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## OBSTETRICS

# Efficacy of a Single Dose Administration of Ibuprofen and Acetaminophen in Comparison with Acetaminophen for the Relief of Perineal Pain after Childbirth: A randomized controlled trial

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**ABSTRACT**

**Objectives:** To determine the efficacy of a single dose of ibuprofen plus acetaminophen versus acetaminophen alone for relief from acute perineal pain after childbirth.

**Materials and Methods:** A randomized, double-blind placebo-controlled trial was conducted on 404 women who gave birth by spontaneous vaginal delivery with mediolateral episiotomy at Queen Savang Vadhana Memorial Hospital between June 2017 and October 2017. Patients were randomized by block computer into 2 groups before delivery: one group received ibuprofen plus acetaminophen and another group received acetaminophen plus placebo. The medication was given immediately after complete perineal suturing. Perineal pain scores of both groups were assessed pre- and post-medication by visual analog scale (VAS). The adverse drug reactions were evaluated at 24 hours after medication.

**Results:** No difference of pre-medication perineal pain score was recorded for both groups. Median of perineal pain scores were 5 vs 5 ($p = 0.067$), respectively. Both groups were relieved their perineal pain within 24 hours. The median different pain relief scores were 5 vs. 3 ($p = 0.006$), respectively. There was dramatic pain relief in the short-term in the ibuprofen plus acetaminophen group, more than for the patients in the acetaminophen alone group (at 2-hours after taken medication). There was no adverse drug reaction.

**Conclusion:** A regimen of single dose ibuprofen plus acetaminophen has higher efficacy for relief from acute perineal pain than a conventional regimen with acetaminophen alone, and is safe to use for pregnant women after childbirth.

**Keywords:** episiotomy, perineal pain, ibuprofen, acetaminophen.

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# *การศึกษาประสิทธิภาพการใช้ยา ibuprofen ร่วมกับยา acetaminophen เปรียบเทียบกับการใช้ยา acetaminophen ในการลดความเจ็บปวดของแผลฝีเย็บภายหลังการคลอดบุตร*

***ปรียาภรณ์ หาระสาย, นุชนารถ พัฒนาปัญญาสัตย์***

## *บทคัดย่อ*

***วัตถุประสงค์:*** *เพื่อหาประสิทธิภาพของยา ibuprofen ร่วมกับ acetaminophen เปรียบเทียบกับacetaminophen อย่างเดียวเพียงหนึ่งครั้งเพื่อลดอาการปวดเฉียบพลันของแผลฝีเย็บหลังการคลอดทางช่องคลอด*

***วัสดุและวิธีการ:*** *รูปแบบการศึกษาเป็นการสุ่มตัวอย่างแบบปิดบังสองทางในกลุ่มหญิงตั้งครรภ์ที่คลอดโดยวิธีคลอดทางช่องคลอดและตัดฝีเย็บ ในโรงพยาบาลสมเด็จพระบรมราชเทวี ณ ศรีราชา ระหว่างเดือนมิถุนายน พ.ศ. 2560 ถึงตุลาคม พ.ศ. 2560 จำนวน 404 ราย ผู้ป่วยได้รับการสุ่มตัวอย่างแบบบล็อกด้วยคอมพิวเตอร์ก่อนคลอด เป็น 2 กลุ่ม: กลุ่มหนึ่งได้รับ ibuprofen ร่วมกับ acetaminophen อีกกลุ่มได้รับ acetaminophen เพียงอย่างเดียว โดยได้รับยาทันทีหลังจากการเย็บแผลฝีเย็บเรียบร้อย คะแนนความเจ็บปวดของฝีเย็บหลังคลอดทั้งสองกลุ่มจะได้รับการประเมินก่อนและหลังการให้ยาด้วย "10-cm visual analogue scale" และอาการไม่พึงประสงค์จากยาทั้งสองกลุ่มจะได้รับการประเมินที่ 24 ชั่วโมงหลังการใช้ยา*

