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Original Research Paper

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ANALGESIC EFFECT OF NAPROXEN WITH ACETAMINOPHEN AFTER CESAREAN DELIVERY UNDER GENERAL ANESTHESIA

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ABSTRACT

Objectives : To evaluate the efficacy of naproxen combined with acetaminophen rectal suppository for reducing postoperative pain from cesarean delivery under general anesthesia. **Materials and methods:** This study is designed to be a double-blinded, randomized-controlled trial in 34 pregnant women who underwent elective cesarean delivery under general anesthesia in Maharat Nakhon Ratchasima Hospital during November 1st, 2019 to February 29th, 2020. These participants were randomly allocated to either intervention or controlled group. The intervention group received single dose of naproxen 500 mg and acetaminophen 500 mg, while the controlled group received placebo. Primary outcome is postoperative pain score measured by Visual Analog Scale (VAS) after operation 4 and 24 hours. Secondary outcomes are cumulative morphine use, time to first ambulation, patient satisfaction and adverse effect at 24 hours postoperatively. **Results:** Baseline characteristics are similar between groups. There is a significant reduction in VAS for naproxen and acetaminophen group (4.8 vs 7.8, p value < 0.001, 95%CI 1.11-2.75 and 3.2 vs 5.1, p value = 0.002, 95%CI 0.4-1.85 at 4, 24 hours respectively). However, there is no significant difference for cumulative morphine use, time to first ambulation, patient satisfaction, no adverse effect of naproxen and acetaminophen is documented at 24 hours after operation.
Conclusion: A single dose of naproxen combined with acetaminophen rectal suppository significantly reduces VAS at 4, 24 hours after cesarean delivery under general anesthesia.

KEYWORDS : Postoperative Pain, Cesarean Delivery, Naproxen, Acetaminophen, General Anesthesia

INTRODUCTION

Cesarean delivery is one of the most common operations performed globally and the rate of procedure is increasing over the past ten years. In Asia, approximately 19% of child births are from cesarean delivery[1].

Suboptimal postoperative pain management leads to several complications, for instance, delayed ambulation, urinary tract infection, breastfeeding difficulty, prolonged hospitalization and expensive cost of care[2]. Furthermore, excessive opioid consumption provokes impairment of bowel function and delayed mobilization, and all of mentioned aspects could interrupt postoperative recovery[3].

Most elective cesarean delivery is performed under regional anesthesia, which is associated with less postoperative pain[4], however, general anesthesia is a necessary alternative choice in some situations, for example, patient request, regional anesthesia contraindication or emergency condition.

Recently, there are many researches about postoperative pain management for cesarean delivery under regional anesthesia using non-opioid drug such as Non-Steroidal Anti-Inflammatory Drug (NSAIDs) and acetaminophen[(6-7)], most of these drugs have correlated results that it effectively reduces postoperative pain under regional anesthesia, however, the study under general anesthesia is considerably limited.

This research aims to study whether naproxen combined with acetaminophen rectal suppository could reduce postoperative pain for cesarean delivery under general anesthesia.

The rationale for using NSAIDs and acetaminophen is that both medications are evidently effective and safe analgesics[8], moreover, naproxen has long half-life for approximately 10 hours and it has bioavailability in rectal form 94.6% compared with oral form (100%)[9]. For acetaminophen, bioavailability of rectal form is approximately 80% of oral form and the rate of absorption is slower with maximal concentration at 2-3 hours after administration[10].

The reason for selecting rectal route is convenient administration as general anesthesia often causes patients to be drowsy and not consciously cooperated after procedure. Oral route might trigger aspiration and respiratory complication. To avoid this issue, rectal suppository is alternative choice with comparable bioavailability.

METHODOLOGY

This study is a randomized-controlled trial conducted at Maharat Nakhon Ratchasima Hospital from November 1st, 2019 to February 29th, 2020 after approval by the Ethic Committee of Maharat Nakhon Ratchasima Hospital.

Eligible participants are term, singleton pregnant women underwent elective cesarean delivery under general anesthesia. Exclusion criteria consist of body mass index > 35 kg/m^2, allergic history to naproxen or acetaminophen, history of liver, renal, coronary or cerebrovascular disease, active peptic ulcer, unable to communicate in Thai language, and decline to participate in study. Any participant who experienced cesarean hysterectomy during operation is excluded from study.

Pregnant women with this criteria were informed about study protocol and asked to consent.

SAMPLE SIZE CALCULATION

The sample size is calculated based on pilot study identifying whether naproxen combined with acetaminophen could reduce postoperative pain after cesarean delivery under general anesthesia. The formula is to test the difference between two independent groups with Alpha = 0.05, Power = 90%. The total sample size is 34 persons. All participants were randomly allocated before the procedure by a block-of-four pattern generated by computer, group assignments were written down and placed into opaque envelopes.

