The effect of propacetamol in post-cesarean pain control - a randomized controlled study

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Background: Multimodal analgesia for acute pain provides better analgesia and fewer adverse effects of opioids. Propacetamol is a pro-drug of paracetamol that is the most widely used drug for acute pain. The study aimed to investigate the adjuvant analgesic effect of propacetamol in post-cesarean section pain relief within 48 hours.

Methods: We performed a prospective, randomized, placebo-controlled trial for single-dose intravenous propacetamol as an adjuvant to patient-controlled epidural analgesia (PCEA) after cesarean period. The parturients were allocated to additional propacetamol (Group P) or saline (Group C) injection immediately after the delivery of the placenta. Primary outcome was assessed by pain intensity at rest or during movement. We recorded postoperative pain scores by using the numeric rating scale (NRS 0-10) at postoperative care unit (PACU), 2, 6, 24 and 48 hours postoperatively. In addition, the total dosage of PCEA, rescue analgesic, motor block, adverse effects and maternal satisfaction were also recorded.

Results: A total of 60 obstetric patients agreed to participate and 59 completed the study (n=30 in Group P and n=29 in Group C). Pain intensity at rest in Group P was significantly lower compared to Group C within the initial 2 hours (p=0.04). Overall dosage consumption of PCEA and patient-requested rescue analgesic did not differ significantly between the two groups (p>0.05). There was also no obvious difference between groups with respect to muscle tone, adverse effects and satisfaction (P>0.05).

Conclusion: The combination of single-bolus intravenous 1 g propacetamol plus PCEA provided better pain relief at rest within 2 hours of administration.

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Key Words:
Multimodal analgesia, post-cesarean analgesia, propacetamol, patient-controlled epidural analgesia

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Introduction

The prevalence of cesarean sections has been dramatically raised [1], and it often involves moderate to severe pain after cesarean delivery. [2] Postoperative pain might result in adverse effects and interfere with breast-feeding of the parturients. [3-5] The ideal analgesic regimen should provide adequate pain relief, have no impact on ability to take care of the infant, and provide minimal drug transfer during breast-feeding. Adequate post-cesarean analgesia is important to enhance the obstetric patients' recovery and improve maternal and fetal outcomes. There is no "golden standard" for post-cesarean pain management, and improved pain control quality in obstetric populations is a crucial issue of clinicians. Various modalities are utilized for post-cesarean analgesia such as systemic pharmacological strategies (opioids or non-opioid analgesia) and neuraxial analgesic techniques. [6-9] Systemic opioids alone or combined with non-opioid analgesics (such as paracetamol and non-steroidal anti-inflammatory drugs) might be effective in pain relief after cesarean sections; however, several adverse events have been noted and low levels of opioids have been detected in breast milk. [10] Presently, patient-controlled epidural analgesia (PCEA) has gained wide acceptance as a mainstay for pain relief not only in obstetric settings but for early recovery after surgery as well. [11-15]

Multimodal analgesia can reduce PCEA opioid consumption and enhance recovery by minimizing opioid-related adverse effects. The combination of non-opioid analgesics may have opioid dose-sparing effect for mothers undergoing cesarean delivery. It is also expected to reduce opioid-related concerns and opioid transfer during breast-feeding.[16] Paracetamol (known as acetaminophen) is one of the most popularly used non-opioid analgesics for the treatment of acute pain including postoperative pain.

It is also the choice in patients who cannot tolerance non-steroidal anti-inflammatory drugs (NSAID) such as pregnant or breast-feeding women. [17] The mechanism of action is complex and still not fully elucidated. Paracetamol provides analgesic effect via selectively inhibiting cyclooxygenase (COX) [17] in peripheral and central anti-nociception transmission. A previous study suggested oral acetaminophen had similar pain-relief effect to NSAID in dysmenorrhea and inhibition of human endometrial prostaglandin production. [18] In addition, its metabolite may suppress prostaglandin synthesis in activated microglia by inhibiting COX activity. [19] Propacetamol is an intravenous prodrug form of paracetamol. Three major advantages of propacetamol for post-cesarean analgesia are being safe during breast-feeding, lacking platelet function inhibition, and being feasible even under asthmatic, peptic ulcers or renal insufficiency conditions. [9,20]

To our knowledge, some previous randomized controlled studies have reported that perioperative propacetamol infusion has ambiguous results on the consumption of oral or intravenous narcotic agents following cesarean delivery [21-23]. However, little data has been reported concerning additional intraoperative propacetamol administration to PCEA regimen in parturients who suffered from post-cesarean analgesia in early stages; therefore, we conducted a randomized, double-blind, placebo-controlled study to investigate the effects of intraoperative intravenous propacetamol versus placebo on decreasing PCEA consumption and reducing postoperative pain score within 48 hours after cesarean delivery.

