ประสิทธิภาพของการใช้ยาทา lidocaine prilocaine cream เปรียบเทียบกับการฉีดยาเฉพาะที่ 2% lidocaine ในการลดความเจ็บปวดของแผลฝีเย็บหลังการคลอดบุตร: การศึกษาทดลองแบบสุ่มมีกลุ่มเปรียบเทียบ

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาเปรียบเทียบประสิทธิภาพของการใช้ยาทาเฉพาะที่ Lidocaine-Prilocaine cream และการฉีด 2% Lidocaine HCL ในการลดความเจ็บปวดแผลฝีเย็บหลังการคลอดบุตร

วัสดุและวิธีการ: ในช่วง 24 กันยายน 2022 ถึง 4 ธันวาคม 2022 พบหญิงตั้งครรภ์จำนวน 779 ราย มาที่ห้องคลอด โรงพยาบาลสรรพสิทธิประสงค์ด้วยอาการเจ็บครรภ์คลอด หลังจากการคัดออก หญิงตั้งครรภ์จำนวน 42 ราย เข้าสู่การศึกษา และถูกแบ่งเป็นสองกลุ่มโดยสุ่ม เพื่อให้ได้รับ 1) 2%Lidocaine HCL ชนิดฉีด (N=21) หรือ 2) lidocaine prilocaine cream ชนิดทาเฉพาะที่ โดยอาสาสมัครที่ได้เข้ากลุ่ม 2% Lidocaine HCL ชนิดฉีดจะได้รับการฉีดยาที่ฝีเย็บตามแนวของแผลฝีเย็บที่จะตัดด้วย 10 มิลลิลิตรของ 2% Lidocaine HCL 5 นาทีก่อนการตัดฝีเย็บ และอีก 10 มิลลิลิตร ฉีดที่แผลฝีเย็บหลังการคลอดบุตร ส่วนอาสาสมัครในกลุ่ม lidocaine prilocaine cream จะได้รับการทายา 10 กรัม ด้านนอกของบริเวณฝีเย็บเป็นพื้นที่ 10 ตารางเซนติเมตร ขณะปากมดลูกเปิดตั้งแต่ 9 เซนติเมตร เป็นต้นไป และทายาอีกครั้งด้วย 10 กรัม lidocaine prilocaine cream ตามแนวของแผลที่ช่องคลอดด้านในและผิวหนังที่แผลฝีเย็บทางด้านนอกหลังการตัดฝีเย็บและคลอดบุตร ลักษณะพื้นฐานของประชากรและข้อมูลทางคลินิกของอาสาสมัครจะถูกบันทึก ผลการศึกษาเช่นคะแนนความเจ็บปวดจะถูกประเมินด้วย มาตรวัดความเจ็บปวดด้วยสายตา (VAS) ขนาด 10 เซนติเมตร ทันทีหลังจากการเย็บแผลฝีเย็บ และที่ 6, 12, 18 และ 24 ชั่วโมงหลังคลอด รวมถึงความต้องการยาแก้ปวดเพิ่มเติม ระยะเวลาหลังคลอดที่เริ่มขอยาแก้ปวดครั้งแรก และระดับของการรบกวนชีวิตประจำวัน ระดับของความวิตกกังวล และระดับของความพึงพอใจเพื่อนำมาเปรียบเทียบระหว่างกลุ่ม

ผลการศึกษา: อาสาสมัครทั้งหมดเป็นหญิงตั้งครรภ์ที่เคยคลอดบุตรมาแล้วอย่างน้อย 1 ครั้งจำนวน 42 ราย อายุครรภ์ตั้งแต่ 37-42 สัปดาห์ เป็นครรภ์เดี่ยว ทารกอยู่ในท่าศีรษะ ที่นำเข้ามาศึกษานั้น พบว่าลักษณะทางคลินิก ลักษณะทางสูติศาสตร์ และความก้าวหน้าของการคลอดไม่แตกต่างกันในอาสาสมัครทั้งสองกลุ่ม โดยอาสาสมัครทุกรายคลอดทางช่องคลอด ได้รับการตัดฝีเย็บแบบ mediolateral เพื่อช่วยในการคลอดศีรษะทารก และมีการฉีกขาดของแผลฝีเย็บระดับที่สอง พบว่าระดับคะแนนความเจ็บปวดในกลุ่ม lidocaine prilocaine cream มีคะแนนต่ำกว่ากลุ่มที่ได้รับยา

