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Acetaminophen/tramadol Rectal Suppository for the Relief of Perineal Pain after Normal Vaginal Delivery: A randomized controlled trial

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ABSTRACT

Objectives: To compare the effectiveness of acetaminophen /tramadol rectal suppository and placebo for pain relief after vaginal delivery

Materials and Methods: Two hundred parturients who delivered vaginally were recruited. Twelve cases were excluded. Cases were randomly divided into two groups; study and control group. Acetaminophen/tramadol was given to the study group and placebo in control group immediately after vaginal delivery. Pain level was measured by visual analogue scale (VAS) at immediate, 6, 12 and 24 hours after delivery. Side effects and additional analgesic medication (acetaminophen) were recorded.

Results: A total of 188 parturients were enrolled. Study and control groups consisted of 98 and 90 cases, respectively. Mean age of cases in this study was 27 years old. Forty percent of cases were nulliparous. All subjects were full term pregnancy with normal body mass index and equally demographic character. Pain score measured by VAS in both groups had no significant difference at all times (0, 6, 12 and 24 hours after delivery). There was no adverse event in this study.

Conclusion: Acetaminophen/tramadol rectal suppository could not relieve perineal pain after normal vaginal delivery when comparing to placebo.

Keywords: acetaminophen/tramadol, pain, vaginal delivery, rectal suppository

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ประสิทธิภาพของยาอะเซตามิโนเฟน/ทรามาดอลเหน็บทางทวารหนักเพื่อลดอาการปวดแผลฝีเย็บในมารดาที่คลอดปกติทางช่องคลอด โดยวิธีการแบบสุ่มและมีการควบคุม

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บทคัดย่อ

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการใช้ยา acetaminophen/tramadol เหน็บทางทวารหนักในมารดาหลังคลอดปกติทางช่องคลอด เพื่อลดอาการปวดแผลฝีเย็บ เปรียบเทียบกับการใช้ยาหลอก*

วัสดุและวิธีการ: *ทำการศึกษาในสตรีตั้งครรภ์ครบกำหนดที่คลอดปกติทางช่องคลอดจำนวน 200 ราย ซึ่งถูกคัดออกเพิ่มเติม 12 ราย ตามข้อบ่งห้ามของการศึกษา นำผู้เข้าร่วมการวิจัยแบ่งโดยสุ่มออกเป็น 2 กลุ่ม กลุ่มที่ทำการศึกษาได้รับยาแก้ปวดอะเซตามิโนเฟน/ทรามาดอล ทางทวารหนักหลังคลอด ประเมินความปวดโดยวัดเป็นคะแนน visual analogue scale เทียบกับกลุ่มที่ได้ยาหลอก ที่เวลาหลังคลอดทันที 6, 12 และ 24 ชั่วโมงหลังคลอด รวมทั้งเก็บข้อมูลถึงผลข้างเคียงของยาที่ใช้ และจำนวนยาแก้ปวด (อะเซตามิโนเฟน) ที่ขอเพิ่มในแต่ละกลุ่ม*

ผลการศึกษา: *จำนวนผู้เข้าร่วมการศึกษาทั้งหมดจำนวน 188 ราย แบ่งเป็นกลุ่มศึกษา 98 ราย และกลุ่มควบคุม 90 ราย อายุเฉลี่ยของผู้เข้าวิจัยคือ 27 ปี เป็นหญิงตั้งครรภ์แรกคิดเป็นร้อยละ 40 ทุกรายที่เข้าร่วมการศึกษาเป็นหญิงที่ตั้งครรภ์ครบกำหนดทั้งหมด และมีข้อมูลประชากรทั่วไปไม่แตกต่างกันในทั้ง 2 กลุ่มทดลอง คะแนนความปวดที่ประเมินที่ช่วงเวลาหลังคลอดทันที 6, 12 และ 24 ชั่วโมง หลังคลอดของทั้งกลุ่มศึกษาและกลุ่มควบคุมไม่มีความแตกต่างอย่างมีนัยสำคัญ ในการศึกษานี้ไม่พบภาวะข้างเคียงที่ไม่พึงประสงค์*

สรุป: *อะเซตามิโนเฟน/ทรามาดอลเหน็บทางทวารหนัก ไม่สามารถระงับความปวดฝีเย็บหลังคลอดปกติทางช่องคลอด เมื่อเทียบกับกลุ่มที่ได้รับยาหลอก*

