomy patients.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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