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ฉีด lidocaine ที่เวลา 6, 18 และ 24 ชั่วโมงหลังคลอด แต่ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ณ เวลาหลังสิ้นสุดการเย็บซ่อมแผลทันที และที่ 12 ชั่วโมงหลังคลอด ทั้งนี้ไม่รายงานของภาวะตกเลือดหลังคลอด การติดเชื้อแผลฝีเย็บ หรือผลข้างเขียงจากยาที่ใช้ในการศึกษา ไม่พบว่ามีความแตกต่างกันของน้ำหนักทารกแรกคลอด และ Apgar score ที่ 1, 5, 10 นาทีของทารกระหว่างสองกลุ่ม รวมถึงไม่พบว่ามีการรายงานการเกิดภาวะแทรกซ้อนของทารกที่เกี่ยวข้องกับยาที่ใช้ในการศึกษา

สรุป: การใช้ยา lidocaine prilocaine cream ชนิดทาเฉพาะที่บริเวณแผลฝีเย็บมีประสิทธิภาพในการลดความเจ็บปวดของแผลฝีเย็บถึง 24 ชั่วโมง หลังคลอดโดยไม่พบภาวะแทรกซ้อนอย่างมีนัยสำคัญต่อมารดาและทารก

คำสำคัญ: Lidocaine ชนิดฉีด, Lidocaine prilocaine cream, แผลฝีเย็บ, การบรรเทาปวดหลังคลอด

Introduction

Vaginal delivery is the recommended route of delivery for uncomplicated term singleton pregnancy with the low rate of serious complications and the benefit of rapid recovery in postpartum period [1]. Episiotomy is a common procedure performed to assist fetal head delivery. It may help shortening of the second stage, thereby reducing maternal exhaustion, and blood loss, preservation of the pelvic floor, and may serve as a preventative strategy against levator ani disruption at the time of delivery [2]. Metanalysis showed that selective episiotomy may result in 30% fewer women experiencing severe perineal trauma, less blood loss at delivery, but no difference in Apgar score less than seven at five minutes, moderate or severe perineal pain, and perineal infection [3]. However, episiotomy and episiorrhaphy could cause disturbing perineal pain that might limit ability to take care of themselves and their babies; in addition, perineal pain at 4–6 weeks postpartum showed an increased risk for depression at 4–6 weeks and 6 months [4].

There are various analgesic methods using to relieve perineal postpartum either non-pharmacological or pharmacological methods [5]. The non-pharmacological methods included warm compress, cold compress, perineal massage [6], infrared irradiation, and sitz bath [7]. For pharmacological methods in relieving pain used in stepwise, from local anesthetic, non-opioid analgesics (e.g. acetaminophen or nonsteroidal anti-inflammatory drugs [NSAIDS]) and opioids (e.g. oral tramadol, parenteral morphine or fentanyl) [5]. Even though, the meta-analysis [8] showed no difference in pain relief when the topical anesthetic was compared with placebo, the local anesthetic with or without additional oral analgesic such as acetaminophen might achieve successful pain control without the opioid side effects such drowsiness, disturbance of daily-living activity, and constipation [9].

Since 1992, there are many trials demonstrated new route of anesthetic e.g., topical cream, gel, peel, cap to replace of injection in minor dermatologic surgery [10], minor procedures at genitalia [11-13] especially in pediatric population [14-16]. Lidocaine prilocaine (EMLA®) cream provides dermal anesthesia through the release of lidocaine and prilocaine from the cream into the epidermal and dermal layers of the skin and the vicinity of dermal pain receptors and nerve ending. The systemic absorption is very low and rarely to caused systemic toxicity. Both lidocaine and prilocaine stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses, thereby producing local anesthesia. The onset of Lidocaine-Prilocaine cream on female genital mucosa is 5-15 min and duration of action is 1-2 hours. The quality of anesthesia depends upon the application time and the dose [17].

For relief pain of episiotomy, local anesthetic infiltration was traditionally used for several decades with the purpose of relief pain during episiorrhaphy and a period of postpartum. However, the lidocaine injection

cause unavoidable pain while performing and might attribute to some harms if accidentally intravascular administration, so the topical anesthetic is another alternative administration. The earlier trials [18-20] using topical lidocaine prilocaine cream showed more favorable effect for pain relief when compared with placebo or anesthetic infiltration. More recent studies [21-23] using lidocaine prilocaine cream had no different pain-relieving effect when compared with lidocaine injection. In addition, there are studies [24,25] reported of using lidocaine prilocaine cream applying in mucosa to achieve faster onset without serious complications from systemic absorption.

This study aimed to compare the effects of topical lidocaine-prilocaine cream and 2% lidocaine injection for postpartum pain relief of episiotomy wound. The primary outcome was pain scores evaluated at immediately finish repairing, 6, 12, 18 and 24 hours postpartum. The secondary outcomes included need for additional analgesics, satisfaction, maternal and neonatal complications in low-risk pregnant women came with spontaneous labor in Sunpasitthiprasong Hospital. Findings from this study could provide pharmacological method to relieve episiotomy pain after delivery other than traditionally using of lidocaine injection.