คำสำคัญ: *อะเซตามิโนเฟน/ทรามาดอล, ความปวด, คลอดปกติทางช่องคลอด, ยาเหน็บทางทวารหนัก*

Introduction

Vaginal delivery is the natural birth process. These days natural birth canal injury is mostly prevented by episiotomy. Episiotomy in vaginal birth causes postpartum pain to the new mother. The depth of episiotomy cut causes various degree of pain. It disturbs the parturient's ambulation, newborn care and lactation[1]. There are many methods for pain relief. Cold packing is commonly used for non-medical postpartum pain relief. Acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed medicine for pain relief. If the pain is more than usual, opioid-derivatives would then be considered for the patients[1].

The most commonly used medication for pain relief after vaginal delivery is acetaminophen, a non NSAIDs pain reliever. It is a good option for analgesia in nursing mothers because of its safety, but it has less efficacy than NSAIDs[1]. Although NSAIDs are known for their effectiveness in pain control, however, they are excreted in breast milk and might have physiologic effect on the newborns. Gastric irritation is the common effect of NSAIDs in lactating mothers especially in those who were emptying gastric contents during their parturition[2].

Tramadol, a weak opioid agent, has adequate effectiveness for moderate pain control. However, its active metabolite, O-desmethyltramadol, is questioned for its side effect when received by newborn. A serious side effect of tramadol active metabolite is neonatal abstinence syndrome (opioid withdrawal syndrome). It usually occurs in newborns that have prenatal history of maternal opioid usage. This condition is a subject of concern in postpartum women who use opioid during lactation. However, Ilett's work showed that the amount of tramadol excreted via breast milk was very low. No adverse effect was observed in the infant. So, tramadol was acceptable for pain control in postpartum women[3-4]. The use of tramadol was reported in combination with acetaminophen for postoperative pain relief. Synergistic effect of this combination resulted in decreased dosage of opioid derivative[5].

Fixed combination of acetaminophen (325 mg)/tramadol (37.5) (Ultracet®, Janssen-Cilag, USA) was used in this study. The peak blood level of oral form tramadol and acetaminophen are 64.3 and 4.2 ng/mL. Time to peak blood level and half-life are 0.9-1.8 and 2.5-5.1 hours, respectively[6]. For rectal suppository of the tramadol, an absolute bioavailability was 77% (95% confidence interval of 70.8-83.6%)[7]. The peak serum concentration of tramadol rectal administration was 2 to 6 hours and its half-life was 5.7±1.0 hours[7]. For acetaminophen rectal suppository, the study showed that time to peak plasma concentration was 2 hours. The rectal bioavailability was 78% (95% confidence interval of 55-101%). The serum concentration of acetaminophen can be detected for 6 hours[8].

In birthing mother, after perineorrhaphy was done, doctors routinely perform digital rectal examination to make sure that suture material was not perforated in to rectum. We proposed that there was an opportunity to give patients rectal suppository analgesic medication to relief postpartum pain. Rectal administration of tramadol in its commercial suppository preparation gave more rapid therapeutic effect in its oral administration. This finding may be from the absent of first-pass metabolism of tramadol via rectal administration[7].

This study aimed to evaluate the perineal pain control efficacy by fixed combination of acetaminophen (325 mg) and tramadol (37.5 mg) via rectal suppository route in women who underwent episiotomy and perineorrhaphy after vaginal delivery.

Materials and Methods

The study was approved by Human Research Ethics Committee of Thammasat University (COA 064/2559, RCT).

The cases were recruited from healthy singleton parturients who underwent natural vaginal delivery at Thammasat University Hospital (TUH) between February and April 2017. The participants were between 18-40 years old. Inclusion criteria

were gestational age at least 37 completed weeks, and the degree of episiotomy vaginal laceration between 2 and 3. All subjects signed informed consent after counseling. Exclusion criteria were the first and the forth degree of vaginal lacerations, complication of episiotomy wound, any underlying disease of liver or kidney, acetaminophen or tramadol allergic history and patients who refused to take part in this study.

For sample size calculation, we chose Pandleton's study[9] because this research studied about perineal pain control after acetaminophen/tramadol usage. Sample size that calculated from this study was 83.9 cases as that can be rounded up to 85 cases in each group.