Materials and Methods:

The clinical study was approved by the Institutional

Review Board of the Kaohsiung Medical University Hospital Chung Ho Memorial Hospital, Kaohsiung, Taiwan (Hsueh-Wei Yen) on 16 October 2015. (protocol No: KMUH-IRB-F(I)-20150076). After obtaining written informed consent, the parturient was recruited to this prospective, randomized, controlled double-blind study if she was mentally oriented, physically healthy (American Society of Anesthesiologists Class I-III) and had undergone elective cesarean delivery with postoperative PCEA use. Parturients with known premature birth less than 32 weeks of gestation, stillbirth, and contraindications for epidural anesthesia; had drug or alcohol abuse, history of chronic pain with pain killers, previous adverse reactions to local anesthetics, opioids or paracetamol, bleeding tendency, eclampsia, HELLP syndrome and limited comprehension to understand Chinese were excluded from the study.

Before anesthesia, all parturients were randomized to either propacetamol (Group P) or control (0.9% saline; Group C) groups. Randomization was performed using a sealed opaque envelope with a computer-generated block random allocation. The preparation of the propacetamol 1 g or 0.9% saline regimen was dissolved in 5 ml syringe by a nurse anesthetist blinded to the study. All parturients received epidural anesthesia for Caesarean section in left decubitus position by senior anesthesiologists following standard clinical practice and operating procedures of our department. Epidural space at either L2-3 or L3-4 interspace was chosen for epidural catheter indwelling. The epidural space was identified by loss of resistance to air technique with 18-gauge Tuohy needle. After epidural space was identified, an 18-gauge multi-orifice epidural catheter (Perifix One 401 Filter Set, B. Braun Medical Inc.) was threaded in a cephalic direction. The catheter was advanced 4~5 cm into the epidural space. Each parturient received a test dose of local anesthesia 3 ml of 2% lidocaine with epinephrine (1:200,000). After epidural catheter was fixed, each parturient immediately returned to a supine position. Intermittent epidural injections of 2% lidocaine were administered slowly until target dermatome was achieved and the operation was allowed. If adequate anesthesia was not achieved after 15 min (failure of epidural anesthesia), additional anesthetics were administered and these patients were excluded.

Parturients received either intravenous 1 g propacetamol or 0.9% saline slowly after the delivery of the placenta. All parturients were provided with PCEA regimen at the end of surgery. The analgesic solution of PCEA of bupivacaine 0.1% plus fentanyl 1 μg/ml was used. The PCEA setting was a baseline infusion of 2 mL/h with a PCEA bolus of 3 ml and lockout interval of 20 minutes according to our clinical standard. At the end of cesarean delivery, all patients were monitored for 2 hours in the post-anesthesia care unit (PACU). PCEA was stopped 48 hours after cesarean delivery and the epidural catheter was removed. Inadequate analgesia (NRS >5) during the period was treated with rescue analgesic. Parecoxib 40mg was given intravenously for inadequate pain relief.

The primary outcome was measured by pain intensity at rest and during movement (active movement of lower extremities) after cesarean delivery. Pain intensity was assessed by numeric rating scale (NRS 0-10) at PACU, 2, 6, 24 and 48 hours postoperatively. The secondary outcomes included PCEA dosage requirement, rescue analgesics, motor ability, opioid-related side effects (nausea, vomiting, dizziness, pruritus, numbness, prolonged urinary catheterization >48 hours) and overall satisfaction. Motor ability was graded by Bromage scale 0-3, 0= Complete motor block of the lower limbs, 1= Inability to raise extended leg and move knee, able to move feet, 2= Inability to raise extended leg, able to move knees and feet, 3= No motor block. The incidence

of postoperative side effects (nausea, vomiting, dizziness, pruritus, numbness) was documented. The maternal satisfaction of postoperative pain relief was measured by a four points scale; 1=poor, 2=fair, 3=good, 4=excellent.

All data were expressed as mean ± standard deviation. Differences of NRS at rest and during movement between the two groups were calculated by Mann-Whitney-U test. Other numerical variables were analyzed by Student t-test. Categorical data were analyzed using $\chi 2$ or Fisher's exact test as appropriate. A $P< 0.05$ was considered as statistically significant.