***ผลการศึกษา:*** *ไม่พบความแตกต่างในคะแนนความเจ็บปวดของแผลฝีเย็บก่อนการรักษาทั้งสองกลุ่ม (ค่ามัธยฐานคือ 5, p = 0.067) การได้รับยาทั้งสองกลุ่มสามารถลดความเจ็บปวดของแผลฝีเย็บภายใน 24 ชั่วโมง ได้แตกต่างกันอย่างมีนัยสำคัญ (ค่ามัธยฐานคือ 5 เทียบกับ 3 ตามลำดับ, p = 0.006) และสังเกตได้ว่ามีการบรรเทาอาการปวดในระยะสั้นอย่างรวดเร็วกว่าในกลุ่มที่ได้รับการยา ibuprofen ร่วมกับ acetaminophen เมื่อเทียบกับกลุ่มที่ได้รับยา acetaminophen เพียงอย่างเดียว (2 ชั่วโมง หลังการใช้ยา) ไม่พบอาการไม่พึงประสงค์จากยาทั้งสองกลุ่ม*

***สรุป:*** *การใช้ยา ibuprofen ร่วมกับ acetaminophen เพียงครั้งเดียวมีประสิทธิผลมากขึ้นในการลดอาการปวดเฉียบพลันของแผลฝีเย็บในหญิงตั้งครรภ์หลังคลอดมากกว่าการได้รับ acetaminophen เพียงอย่างเดียว*

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## Introduction

Episiotomy is the surgical enlargement of the vaginal orifice by an incision of the perineum during the last part of the second stage of labor to increase the diameter of the vaginal outlet during childbirth. The benefits of episiotomy with mother include reduced third-degree tear; preservation of the muscle relaxation of the pelvic floor and perineum, leading to improved sexual function; reduced risk of fecal and or urinary incontinence; and due to the straight, clean incision, easier repair and healing of an episiotomy than a laceration. Moreover, the neonatal benefits of episiotomy are that a shortened second stage of labor could prevent fatal asphyxia, cranial trauma, cerebral hemorrhage, and mental retardation. Hence, episiotomy has become one of the most commonly performed surgical procedures in the world[1].

Hence, perineal trauma is a determinant factor for postpartum perineal pain especially on the first day after delivery. In the puerperal period, the presence of pain entails difficulties to practice motherhood and perform daily activities, such as self-care and newborn care. It also interferes with the women's sleep, rest, movements, urination, evacuation, and appetite. These difficulties can cause important physical, psychological, and emotional problems that contribute towards a negative delivery experience. Pain management is important for pregnant women who give birth by spontaneous vaginal delivery[2].

Pharmacological and non-pharmacological treatments have been investigated for perineal pain control after vaginal delivery. Traditionally, oral analgesics (acetaminophen, nonsteroidal anti-inflammatory agents), local anesthetics, and cold and warm sitz baths are used in postpartum care to treat perineal lesions. Music therapy is an alternative medicine which has been found to be effective in reducing the perceived perineal pain[3]. Acetaminophen is the most common analgesic used for perineal pain. Other analgesia is also used such as opioid, non-opioid, and the combination of both. For example, in Thailand, the combination of acetaminophen/tramadol tablet is used as a rectal suppository for reducing perineal pain[4]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for relief pain in clinical practice. Ibuprofen has a similar efficacy and fewer adverse effects. The NSAIDs are used commonly with minimal secretion in breast milk[5, 6].

The management of perineal pain was reviewed by the Cochrane Database of systematic reviews in 2013. The result of ten studies included states that more women experienced pain relief with paracetamol compared with placebo. In addition, there were significantly fewer women having additional pain relief with paracetamol compared with placebo[7]. In 2016, the result from twenty-eight studies of a single dose of NSAIDs for the perineal pain during the postpartum period revealed that a single dose of NSAIDs achieved adequate pain relief at four hours and at six hours. And NSAIDs versus paracetamol were also more effective for adequate pain relief at four hours but not at six hours post-administration[8].

Kamondetdecha R., studied about ibuprofen versus acetaminophen for the relief of perineal pain after childbirth, in Thailand. In the randomized controlled trial, two hundred and ten pregnant women were randomly allocated to receive either ibuprofen or acetaminophen. Pain in the ibuprofen group was considerably more reduced than the acetaminophen group at one hour of treatment (mean pain rating 2.18 vs. 2.88, respectively; $p < 0.003$). After two hours, both groups had similar analgesic properties[9].