Two hundred cases that met the inclusion criteria were recruited in this study. The population was divided into two groups, study and control. The study design was a double-blind randomized controlled trial. Group member selection was performed during childbirth using prepared computer generated number in sealed opaque envelop. The sealed envelope was opened when the cases was in the second stage of labor.

All subjects received 10 mL of 1% lidocaine via local infiltration at perineorrhaphy site after birth immediately before suturing. The study group received combination of acetaminophen/tramadol tablet (325/37.5 mg, Ultracet®, Janssen-Cilag, USA) via rectal suppository. The control group received placebo in the same manner as the study group. Placebo agent was 1000 mg of vitamin C (1000 mg, ACORBIC®, JP natural, USA). It had a similar appearance to acetaminophen/tramadol tablet. The pills were administered immediately after perineorrhaphy completion by physicians who completely performed perineorrhaphy. Routine practice of postpartum care, namely regular vital signs measurement, bleeding observation and administration of oral acetaminophen tablet as requested were provided to the new mothers. Pain score was evaluated at 0, 6, 12 and 24 hours postpartum. Time "0" is start form the completion of episiotomy wound repair. We used visual analogue scale (VAS) for perineal pain. The score was from 0 to 10. The participants were evaluated by structural questionnaire nurse who did not know the type of analgesia. Amount of additional analgesics provided and side effects were recorded.

Data were analyzed using statistical software package SPSS (v 23 SPSS Inc, Chicago, IL, USA.) Continuous data was analyzed by using mean and unpaired t-tests. Chi-square tests were used for categorical data. Level of statistical significant was set at p value < 0.05.

Results

Two hundred parturients were enrolled during the study period. (Fig. 1.) Twelve cases were excluded from the study after exclusion criteria. The study and control group consisted of 98 and 90 cases, respectively. Mean age of both groups were 27 years old. Forty percent of cases were nulliparous. All cases were full term pregnancies with normal body mass index (BMI).

Housewives and office workers both comprised one quarter of the participants (Table 1). Forty percent of cases had monthly income less than 10,000 Baht. One-fifth of cases had higher education than bachelor degree level. Fourteen and eighteen percent of subjects graduated primary school degree in control and study group, respectively. The percentage of diabetes mellitus, hypertension and anemia in both groups had no statistical difference (Table 1). Most cases underwent mediolateral episiotomy. Average newborn weight was three kilograms. Average inner and outer wound lengths were around 7 centimeters. Estimated blood loss was 180 ml and perineorrhaphy time was 30 minutes.

Median of pain score (50th percentile) at 0, 6, 12 and 24 hours after delivery were the same in both groups (4, 3, 3 and 2, respectively) as shown in Table 2. We categorized subjects in to 2 groups of nulliparous and multiparous parturient, but there was no statistical differences. There was no reported of side effect of analgesic used in this study. Eleven