Materials and methods

Setting and study population

The randomized controlled trial (RCT) was conducted from September 24th, 2022, to December 4th, 2022, at delivery room, Department of Obstetrics and Gynecology, Sunpasitthiprasong Hostipal, Ubon Ratchathani, Thailand. This study was registered at www.thaiclinicaltrials.org, September 20th, 2022 (TCTR20220920003) and was approved by the Sunpasitthiprasong Hospital Ethics Committee, September September 21st, 2022 (Ref. no 052/65 C).

There were 779 pregnant women, aged 18-40 years old, who were in labor admitted at delivery room during period of study. Multiparous women, with no underlying disease and no history of previous cesarean section, gestational age of 37-42 weeks, with singleton fetus in cephalic presentation who presented with spontaneous labor were eligible to the study. Participants were excluded if they had complications e.g., hypertensive disorder complicating pregnancy, placenta previa, prolapsed cord, non-reassuring fetal heart rate status, fetal abnormality, and genital lesions which vaginal delivery should be avoided. The written informed consent was obtained when the participants had a labor progression of 6-9 cm cervical dilatation. The women who delivered by instrumental vaginal delivery, had third- or fourth-degree perineum tear, had history of allergy to lidocaine or prilocaine, and do not voluntarily participate in the program were also excluded.

Randomization and interventions

After giving written informed consent, 42 participants were randomized into two groups according to the randomized sequence generated by block randomization. The allocated numbers were inserted into identical, opaque and sealed envelopes placed in delivery room.

The attending physicians or nurses opened an envelope to assign the participants to each group. The demographic data e.g., maternal age, education, address, occupational status, religion, medical treatment rights were obtained. The baseline clinical characteristics including gravidity, parity, gestational age, pre-pregnant and recent body mass index (BMI), total weight gain, number of antenatal care (ANC), gestational age at first ANC, antepartum complications, presenting symptoms, cervical dilatation at randomization were recorded. All participants would receive standard obstetric care during intrapartum period such as uterine contraction evaluation every 30 minutes, vaginal examination every 2 hours, and continuous fetal monitoring. Participants would receive prostaglandin E2 for ripening of cervix and oxytocin for augmentation as standard indications. Participants who had pain score of 8 or more would receive intravenous pethidine for analgesia.

Participants who were assigned to 2% lidocaine HCl infiltration were injected at perineum along the anticipated episiotomy site with 10 ml of 2% lidocaine 5 minutes before performing episiotomy. Another 10 ml of 2% lidocaine was injected at episiotomy wound, with frequently aspirations to avoid intravascular injection then wait for 5 minutes before repairing episiotomy. Participants who were assigned to topical lidocaine-prilocaine cream group were applied 10-gm cream at outside of 10 cm^2 area perineal area at 9 cm or more of cervical dilatation. Another application of 10 gm prilocaine-lidocaine cream was applied to the episiotomy wound either along the vaginal mucosal laceration and perineal skin after episiotomy and delivery of fetus, then wait for 5 minutes before start repairing. Episiotomy was done when participants reported as no pain when using of forceps to test analgesic effect. All mediolateral episiotomy was performed from the top of contraction when fetal head crowning. The standard spontaneous vertex delivery was performed with assisting delivery of fetal head and avoiding contact of cream to baby's eyes which might cause eye irritation. All perineal trauma was repaired with continuous locking suture to close vaginal mucosa; continuous suture to close muscular layer of perineum; subcuticular suture to close the skin with the same chromic catgut 2/0.

Outcomes ascertainment

The primary outcome was pain score at the time of immediately finishing epapisiorrhhy, at 6, 12, 18, and 24 hours postpartum. The secondary outcomes were need for additional analgesia, time to first request for additional analgesia, activity-disturbing effect, worrying level, and satisfaction. Pain score evaluated by using 10 cm visual analogue scale (VAS), where 0 cm means no pain and 10 cm means unbearable pain. The participants were asked to mark the point that best indicated the perception of her pain on the VAS by themselves. Activity-disturbing effect, worrying level, and satisfaction were evaluated into four categories (no effect, minimal, moderate, marked effect). Maternal outcomes included latent phase, active phase, second stage duration, estimated blood loss, episiotomy types, degree of perineal tear, suturing person, sutured time, postpartum complications e.g., postpartum hemorrhage, puerperal infection,

infected episiotomy wound, and maternal length of stay were recorded. The allergic effect and side effects of investigating drugs such as burning sensation, pruritus, erythema, edema at application site were observed. Neonatal outcomes e.g., birthweight, Apgar scores at 1, 5, 10 minutes, head circumference, meconium-stained amniotic fluid, neonatal complications e.g., delayed adaptive, meconium aspiration syndrome, neonatal infection and sepsis, neonatal jaundice, neonatal intensive care unit (NICU) admission, need of respiratory support by oxygen box or others. According to degree of perineal tear, first degree defined as superficial injury of vaginal mucosa and perineal skin, second degree defined as injury involving vaginal mucosa and perineal body, third degree defined as second degree laceration with anal sphincter involvement, and fourth degree defined as third degree laceration with rectal mucosa involvement. Postpartum hemorrhage defined as blood loss more than 500 ml in vaginal birth and 1000 ml in cesarean delivery. Data of using uterotonic and analgesic drugs were also obtained.