Results:

At the time of January 2016 to September 2017, sixty-six women admitted for elective cesarean delivery met the inclusion criteria, with sixty agreeing to participate in the study. After signed consent was obtained, the parturients were randomly assigned to either the propacetamol or control group. Fifty-nine of them completed the study as in the flowchart. One case in the control group was excluded from the study for inadequate epidural block. The flowchart of trail profile is shown in Figure 1. There were no significant differences across the groups in baseline characteristics of the parturients as the results show in Table 1. The primary results demonstrated that pain intensity at rest in Group P was significantly lower compared to Group C only within the initial 2 hours following delivery ($P<0.05$). The pain intensity at rest in the PACU were 0.7±1.5 and 1.4±1.9 for group P and C respectively ($P<0.05$). The pain intensity at rest at post-op 2 hour were 0.8±1.7 and 1.6±1.5 for group P and C respectively ($P<0.05$). However, there were no significant differences between the two groups in pain intensity during movement at different time points (Figures 2 and 3). The pain intensity at rest and during movement both reached peak at 6 hours in both groups post-delivery.

Total dosage requirements of PCEA (mixture of fentanyl plus bupivacaine) and proportion of parturients who received rescue analgesic are shown in Table 2. No significant difference was observed regarding mean PCEA requirements between the two groups at different time points. While there were slightly more cases requiring rescue analgesic in Group P (n=10) than in Group C (n=7), this had no significant difference between the two groups (P=0.49)

The degree of motor block by Bromage scale is shown in Table 3 at different time points, with no significant differences between the two groups in the recovery of muscle power, as neither did the incidence of all adverse events (PONV, dizziness, pruritus, numbness and prolonged urinary catheterization> 48 hours) differ significantly at all time points. Finally, most patients rated their satisfaction about post-cesarean pain relief as "satisfied" or "very satisfied" in both groups. The maternal satisfaction was slightly higher in Group P, with a mean of 3.07 ± 0.37 for Group P compared to 2.93 ± 0.53 for Group C; although this did not reach significance between the two groups (P=0.26).

Discussion:

The therapeutic benefit of PCEA in the obstetrical setting is well-accepted and an ideal PCEA program provides adequate pain relief in parturients without affecting neonatal outcomes. The combination of opiates plus local anesthetics in PCEA reduces local anesthetic requirements and provides better analgesia quality [24,25] Matsota et al. [26] utilized ropivacaine (0.15%) plus fentanyl (2 μg mL-1) in PCEA formulation and reported mean NRS scores (0-10) of 2.3 at rest and 4.4 during movement at 12 hours after cesarean delivery.

In the study of Kaufner et al. [8], obstetrical patients receiving a PCEA for 48 hours with ropivacaine (0.1%) plus sufentanil (0.5 μg mL-1) showed mean Visual Analogue Scale (VAS 0-100 mm) of 20 at rest and 45 during movement at 24 hours after cesarean section.

Multimodal analgesia is a widely accepted concept that combines effective individual analgesics in optimal dosage to obtain synergistic analgesic efficiency and minimal adverse effect of drugs in post-operative pain management, including cesarean delivery. [27] Additional diclofenac administration reduced morphine consumption and improved analgesia after cesarean delivery in patients receiving intravenous morphine PCA. [28] The use of neuraxial opioids combined with systemic NSAID adjuncts, including parecoxib provides adequate postcesarean analgesia. [12,29-31] Till now, adequate evidence of the effectiveness from the use of parecoxib in pregnant women and during labor is lacking. Even a single dose of parecoxib to lactating mothers after cesarean delivery can lead to transfer of parecoxib and its active metabolite into human milk. Furthermore, breast-feeding is a major public health policy and we avoided parecoxib and other NSAIDs in the study design to ensure the safety of both newborn and parturient.

Paracetamol acts as a COX-3 inhibitor within the CNS, and a weak inhibitor of inducible COX-2 and constitutive COX-1. The analgesic mechanism of paracetamol is still under-investigated and it mainly acts through a reduction in brain PGE2 concentrations. [32,33] This might explain the possible reasons for the statistical differences at PACU and first postop 2h of the resting pain between groups.

Other NSAIDs produce analgesia by the inhibition of COX-1 and COX-2, mediating the production of prostaglandins. Paracetamol has fewer side effects and does not impair platelet function when compared to NSAIDs. McNicol et al. demonstrated the efficacy and safety of intravenous propacetamol providing acute postoperative analgesia within 4 hours in 37% of patients including both adult and pediatric populations. [20] Patients were given repeated intravenous acetaminophen (15mg/kg every 6 hour for a total 12 doses) to decrease postoperative morphine PCA consumption associated with shorter hospital length of stay following posterior spinal fusion. [34] However, the adjuvant epidural analgesic effect of intravenous propacetamol is not well established, although Peach et al. suggested additional paracetamol to pethidine PCEA in post-caesarean analgesia did not provide an opioid dose-sparing effect during the first 24 hours. [9] A recent randomized, double-blind, placebo-controlled clinical trial enrolled 80 primipara undergoing labor epidural analgesia, and the authors indicated intravenous 1 g paracetamol had an opioid sparing effect and statistically significantly reduced the mean hourly drug consumption at first 2 hours compared with placebo. [35]