These two compounds differ in their mode of action. Ibuprofen is an NSAID that inhibits cyclooxygenase (COX) enzymes: COX-1 and COX-2 and subsequent synthesis of prostaglandins and related compounds at peripheral sites within injured tissue. The mode of action of acetaminophen is not completely understood but appears to be related to the inhibition of a sub-class of COX enzyme isoforms in the central nervous system[10]. Cochrane Databases of systematic review in 2013 reviewed the single oral dose of ibuprofen plus paracetamol for acute postoperative pain. The results achieved at least 50% maximum pain relief over six hours in combination drugs more than ibuprofen alone or placebo and resulted in longer times to remediation than placebo[11].

However, studies of the single dose of combining two or more drugs with different mechanisms of action, such as NSAIDs and acetaminophen, for perineal pain relief after delivery have been limited. The hypothesis is that in pregnant women who give birth by spontaneous vaginal delivery with episiotomy, this combination of ibuprofen and acetaminophen provides superior analgesia than acetaminophen alone.

The main purpose of the present study was to evaluate the efficacy of ibuprofen and acetaminophen versus acetaminophen and placebo for relief from perineal pain after childbirth in 1, 2, 4, 6, and 24 hours after taking medication, using 10-cm visual analog scale for evaluation median of different pain relief scores. The secondary objectives were to evaluate side effects between both groups within 24 hours.

## Materials and Methods

The study collected data from June 2017 to September 2017 at Queen Savang Vadhana Memorial Hospital, Chonburi, Thailand. The study was conducted on the pregnancy women who chose vaginal delivery in this presenting time. The inclusion criteria were performed in the latent phase of first stage of labor. They consisted of single fetus pregnancy, vertex presentation, term pregnancy, history of antenatal care more than 4 times, no history of allergy to ibuprofen or acetaminophen, no history of medical condition known to be potentially exacerbated by acetaminophen or NSAIDs, include a history of asthma, significant renal or liver impairment, gastrointestinal ulcer. Pregnant women who met the criteria was given information of the research and were asked to consent before admission. The study was approved by the Research and Ethical Committee of the Queen Savang Vadhana Memorial Hospital, No. 3/2560.

The sample size was calculated based on previous study of Kamondetdecha R., the study about ibuprofen versus acetaminophen for the relief of perineal pain after childbirth in Thailand, that analysis standard deviation difference of pain rating score at 4 hour, showed 80% power of study, the target sample size was 338 women (169 per group)[9]. As potential loss to follow-up in each group was estimated at 20%, total sample size was set at 404 women. Finally, 404 pregnant women were enrolled in this study. All participants were randomly picked to receive either ibuprofen plus acetaminophen or placebo plus acetaminophen orally by computer block randomization technique. The placebo pills were physically similar to the real drug of ibuprofen. Intrapartum management was the same for both, using the standard protocol in hospital. Mediolateral episiotomies and repairs were performed by staff, residents, nurses, and medical students that were covered by staff or resident in all case using the standard procedures under local anesthesia. All participants received the drug immediately after complete perineal suturing by the first investigator in labor room. After that all participants were asked, by the second investigator, to give pain score by visual analog scale after perineal repair, before taking the drug and at 1, 2, 4, 6 and 24 hours after treatment. Patients were allowed to use a supplemental analgesic, that is acetaminophen. The patient, first and second investigator were blinded to the medication.

Women with mediolateral episiotomy with a third or fourth-degree tear after normal vaginal delivery, who had complications of delivery such as postpartum hemorrhage, delivery by cesarean section route, delivery by operative vaginal delivery were excluded. Moreover, the patients who were allowed to use of any intravenous analgesic drug within 24 hours or left the research were identified as drop-outs. Excluded and drop-out patients were not included in the trial.