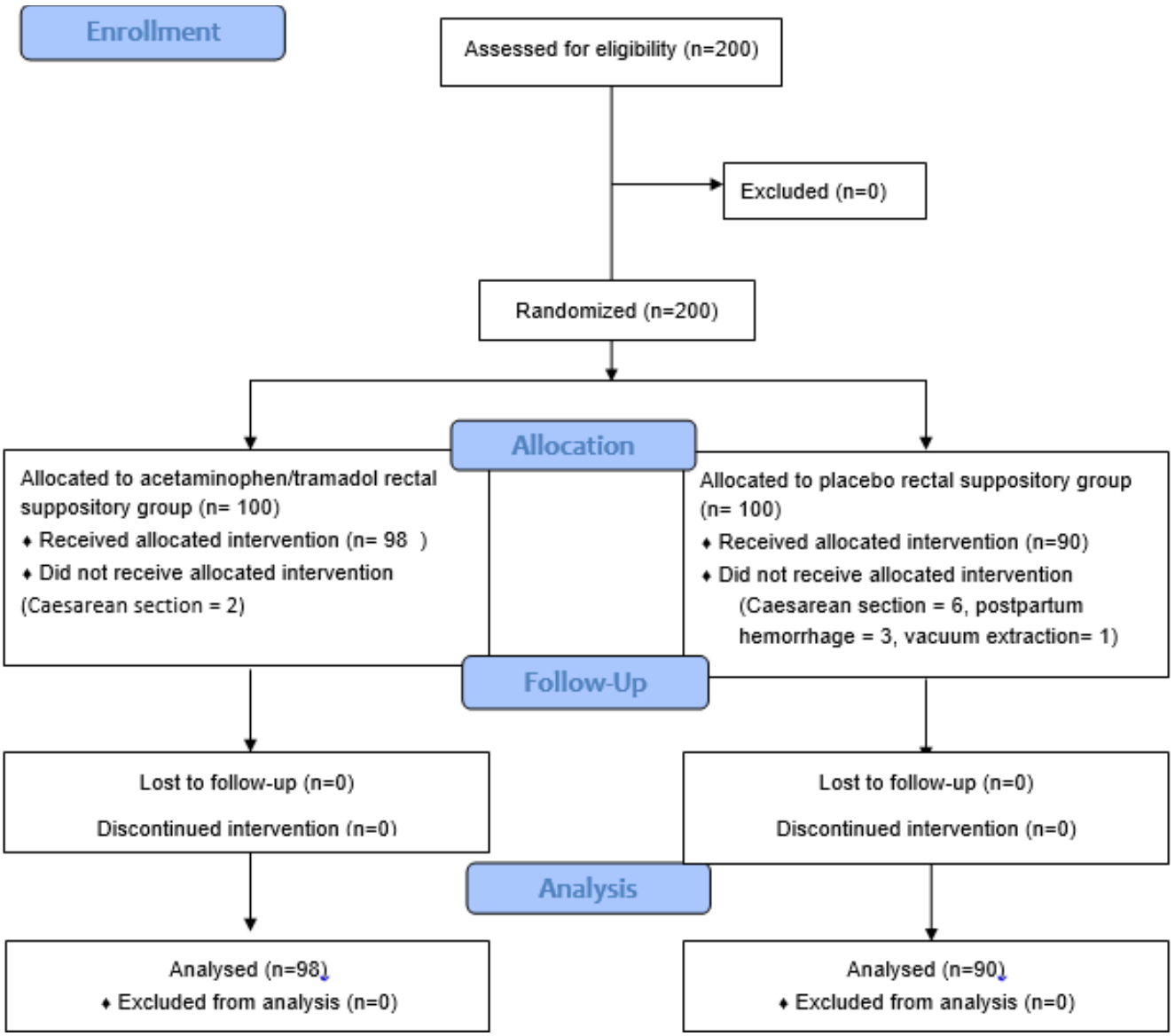

Fig. 1. Participants flow diagram.

patients requested one tablet of 500 mg acetaminophen for additional rescue analgesia (at 6-hours after delivery). Two patients requested two tablets of 500 mg acetaminophen (at 12-hours after delivery).

Discussion

Tramadol is a commonly prescribed drug to treat mild to moderate pain. It is a synthetic opioid of the benzenoid class. O-desmethyltramadol is a metabolite product of tramadol. It gives a better pain relief effect than its precursor[10]. This study was conducted on immediate postpartum women with single application of acetaminophen/tramadol combination to bypass tramadol excretion via breast milk.

During parturition, pregnant subjects were voided of any oral consumption. This protocol was to prevent any gastric aspiration. The Mendelson's syndrome was

Table 1. Demographic data.

Characteristics	group		p value
	control (n=90)	study (n=98)	
Age (years)*	27.5 ± 5.5	27.68 ± 5.6	0.86
Parity#	1 (0-3)	1 (0-3)	0.80
GA (weeks)*	38.04 ± 1.0	38.71 ± 1.0	0.94
BMI (kg/m^2)*	21.8 ± 3.3	21.9 ± 3.2	0.76
ANC risk**			
DM	7 (7.7)	9 (9.2)	0.42
HT	2 (2.2)	2 (2.0)	0.65
Anemia	4 (4.4)	5 (5.1)	0.73
Occupation**			0.07
House wife	23 (25.6)	24 (24.5)	
Own business	14 (15.5)	19 (19.4)	
Employee	46 (51.1)	48 (49.0)	
Government officer	7 (7.8)	7 (7.1)	
Income (Bath/month)**			0.35
≤ 10,000	39 (43.3)	40 (40.8)	
> 10,000	51 (56.7)	58 (59.2)	
Education**			0.70
Primary school	13 (14.5)	18 (18.3)	
Secondary school	31 (34.4)	28 (28.6)	
High school	29 (32.2)	32 (32.7)	
Bachelor or higher	17 (18.9)	20 (20.4)	

* : mean ± standard deviation (SD), # : Median (50th percentile) with range, GA : gestational age, BMI : body mass index, ANC: antenatal care

** n(%), DM: diabetes mellitus, HT: hypertension

a possible serious phenomenon for lung aspiration from gastric content[11]. Rawal et al reported that fixed tablet combination of acetaminophen (325 mg) and tramadol (37.5 mg) given orally had a comparable effect to tramadol 50 mg and less side effect in orthopedic hand surgery cases[12]. The study proved that combination of these two drugs had synergistic efficacy for pain control and allowed the use of smaller dosage of opioid.