Statistical analysis

The sample size was calculated based on the study in Italy [18] which mean pain score (±standard deviation; SD) during perineal suturing was 1.7±2.4 in lidocaine prilocaine cream VS 3.9±2.4 in mepivacaine infiltration, with 80% power, 95% confidence interval, and 10% loss of follow up, a sample size of 21 participants in each group were required. An intention-to-treat analysis was used with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov normality test was used to determine the distribution of continuous data. Categorical data were reported as number (percent) and continuous data reported as means ± SD or medians (interquartile ranges; IQR). Continuous data were compared using independent t-test and Mann-Whitney U test for normally and non-normally distributed variables, respectively. Categorical data were compared using Chi-square test. A P-value of < 0.05 was considered statistically significant.

Results

A total of 779 women were presented with spontaneous labor at the delivery room of Sunpasitthiprasong Hospital during the study period. There were 609 women who did not meet inclusion criteria such as nulliparous, age less than 18 years old or more than 40 years old, preterm labor, postterm, multifetal gestation, previous cesarean section, and non-vertex presentation, leaving the participants of 170 eligible. After history review, there were 128 participants were excluded due to hypertensive disorder in pregnancy, cephalopelvic disproportion, genital warts, placenta previa, prolapsed cord, fetal distress, and fetal hydrocephalus. The total of 42 participants were randomized into two groups. There was no participant lost follow up during this trial, leaving a final study sample of 42 participants to analyze (Figure 1).

Figure 1: Flow chart of participant recruitment

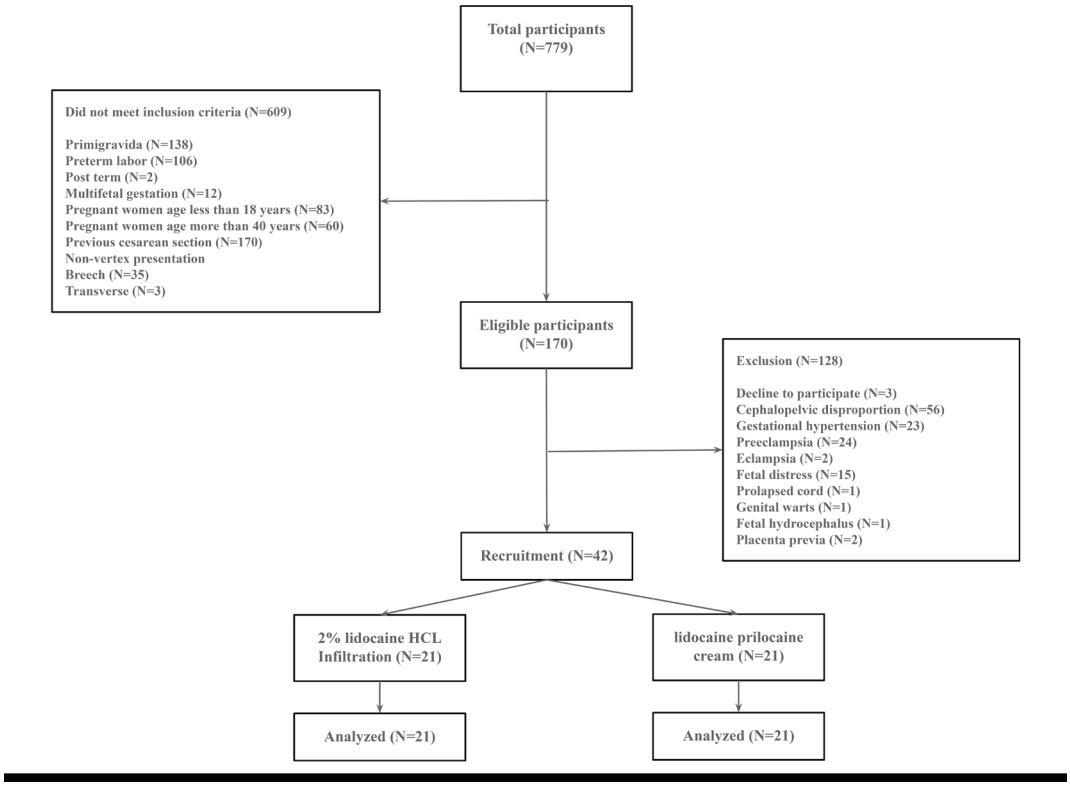


Table 1: Baseline characteristics of participants, by groups of intervention (N=42)