The primary outcome of the present study was to evaluate the efficacy of ibuprofen and acetaminophen versus acetaminophen and placebo for relief from perineal pain after childbirth in 1, 2, 4, 6, and 24 hours after taking medication, using 10-cm visual analog scale from 0 (“no pain”) to 10 (“worst pain ever”) for evaluation median of different pain relief scores. The perineal pain score was recorded before the subject took the first dose of analgesia and at 1, 2, 4, 6, and 24 hours after treatment.

The secondary outcomes evaluated were for side effects, including nausea, vomiting, stomach pain and dizziness after 24 hours of treatment. All the data were

collected by two investigators (first investigator in labor room and second investigator in the postpartum room) who were blinded to group assignment.

The data analyses by intention to treat were performed using SPSS Statistics version 20 (SPSS Inc., Chicago, IL). Demographic and clinical characteristic data were history of vaginal delivery, degree of perineal tear, type of vaginal technique suture, type of skin technique suture, operator, that were presented as number and percentage (%) for categorical variables and were compared between the groups using the chi-square test. The other demographic and clinical characteristic data were maternal age, maternal weight, gestational age, birth weight, length of 2nd stage of labor, length of suturing, and volume of blood loss, that were presented as mean ± standard deviation for continuous variables, and were compared between the groups using independent samples t-test. The outcome of continuous variables, such as sequential measures on the visual analog pain scale and overall satisfaction measures on visual analog scales were compared between the groups using Mann-Whitney U test. And the outcome of categorical variables, such as the presence of side effects were compared between the groups using the chi-square test. Adjusted 95% confidence interval (CI) were estimated. A p value of $< 0.05$ was considered to be statistically significant.

## Results

During the study period four hundred and four women were screened for inclusion criteria in the present trial, and signed consent form (Fig. 1).

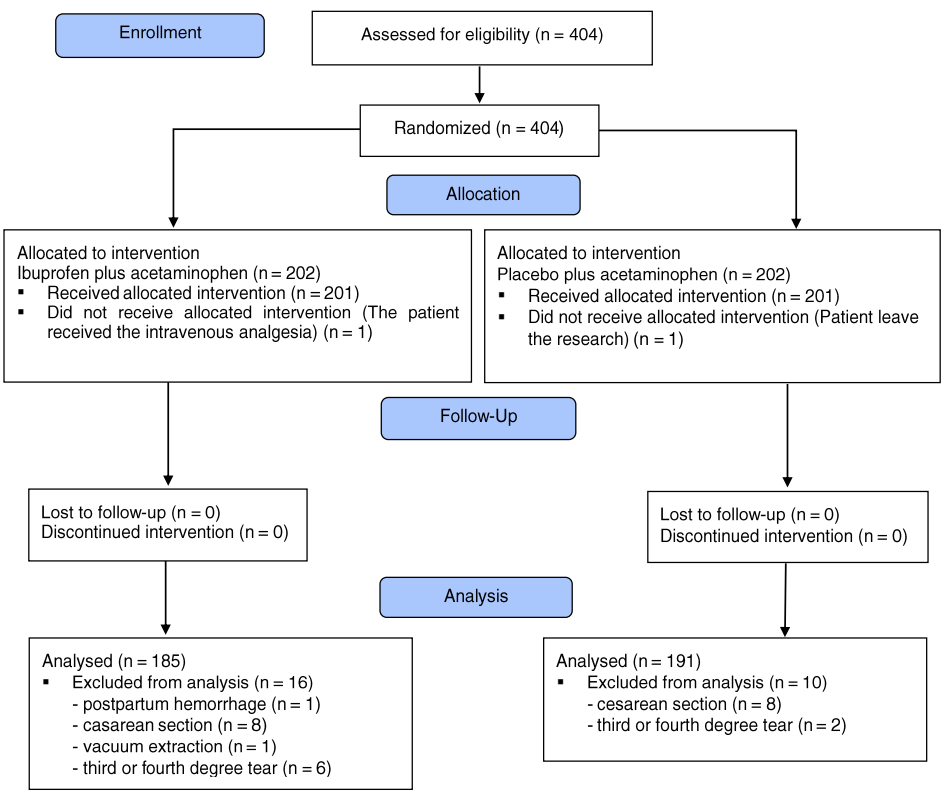


**Fig. 1.** Study flow diagram.

Then the 202 pregnant women were randomly assigned to receive ibuprofen 400 milligrams and acetaminophen 1,000 milligrams (treatment group), and 202 to receive placebo and acetaminophen 1,000 milligrams (control group). The treatment group excluded 16 pregnant women due to postpartum