The fixed combination of acetaminophen/tramadol was chosen in this investigation for postpartum pain relief. Rectal administration of tramadol in its commercial suppository preparation gave the more rapid therapeutic effect than the oral administration of tramadol, possibly from the absent of first-pass metabolism of tramadol via rectal administration[7].

Rectal administration of oral NSAIDs tablet in immediate postpartum women were reported by a few groups of researchers[13-15]. Achariyapota's and

Table 2. Clinical characteristic of labor and VAS.

Characteristics	group				p value
	control (n=90)		study (n=98)		
Sutured time (min)*	26.9 ± 18.3		31.1 ± 21.2		0.17
Baby birth weight (g)*	3058.7 ± 365.1		3041.9 ± 350.6		0.76
Episiotomy type**					
Median	4 (4.4%)		5 (5.1%)		0.57
Mediolateral	86 (95.6%)		93 (94.9%)		
Wound Length (cm)*					
Inner	3.3 ± 1.2		3.2 ± 1.2		0.51
Outer	3.5 ± 0.9		3.5 ± 0.9		0.84
Degree of laceration**					
Second degree	87 (96.7%)		96 (98.0%)		0.621
Third degree	3 (3.3%)		2 (2.0%)		
EBL (ml)*	183.8 ± 71.9		182.3 ± 81.5		0.89
Pain score (VAS)$^{\int}$					
Immediate	4 (0-10)		4 (0-10)		0.81
6-hours	3 (0-7)		3 (0-7)		0.33
12-hours	3 (0-5)		3 (0-5)		0.85
24-hours	2 (0-8)		2 (0-5)		0.36
Pain Severity**					
	PS < 4	PS ≥ 4	PS < 4	PS ≥ 4	
Immediate	41 (45.6%)	49 (54.4%)	48 (48.9%)	50 (51.1%)	0.64
6-hours	54 (60%)	36 (40%)	56 (57.1%)	42 (42.9%)	0.87
12-hours	72 (80%)	18 (20%)	76 (77.5%)	22 (22.5%)	0.86
24-hours	79 (87.8%)	11 (12.2%)	83 (84.7%)	15 (15.3%)	0.79
Side effect	none		none		-
Additional analgesia (tab)$^{\int}$	0 (0-2)		0 (0-2)		1.00

VAS: Visual analogue scale, min: minutes, * mean ± standard deviation (SD), g : grams, ** number, cm: centimeter, EBL: estimated blood loss, $^{\int}$: Median (50th percentile) with range, PS: pain score

Dodd's studies used diclofenac rectal suppository with a favorable result[13,15]. Oral naproxen was used as rectal suppository in Wilasrusmee's study with a favorable effect[14]. The use of tramadol rectal suppository was reported in Srimaekarat's study. The dosage was 100 mg of tramadol. However, it gave equal effect to placebo[16]. The present study conducted on larger group of subjects than Srimaekarat's study.

In this study, subjects were parturients who gave vaginal delivery. The average VAS of both groups was only 3 from 10 level. Both groups

showed no significant difference of pain score level between acetaminophen/tramadol and placebo groups.

From many studies that mention above, we found that single agent rectal analgesia gave satisfactory results. Hence, we chose a combined medication in this study because we desired the synergistic effect. However, the result was not demonstrated what we expected.

The pain level from normal vaginal delivery was mild to moderate. The limitations of this study were an inadequate dosage of tramadol chosen for the study and low pain level of participating subjects. The next study should be conducted in higher pain level cases, i.e., cesarean section with an improved suppository formulation.

Conclusion

Acetaminophen/tramadol tablet used as rectal suppository was not significantly different in relieving perineal pain after normal vaginal delivery when comparing to placebo. Side effect was not found in this study.

Potential conflicts of interest

The authors declare no conflict of interest.

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