	Total (N=42)	2%lidocaine injection (N=21)	Lidocaine-prilocaine cream (N=21)	P value*
Age, year, mean±SD	29.36±5.8	29.29±6.4	29.43±5.4	0.938
Education, n (%)				0.471
- Primary school	2 (4.8)	1 (4.8)	1 (4.8)	
- Secondary school	26 (61.9)	14 (66.7)	12 (57.1)	
- Bachelor's degree	8 (19.0)	4 (19.0)	4 (19.0)	
- Master's degree or more	1 (2.4)	1 (4.8)	0 (0.0)	
- Vocational	5 (11.9)	1 (4.8)	4 (19.0)	
Medical treatment rights, n (%)				0.496
- Universal coverage	22 (52.4)	11 (52.4)	11 (52.4)	
- Social welfare	18 (42.8)	8 (38.1)	10 (47.6)	
- Government-pay	1 (2.4)	1 (4.8)	0 (0.0)	
- Self-pay	1 (2.4)	1 (4.8)	0 (0.0)	

	Total (N=42)	2%lidocaine injection (N=21)	Lidocaine-prilocaine cream (N=21)	P value*
Religion, n (%)				-
- Buddhism	42(100.0)	21(100.0)	21(100.0)	
Occupational status, n (%)				0.652
- Employed	34 (81.0)	17 (81.0)	17 (81.0)	
- Unemployed	8 (19.0)	4 (19.0)	4 (19.0)	
Antenatal care, n (%)				0.929
- Sunpasitthiprasong hospital	18 (42.9)	2 (28.6)	12 (57.1)	
- Other hospitals	21 (50.0)	12 (57.1)	9 (42.9)	
- Private clinic	3 (7.1)	3 (14.3)	0 (0.0)	
Number of antenatal visits, median (IQR)	10 (6.7,12.0)	10 (8.0,11.5)	10 (5.5,12.0)	0.929
GA at first ANC, weeks, mean±SD	14.38±4.1	14±3.3	14.7±4.8	0.556
Prepregnancy BMI, kg/m^2, mean±SD	22.1±3.4	21.2±3.4	22.9±3.4	0.104
Recent BMI, kg/m^2, mean±SD	25.9±3.9	25.7±4.3	26.1±3.5	0.713
Total weight gain, kg, mean±SD	10.5±4.3	10.4±4.4	10.7±4.3	0.836
Gravidity, median (IQR)	2.0 (2.0,3.0)	2.0 (2.0,3.0)	3.0 (2.0,3.0)	0.329
Parity, median (IQR)	1.0 (1.0,2.0)	1.0 (1.0,2.0)	1.0 (1.0,2.0)	0.670
Abortion, median (IQR)	0 (0,0)	0 (0,0)	0 (0,0)	0.220
Gestational age, weeks, median (IQR)	39.0 (38.0,40.0)	39.0 (38.0,40.0)	39.0 (38.0,39.5)	0.948
Presenting symptoms				
- Labor pain, n (%)	40 (95.2)	20 (95.2)	20 (95.2)	1.000
- Mucous bloody show, n (%)	8 (19.0)	5 (23.8)	3 (14.3)	0.697
- Membrane ruptured, n (%)	8 (19.0)	5 (23.8)	3 (14.3)	0.697
Initial cervical dilatation, cm, median (IQR)	4.0 (2.0,5.0)	4.0 (2.0,5.0)	4.0 (2.0,6.0)	0.703
Prostaglandin E2 administration, n (%)	5 (11.9)	2 (9.5)	3 (14.3)	1.000
Oxytocin administration, n (%)	13 (31.0)	7 (33.0)	6 (28.6)	0.739
Pethidine administration, n (%)	6 (14.3)	1 (4.8)	5 (23.8)	0.184

BW; body weight, BMI; body mass index

*P-value for comparison between the two treatment groups, using chi square test, independent t-test, and Mann-Whitney U test for categorical, normally and non-normally distributed continuous variable respectively.

Table 1 shows clinical and obstetric characteristics of participants, overall and by treatment groups. The demographic characteristic including age, education, occupational status, religion, medical treatment rights was comparable between groups. Obstetric characteristics including gravidity, parity, gestational age, pre-pregnant and recent BMI, total weight gain, number of ANC, gestational age at first ANC were comparable between groups. Intrapartum period, 95.2% of participants came with labor pain as a presenting symptom. With the median initial cervical dilatation of 4 cm, labor progression was comparable as demonstrated that latent phase, active phase, and second stage duration was not different between groups. There was no difference in administration of prostaglandin E2 for induction, oxytocin for augmentation and pethidine for sedation between groups. All participants vaginally delivered their neonates spontaneously without assisted operative procedure. After mediolateral episiotomy was done to assist fetal head delivery, all participants had second degree of perineal injury. All episiotomies were sutured by staffs, residents, or nurses without significant difference between groups. With the same technique of repair, the median suturing time was 13.5 minutes, and not different between groups.