hemorrhage[1], delivery by cesarean section route[8], operative vaginal delivery[1] and third-or fourth-degree tear after normal vaginal delivery[6]. The control group excluded 10 pregnant women due to delivery by cesarean section route[8] and third-or fourth- degree tear after normal vaginal delivery[2]. The total number pregnant women to receive drugs for both groups were 378 with 186 randomly assigned to receive ibuprofen 400 milligrams and acetaminophen 1,000 milligrams, and 192 to receive placebo and acetaminophen 1,000 milligrams. One pregnant woman of the treatment group received the intravenous analgesia drug and one pregnant woman of the control group left the study. The results of these groups were analyzed 185 in the treatment group with 191 in the control group. The two groups were similar in demographic data, clinical features, and the median onset of pain score (Table 1).

**Table 1.** Material demographics and clinical features.

| Variables | Treatment groups | | |
|---|---|---|---|
| | **Ibuprofen plus Acetaminophen (n = 185)** | **Acetaminophen (n = 191)** | **p value** |
| Maternal age (year) | 27.08 ± 5.75 | 26.44 ± 5.88 | 0.286 |
| Maternal weight (kilograms) | 67.42 ± 9.91 | 66.95 ± 9.99 | 0.648 |
| History of vaginal delivery (times) | | | 0.122 |
| Yes | 115 (62.2%) | 96 (56.2%) | |
| 1 | 84 (45.4%) | 68 (35.6%) | |
| 2 | 26 (14.1%) | 22 (11.5%) | |
| 3 | 5 (2.7%) | 6 (3.1%) | |
| Gestational age (weeks) | 38.39 ± 1.08 | 38.54 ± 1.87 | 0.344 |
| Birth weight (kilograms) | 3055.59 ± 375.16 | 3089.63 ± 370.64 | 0.377 |
| Degree of perineal tear | | | 0.056 |
| - First degree tear | 14 (7.6%) | 6 (3.1%) | |
| - Second degree tear | 171 (92.4%) | 185 (96.9%) | |
| Type of vaginal technique suture | | | 0.717 |
| - interrupted | 21 (11.4%) | 24 (12.6%) | |
| - continuous unlock closure | 164 (88.6%) | 167 (87.4%) | |
| Type of skin technique suture | | | 0.688 |
| - Interrupted | 18 (9.7%) | 21 (11%) | |
| - Continuous subcuticular closure | 167 (90.3%) | 170 (89.0%) | |
| Operators | | | 0.532 |
| - Medical student | 5 (2.7%) | 12 (6.3%) | |
| - Nurse | 162 (87.6%) | 161 (84.3%) | |
| - Resident | 15 (8.1%) | 15 (7.9%) | |
| - Staff | 3 (1.6%) | 3 (1.6%) | |
| Length of 2nd stage of labor (minutes) | 20.04 ± 20.80 | 20.10 ± 18.48 | 0.976 |
| Length of suturing (minutes) | 24.6 ± 11.64 | 26.97 ± 12.37 | 0.56 |
| Volume of blood loss (milliliters) | 203.51 ± 42.04 | 202.47 ± 35.39 | 0.795 |
| Median onset of pain score | 5 (5,7)* | 5 (3,6)* | 0.067+ |

* Median (Q1,Q3), + Mann-Whitney U test

There was no difference in the median onset of perineal pain scores which were 5 vs 5 (p = 0.067), respectively. The ibuprofen plus acetaminophen group was consistently better for perineal pain relief than the acetaminophen alone group at short-acting in 2 hours after treatment, the median of perineal relief pain scores was 3 vs 2 (p = 0.001), respectively. And at the long effect at 24 hours after treatment, the median of perineal relief pain scores was 5 vs 3 (p = 0.006), respectively (Table 2). The median severity of perineal pain at first and second hour after treatment of the treatment group (ibuprofen plus acetaminophen) dropped sharply compared with that of the control group (acetaminophen plus placebo) (Fig. 2).