Cesarean delivery was performed by obstetricians or residents. Any participant complicated by cesarean hysterectomy during surgery was excluded from this study.

Immediately after skin closure, naproxen 500 mg with acetaminophen 500 mg or placebo were applied via rectal suppository by the surgeon while patients were still unconscious. placebo is a sugar pill which has a similar appearance to acetaminophen and naproxen, patients and pain recorders were unable to distinguish these tablets after rectal use. All participants received morphine sulphate 10 mg intravenously at the recovery room.

Routine standard postpartum care was similar for both groups, for example, nursing care and vital signs measurement. Postoperative pain was recorded into visual analog scale by instructing participants to point on a 10 cm line corresponding to the severity of pain (0 cm - no pain, 10 cm - worst pain) at 4, 24 hours after operation, this process was supervised by trained obstetrical nurse. Patients were allowed to use additional morphine sulphate 5 mg intravenously for breakthrough pain (pain score ≥ 8) every six hours. At 24 hours after operation, cumulative morphine use, any adverse effect of naproxen or acetaminophen such as urticaria, gastrointestinal discomfort or rectal irritation were recorded.

Time to first ambulation was recorded by an obstetrical nurse when participants were able to walk after the operation. Satisfaction was evaluated by direct participants questioning if they were satisfied with postoperative pain relief or not (yes or no).

An intention to treat analysis uses JASP program version 0.12.1. Continuous variables compared between groups use independent sample T-test. On the other hand, categorical variables are compared by using the Chi-square test. Adjusted 95% confidence intervals are estimated. A p value of < 0.05 is considered to be statistically significant.

RESULT

This study was initially enrolled with forty women but six of them declined to participate in study, so they were excluded. Thirty four women were randomly allocated into two groups. Seventeen participants in the treatment group were assigned to receive naproxen 500 milligrams and acetaminophen 500 milligrams, and the other half in the control group received placebo (Figure 1).

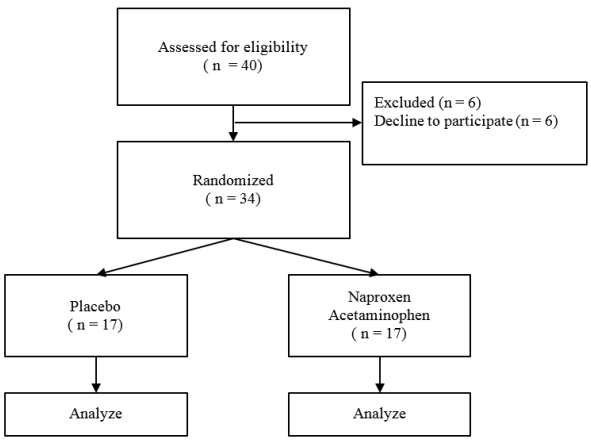

Figure 1. Study flowchart

The demographic data is similar for both groups. There is no significant difference regarding age, body mass index, previous cesarean delivery, type of incision, length of incision, operative time, total blood loss and level of operator.

All participants with a history of cesarean section underwent surgery indicated by previous cesarean delivery (Table 1). No complicated procedure occurred during the study, therefore, none of the participants is excluded by cesarean hysterectomy criteria.

Table 1. Clinical characteristics and demographics

	Naproxen plus acetaminophen (n = 17) Mean ± SD or n (%)	Placebo (n = 17) Mean ± SD or n (%)
Age (year)	28.7 + 6.6	28.2 + 6.1
BMI (kg/m2)	28.0 + 4.6	27.4 + 4.8
Previous cesarean delivery (n)		
Yes	7	7
No	10	10
Incision (n)		
Low midline	8(47.1%)	10(58.8%)
Pfannenstiel	9(52.9%)	7(41.2%)
Length of incision (cm)	12.6 ± 1.4	13 ± 1.2
Operative time (min)	43.0 ± 16.1	39.1 ± 9.3
Blood loss (ml)	352.9 ± 54.4	391.2 ± 73.4
Operator (n)		
Resident	13(76.5%)	12(70.6%)
Obstetrician	4(23.5%)	5(29.4%)

Table 2. Postoperative pain score by Visual Analog Scale

	Naproxen plus acetaminophen (Mean ± SD)	Placebo (Mean ± SD)	P Value
VAS at 4 hours	4.8 ± 1.8	7.8 ± 1.2	< 0.001
VAS at 24 hours	3.2 ± 1.4	5.1 ± 1.9	0.002

For primary outcome, the naproxen and acetaminophen group has significantly lower mean VAS than the placebo group, with 4.8 vs 7.8, p value < 0.001, 95%CI 1.11-2.75 and 3.2 vs 5.1, p value = 0.002, 95%CI 0.4-1.85 at 4, 24 hours after procedure respectively (Table 2) (Figure 2).