Table 2 : Effectiveness of pain relief during postpartum of participants, by treatment groups (N=42)

	Total (N=42)	2% Lidocaine injection (N=21)	Lidocaine-prilocaine cream (N=21)	P value*
Pain score when finish repairing, mean±SD	3.2±2.7	4.6±2.9	4.0±2.6	0.524
Pain score at 6 hours after delivery, mean±SD	2.9±1.3	4.7±2.5	2.8±1.9	0.010
Pain score at 12 hours after delivery, mean±SD	2.9±1.5	3.8±2.4	2.6±1.9	0.080
Pain score at 18 hours after delivery, mean±SD	2.3±1.7	3.3±1.9	2.0±1.7	0.031
Pain score at 24 hours after delivery, mean±SD	1.43±0.96	2.8±1.6	1.1±0.8	<0.001
Need of additional analgesia, n (%)	10 (23.8)	4 (19.0)	6 (28.6)	0.469
Time to first additional analgesia, hours, mean±SD	15.3±7.5	15.0±7.5	15.5±8.2	0.925
Activity-disturbing effect, n (%)				0.676
- Not affected	7 (16.7)	3 (14.3)	4 (19)	
- Minimal affected	26 (61.9)	14 (66.7)	12 (57.1)	

	Total (N=42)	2% Lidocaine injection (N=21)	Lidocaine-prilocaine cream (N=21)	P value*
- Moderate affected	7 (16.7)	2 (9.5)	5 (23.8)	
- Marked affected	2 (4.8)	2 (9.5)	0 (0.0)	
Worrying level, n (%)				0.798
- No worrying	21 (50.0)	11 (52.4)	10 (47.6)	
- Minimal worrying	19 (45.2)	9 (42.9)	10 (47.6)	
- Moderate worrying	2 (4.8)	1 (4.8)	1 (4.8)	
- Marked worrying	0 (0)	0 (0)	0 (0)	
Satisfaction, n (%)				0.518
- Minimal satisfied	5 (11.9)	2(9.5)	3(14.3)	
- Moderate satisfied	13 (31.0)	9(42.9)	4(19.0)	
- Very satisfied	24 (57.1)	10(47.6)	14(66.7)	
Satisfaction level (scales of 0-4), median (IQR)	4.0 (3.0,4.0)	3.0 (3.0,4.0)	4.0 (3.0, 4.0)	0.355

*P-value for comparison between the two treatment groups, using chi square test, independent t-test, and Mann-Whitney U test for categorical, normally and non-normally distributed continuous variable respectively.

Figure 2 Pain scores evaluated at immediately finish episiorrhaphy, 6, 12, 18, and 24 hours postpartum, by treatment groups (N=42)

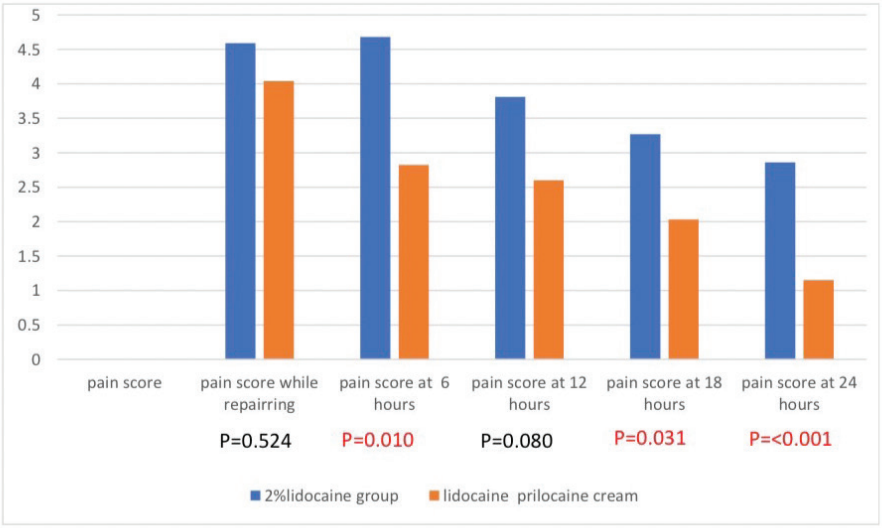


Table 2 shows that lidocaine prilocaine cream group had significant lower pain scores evaluated at 6, 18, and 24 hours postpartum when compared with lidocaine injection group but had no difference at immediately after finish suturing and 12 hours postpartum (Figure 2). There was comparable additional analgesic required at the median of 15 hours postpartum between groups. Most participants reported minimal disturbing-activity effects (61.9%), minimal worrying level (95.2%) and very satisfied experience (57.1%). There was no significant difference in disturbing-activity effect, worrying and satisfaction level evaluated at 24 hours postpartum. There was no report of side effects or allergy of investigating drugs in participants and their neonates.