There was one pregnant woman of the treatment group and three pregnant women of the control group who required for additional analgesia due to the increasing pain score within 24 hours.

**Table 2.** Median pain score and median different pain relief score.

| Variables | Ibuprofen plus Acetaminophen (n = 185) | | Acetaminophen (n = 191) | | p value |
|---|---|---|---|---|---|
| | Pain score | median different pain relief score | Pain score | median different pain relief score | |
| Onset of pain score | 5 | | 5 | | 0.067 |
| at first hour | 3 | 2 (0.5,3) | 4 | 1 (0,2) | 0.002 |
| at 2rd hour | 2 | 3 (1,5) | 3 | 2 (1,3) | 0.001 |
| at 4th hour | 1 | 4 (2,6) | 1 | 3 (2,5) | 0.004 |
| at 6th hour | 0 | 5 (3,6) | 0 | 4 (2,5) | 0.025 |
| at 24th hour | 0 | 5 (3,7) | 0 | 4 (3,6) | 0.006 |

Median (Q1, Q3)

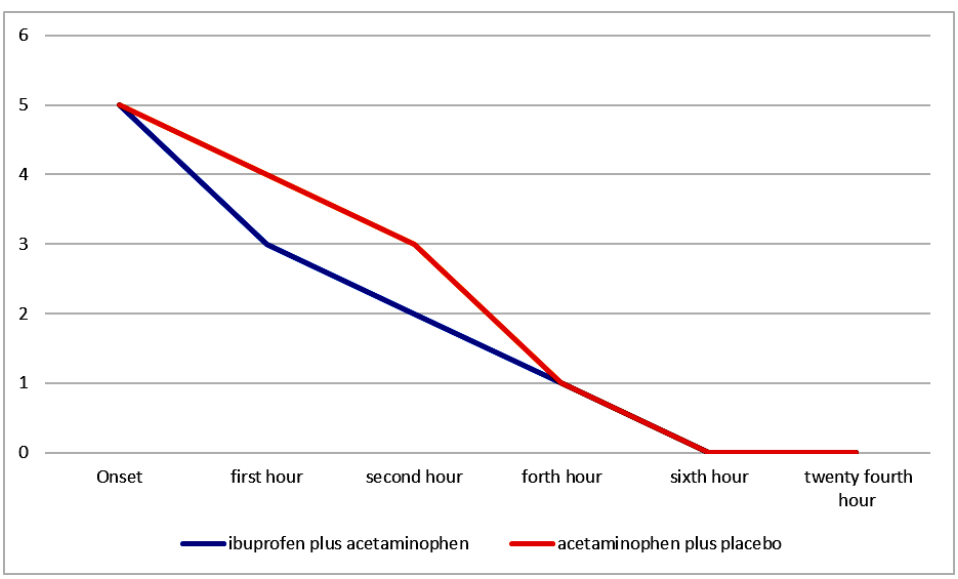


**Fig. 2.** Median pain intensity assessed using the visual analog scale.

Only one pregnant woman in the treatment group had a complication which was postpartum hemorrhage due to uterine atony. No adverse drug reaction was reported in both groups.

## Discussion

This study was designed to test the hypothesis that concurrent administration of ibuprofen and acetaminophen results in greater analgesic efficacy than acetaminophen alone in the management of perineal pain.

The single dose combination of ibuprofen 400 mg and acetaminophen 1,000 mg provided significantly better analgesic efficacy than acetaminophen alone in short time. Significant perineal pain relief was faster in the first and second hour after treatment (Fig. 2). Both groups could control perineal pain in 24 hours, with only one pregnant woman in first group and three pregnant women of second group requiring additional analgesia. So, this difference was manifested by a more rapid onset of action and more prolonged duration of effect (Table 2). Additive or synergistic effects of combined therapy with ibuprofen and paracetamol have been shown by other authors in different diseases and conditions. Combination of ibuprofen and paracetamol provides better analgesia than paracetamol alone after postoperative pain[11, 12] or oral surgery[13, 14].