Regarding secondary outcome, three of seventeen participants in the placebo group complained that they were unsatisfied because of severe pain, while every person in the treatment group was satisfied. There is no statistical difference in mean cumulative morphine use, time to first ambulation after operation. No adverse drug effects reported by participants (Table 3)

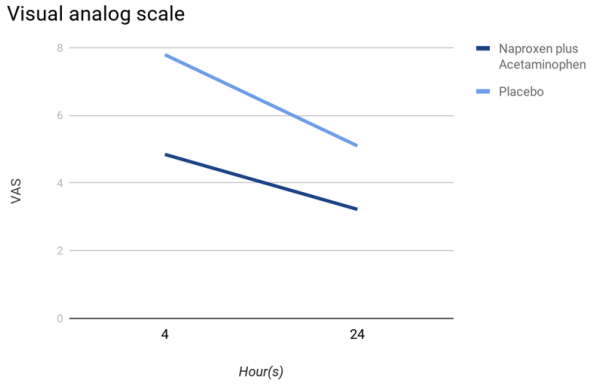

Figure 2. Postoperative pain score on intervention and placebo group

Table 3. Secondary outcome

	Naproxen plus acetaminophen Mean ± SD or n (%)	Placebo Mean ± SD or n (%)	P Value
First ambulation (hr)	12.3 ± 6.1	16 ± 6.5	0.096
Satisfaction			0.070
Yes	17(100%)	14 (82.4%)	
No	0 (0%)	3 (17.6%)	
Morphine use (mg)	8.2 ± 4.4	9.3 ± 6.4	0.575

DISCUSSION

This study aims to identify whether naproxen combined with acetaminophen could reduce postoperative pain in cesarean delivery under general anesthesia. Regarding basic physiology, after tissue damage, hormones, peptides, cytokines and other substances activate phospholipases that release arachidonic acid from membrane phospholipids, which is converted to prostaglandin by cyclooxygenase isoenzyme (COX). Prostaglandins sensitize nociceptors and modifies gene expression in peripheral and central nervous systems cause sensitization and hyperalgesia[11].

The reasons that naproxen and acetaminophen could reduce postoperative pain after cesarean delivery are cyclooxygenase isoenzyme (COX) inhibitor which blocks the hyperalgesic pathway mentioned above, notably that naproxen has systemic effect while acetaminophen has local synergistic effect a central nervous system. As a result, these actions produce an analgesic effect[1]

This study found that at 4 and 24 hours after operation, naproxen combined with acetaminophen could reduce postoperative pain significantly. There are researches having consistent results with this study. For example, Godrat A. and colleagues (2013) found that using Diclofenac or acetaminophen suppository could reduce post-cesarean pain effectively[13]. Furthermore, it can reduce cumulative morphine use at 24 hours after operation.

For another consistent study, Angle and colleagues (2002) found that naproxen could reduce postoperative pain significantly at 36 hours after procedure[14]. It is related to our study due to similar intervention (naproxen) and supportive findings that naproxen could reduce postoperative pain after cesarean delivery. Again, this study can prove that repetitive doses of naproxen could reduce cumulative morphine use significantly.

Although both studies have consistent findings with our result, it is conducted on cesarean delivery under regional anesthesia. However, study on general anesthesia is somehow limited. Consequently, it is the main reason to inspire us to start our research in this topic.

Despite relevant studies, there are studies that have inconsistent findings with our result, for example, A.R. Valentine and colleagues (2015) found that continuous dose of acetaminophen in every 6 hours for 48 hours can decrease morphine use but it cannot reduce pain score compared with placebo[15]. It has inconsistent findings with our result possibly because using acetaminophen solely is not adequate to achieve postoperative pain reduction.

From experience derived from working at Maharat Nakhon Ratchasima Hospital, this intervention could beneficially improve postoperative pain with safety profile. Moreover, naproxen and acetaminophen are easy-to-use, inexpensive, and also widely available in many hospitals. We particularly suggest that it can be used to improve postoperative care after cesarean delivery under general anesthesia.

Even though this intervention could not reduce total morphine use or time to ambulation significantly, there is slight reduction for both. Our limitation is that we have studied only single use of naproxen/acetaminophen which might not be enough to reduce cumulative morphine use or time to first ambulation. For further study, we would recommend investigating whether an additional dose of naproxen combined with acetaminophen could reduce cumulative morphine use or time to first ambulation after cesarean section under general anesthesia.

CONCLUSION

Single use of naproxen/acetaminophen could reduce postoperative pain after cesarean section under general anesthesia.

POTENTIAL CONFLICTs OF INTEREST

The authors declare no conflict of interest.

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