Table 3 Maternal and neonatal outcomes, by treatment groups (N=42)

	Total (N=42)	2%Lidocaine injection (N=21)	Lidocaine-prilocaine cream (N=21)	P value*
Latent phase duration, minutes, median(IQR)	300 (180.0,480.0)	290 (180.0,450.0)	290.0 (180.0,450.0)	0.801
Active phase duration, minutes, median(IQR)	85 (33.7,142.5)	65 (30.0,145.0)	100 (35.0,155.0)	0.472
Second stage duration, minutes, median(IQR)	17.5 (8.0,20.0)	18.0 (7.5,20.0)	12 (9.0,31.0)	0.433
Perineal tear, n (%)				
- First degree	0	0	0	
- Second degree	42 (100)	21 (100)	21 (100)	
- Third and fourth degree	0	0	0	
Sutured person, n (%)				0.202
- Staff	1 (2.4)	1 (4.8)	0 (0)	
- Resident	12 (28.6)	8 (38.1)	4 (19.0)	
- Nurse	29(69.0)	12(57.1)	17(81.0)	0.202
Suture time, minutes, median (IQR)	13.5 (10.0, 20.0)	15.0 (10.0, 20.5)	11.0 (10.0, 20.0)	0.594
Blood loss, ml, mean±SD	145.5±74.5	131.1±60.9	160.0±85.1	0.215
Maternal length of stay, days, median (IQR)	2(2,3)	2(2,3)	2(2,3)	0.439
Neonatal birthweight, grams, mean±SD	3028.0±252.0	3125.0±410.5	3073.3±249.8	0.090
Neonatal head circumference, cm, median (IQR)	33.0 (32.0,34.0)	33.0 (32.0,34.0)	32.5 (32.0,34.0)	0.654
Apgar at first minute, median (IQR)	9.0 (8.8,9.0)	9 (8.5,9.0)	9 (8.5,9.0)	0.932
Apgar at 5 minutes, median (IQR)	10 (10,10)	10 (10,10)	10 (10,10)	1.000

	Total (N=42)	2%Lidocaine injection (N=21)	Lidocaine-prilocaine cream (N=21)	P value*
Apgar at 10 minutes, median (IQR)	10 (10,10)	10 (10,10)	10 (10,10)	1.000
Neonatal ward, n (%)				0.606
- Stay with mother	38 (90.5)	18 (85.7)	20 (95.2)	
- Pediatric ward	4 (9.5)	3 (14.3)	1 (4.8)	
Neonatal length of stay, median(IQR)	3 (2,3.3)	3 (2,3.5)	3 (2, 3.5)	0.574
Neonatal complication, n (%)	5 (11.9)	4 (19.0)	1 (4.8)	0.343
- Delayed adaptation	1 (2.4)	1 (4.8)	0 (0.0)	
- Omphalitis	1 (2.4)	1 (4.8)	0 (0.0)	
- Jaundice	2 (4.7)	1 (4.8)	1 (4.8)	
- Meconium aspiration syndrome	1 (2.4)	1 (4.8)	0 (0.0)	
Respiratory support via oxygen box, n (%)	4 (9.5)	3 (14.3)	1 (4.8)	0.606

*P-value for comparison between the two treatment groups, using chi square test, independent t-test, and Mann-Whitney U test for categorical, normally and non-normally distributed continuous variable respectively.

Table 3 shows delivery outcomes. Postpartum maternal complications were comparable between groups as demonstrated that estimated blood loss and length of stay were not significantly different, with no report of puerperal infection or episiotomy wound infection. For neonatal outcomes, the birthweight of neonates was not different between groups with the mean of 3028 grams. The median Apgar scores at 1, 5, 10 minutes were 9, 10, 10, respectively, and not significantly different between groups. Most of neonates (90.5%) with no complication stayed with mother until discharge in 3 days. There were 5 neonates had minor neonatal complications such as delayed adaption, omphalitis, jaundice, meconium aspiration, and 4 neonates required respiratory support with oxygen box. However, there was no significant difference in neonatal complications between groups.

Discussion

In this two-arm paralleled-group randomized controlled trial, topical lidocaine prilocaine provided better pain relief of episiotomy wound within 24 hours postpartum when compared with lidocaine injection. This trial could demonstrate significant effect of topical lidocaine prilocaine to relieve episiotomy pain at 6 hours, 18 hours, and 24 hours postpartum. However, topical lidocaine prilocaine could not show significant effect in other aspects such as additional analgesic required, pain-disturbing activity effect, worrying level, and satisfaction level.