A recently published review indicated that ibuprofen plus paracetamol combinations provide better analgesia than either drug alone (at the same dose) in the treatment of postoperative pain, with a smaller chance of needing additional analgesia over about eight hours, and with a smaller chance of experiencing an adverse event[11]. The combination of acetaminophen and ibuprofen is superior to acetaminophen alone at 6 hours or acetaminophen and codeine at 4 hours in controlling postoperative pain after Mohs surgery and cutaneous reconstruction[12]. The study confirmed that the treatment group had more pain relief than the control group. But the pain-reduction effect of 6 and 8 hours was different from our research because of differentiation of evaluated pain in the study.

In 2010, randomized, double-blind, placebo-controlled, parallel-group, single-dose, 2-center modified factorial United States study about postoperative dental pain management resulted in concurrent ibuprofen and paracetamol appearing to provide significantly better analgesic efficacy compared with ibuprofen or paracetamol alone at all time intervals, and for the sum of pain relief and pain intensity differences from 4 to 6 hours (all, $p < 0.001$)[13]. In another study, the systematic review in participants after surgical removal of lower wisdom teeth, ibuprofen 400 mg was shown to be superior to 1,000 mg paracetamol with a risk ratio for at least 50% pain relief at 6 hours of 1.47 (95% confidence interval [CI] 1.28 to 1.69). For the combined drug, the risk ratio for at least 50% maximum pain relief over 6 hours was 1.77 (95% CI 1.32 to 2.39) based on total pain relief data[14].

It can be seen that the study of pain reduction in surgical patients results in the same. Although these studies were used in patients with moderate to severe pain, the difference was that these studies were not for a single dose of medication. Therefore, this study could not measure the long term effect of the study.

This study was not consistent with previous studies of pain in patients with soft tissue injury. For example, Hung KKC, et al's study of patients with mild to moderate pain after soft tissue injuries. After visiting the emergency department, there were no difference in analgesic effects or side effects observed after using oral paracetamol, ibuprofen, or a combination of both[15]. In addition, the study by Bondarsky EE, et al., showed that the combination of ibuprofen and acetaminophen did not reduce pain scores or the need for rescue analgesics compared with either agent alone, in emergency department patients with pain secondary to acute musculoskeletal injuries[16]. The differences in this study might be due to different populations. As a result, the mechanism of pain varies.

The strengths of the present study included the use of randomized, double-blind control trial; minimal number of patients who were excluded or dropped out of the study; several measures of pain intensity; and measurement of a variety of side effects. The available data on efficacy of combinations of ibuprofen and

acetaminophen in perineal pain is limited. The result of this study can be widely used because of the use and availability of an ordinary drug. Even though the study has shown that median difference of pain relief score of both groups is truly different by statistics, we can see that a slight difference in pain score would result in the same treatment which is reducing the pain within 24 hours. Therefore, there is no clinical difference significantly.

Limitations of the present study included the evaluation of side effect of neonatal breast feeding. Lidocaine is known to have an onset < 2 min and a duration of 1 to 2 hours[17]. The present study cannot control its dosage in this protocol, so this may affect perineal pain relief score at first and second hour.

Past studies, the results confirmed the same way with this study in combination of ibuprofen and paracetamol provided better analgesia than paracetamol alone after postoperative pain[11,12] or oral surgery[13,14] . And some results were different, that showed the combination of drug did not reduce pain scores after soft tissue injury[15] and patients with pain secondary to acute musculoskeletal injuries[16]. No comparative studies have been conducted with the same drug, included the same population with this study. If further studies are needed to confirm the efficacy of the drug, only moderate to severe pain, the combination of new NSAIDs or opioid for perineal pain relief, do not use local anesthesia to reduce the confounder that evaluation abount pain.

## Conclusion

A regimen of single dose ibuprofen plus acetaminophen has higher efficacy for relief from acute perineal pain rather than a conventional regimen with acetaminophen alone, and is safe to use for pregnant women after childbirth.


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## Potential conflicts of interest

The authors declare no conflict of interest.

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