Although, vaginal delivery accompanying with episiotomy accounted for more than half of total route of delivery in Thailand, management of postpartum pain regarding to perineal pain was a relatively neglected area of clinical research. There were many factors [9] attributing to perineal pain following vaginal delivery with episiotomy such as instrumental-assisted delivery, type of episiotomy, degree of perineal tear and anal sphincter involvement, duration of suturing, technique of suturing [26], suture material used [27], and maternal experience. This study included only multiparous participants who experienced at least once vaginal delivery, delivered spontaneously, and had second degree perineal tear. All participants were sutured in the same technique, and same suture material, with non-significant different suturing duration.

Even though, local anesthesia by injection of lidocaine remains a main stay for pain relief of perineal pain during episiorrhaphy and postpartum for several decades, topical form of anesthetics has emerged as an alternative for many minor operations especially dermatological operations and pediatric surgery [10, 14-16]. Despite its price and its availability in all hospitals, lidocaine infiltration had some disadvantages such as unavoidable pain during administration, need skilled-operator, cause tissue edema, and increase risk of toxicity if accidentally intravascular injection. The advantages of topical lidocaine prilocaine cream included the localized action with negligible systemic absorption, ease of administration, painless application, and absence of edema that distorts wound margins in repairs. In addition, recent studies [12,24] supported safe use of lidocaine prilocaine cream for mucosal anesthesia. Furthermore, lidocaine prilocaine cream exerted only local effect, had no neonatal risk from systemic absorption, could use as conjunction of paracetamol or nonsteroidal anti-inflammatory drugs (NSAID) for pain relief postpartum, and could limit opioid use for breakthrough pain when analgesia becomes inadequate.

The anesthetic effect of lidocaine prilocaine cream depends upon the application time and the dose [17], its effect to relieve pain postpartum still be investigated. For its effect at the time of suturing, the previous data still inconclusive [8,18-23]. In this study, we could not demonstrate significant effect when compared with standard infiltration of lidocaine. This might be explained that lidocaine prilocaine cream has rapid absorption through genital mucosa, so it should be applied at least one hour before procedure [28]. This study shows the significant pain reliving effect at 6 hours postpartum but could not show significant efficacy at 12 hours postpartum which were different from previous study [19]. This might be due to only one-time applying and increased participants' activities such as walking and nursing baby. Furthermore, the pain at 12 hours postpartum might have other sources such as uterine contraction which response to NSAID or complicated external hemorrhoid that nonpharmacological methods e.g., cold pack, sitz bath, and laxative should be added. Furthermore, the significant effect of lidocaine prilocaine cream at 18, and 24 hours postpartum might result from multiple factors including the additional analgesic which approximately 15 hours in this study.

Pain is a complex nervous system function providing the body a signal of potential or actual injury. Human experience of pain is a mixture of physical, cognitive, emotional factors influenced not only by the source of pain but also by factors such as fear and previous experience with pain [9]. Oxytocin can also act as an inhibitory neurotransmitter [29] and may help reduce the amount of pain during lactation. This might explain the findings in this study that showed significant pain relief at 18 and 24 hours postpartum.

Previous systematic review [30] found that more women experienced pain relief with paracetamol compared with placebo. This finding consistent with this study that additional one-dose paracetamol was request for analgesia at mean time of 15 hours postpartum. Although, there is no difference in pain-disturbing activity, the muscles in the perineum are involved in daily walking, bending down, squatting, urination, and excretion. The participants in this study favor of lidocaine prilocaine cream which consistent with previous study [21]. This mainly cause by its easy use, and pain-free administration.

Our study was among the first studies in Thailand examining the effect of lidocaine prilocaine cream for postpartum perineal pain relief, using vigorous randomized control trial design with complete follow-ups and a standard intention-to-treat analysis. However, a few limitations should be considered. First, there might have other factors affecting outcomes that did not mention in this study. Second, even sample size is adequate to answer the main objective, more participants should be included for answer other objectives. Lastly, it was not possible to blind participants and healthcare providers due to the nature of intervention, systematic difference in co-interventions between treatment groups (performance bias) may be possible.

According to the benefit of lidocaine prilocaine cream, it might be considered as an alternative analgesic used postpartum. The proper dose and timing of administration cream for 3rd or more perineal tear remained unknown. Further research might focus on its appropriate dose, and its effect for relief postpartum pain in comparison with other novel topical analgesics that used in other surgery.

Conclusion

Topical lidocaine-prilocaine cream applying at episiotomy wound was effective in pain relief of episiotomy wound in 24 hours postpartum without significant maternal and neonatal complications.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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