In parturients undergoing cesarean delivery, our primary outcome indicated that single-dose intravenous propacetamol as adjuvant to PCEA with bupivacaine (0.1%) and fentanyl (1 μg/ml) provided better analgesia at rest compared to only PCEA within initial 2 hours after delivery. However, there was no significant difference in pain intensity during movement, PCEA dose consumption, rescue analgesics, motor block, adverse events and patient satisfaction at different time points. In addition, the highest pain intensity was observed at 6 hours after cesarean delivery both at rest and during movement. The result was comparable with previous reports describing that peak pain scores occurred at 4-9 hours after cesarean section. [18,31,36] In parturients we provided with additional propacetamol to PCEA, mean NRS score was 2.0 at rest and 3.5 during movement at 24 hours after cesarean delivery. The pain

intensity was similar to previous studies at 24 hours after cesarean section. [8,26]

Although a dose-sparing effect on PCEA (fentanyl/bupivacaine) consumption was not observed in this study, an initial improvement in clinical outcomes was found. The absence of dose-sparing effect might be explained by differences between epidural and systemic opioid analgesia. The epidural opioids resulted in less requirement up to 50% than for intravenous opioids and was associated with better quality of post-cesarean pain control. [37] In Matsota's report, a single dose of celecoxib 200mg did not reduce the total dose of the epidural fentanyl with ropivacaine in parturients receiving PCEA. The total requirement of epidural fentanyl was 154 versus 176 mcg for patients with and without an adjuvant within 24 hours [31]. In our outcome, accumulated epidural fentanyl dose was only 49 and 46 mcg for groups P and C within the first 24 hours respectively. In both reports, the relatively low required opioid dosages made significant dose-sparing effect less possible. Furthermore, single dose 1 g propacetamol may be relatively under-dosed to achieve efficacy and clinicians might consider titrate to higher single bolus dosage or repeated injection for further studies to determine whether propacetamol is beneficial to reduce post-cesarean pain. The limited statistic difference of add-on effect of acetaminophen might be explained by modest analgesic effect to high-potent epidural fentanyl.

Our study failed to show clinical significance of propacetamol with a synergic analgesic effect of PCEA. The finding was comparable to previous reports showing paracetamol does not improve analgesia in patients with moderate baseline pain after caesarean delivery or either in combination with intravenous morphine PCA [28,38]. However, there was no parturient drop-out from the study due to adverse events related to opioids (nausea, vomiting) or epidural analgesia (muscle weakness or difficult urination). With respect to analgesia quality and overall satisfaction, PCEA (0.1% bupivacaine plus 1 μg/ml fentanyl) either with or without propacetamol provides adequate analgesia in most parturients undergoing cesarean delivery within 48 hours.

There are some limitations in this trial. First, the use of higher potent analgesics such as NSAID or COX-2 inhibitor was of potential risk in fetus. Therefore, we used less-potent analgesics-propacetamol. Further, the sample size was also limited because of low birth rate in general population. Further increase in the number of cases might improve the study efficacy. Therefore, in order to improve the current limitations, we continue to conduct case collection and research.

We concluded that in parturients undergoing elective caesarean delivery, additional single-bolus intravenous 1 g propacetamol to patient-controlled epidural analgesia (a mixture of 0.1 % bupivacaine plus 1ug/ml fentanyl) reduced pain intensity within initial 2 hours postoperatively.

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Table 1. Patient characteristics between groups

	R Group P (*n*=30)	Group C (*n*=29)	*P* value
Age (yr)	32.8±4.2	31.4±3.7	0.17
Weight (kg)	67.7±9.4	71.8±10.3	0.11
Height (cm)	160.2±4.9	159.3±7.4	0.07
ASA I/II/III (*n*)	1/27/2	2/24/3	0.67
Pregnancy (weeks)	37.9±1.0	37.7±0.9	0.27
Previous C/S (*n*)	12 (40%)	13 (45%)	0.63
Epidural level (*n*)			
L2-3/L3-4	22/8	20/9	0.65
Epidural depth (cm)	4.03±0.6	4.25±0.7	0.18
2% Lidocaine dose (ml)	12.2±1.3	11.9±1.6	0.42
Intravenous anesthetics (*n*)	5 (17%)	3 (10%)	0.51
Operation period (min)	70.5±19	72.1±22	0.67

Figure 1

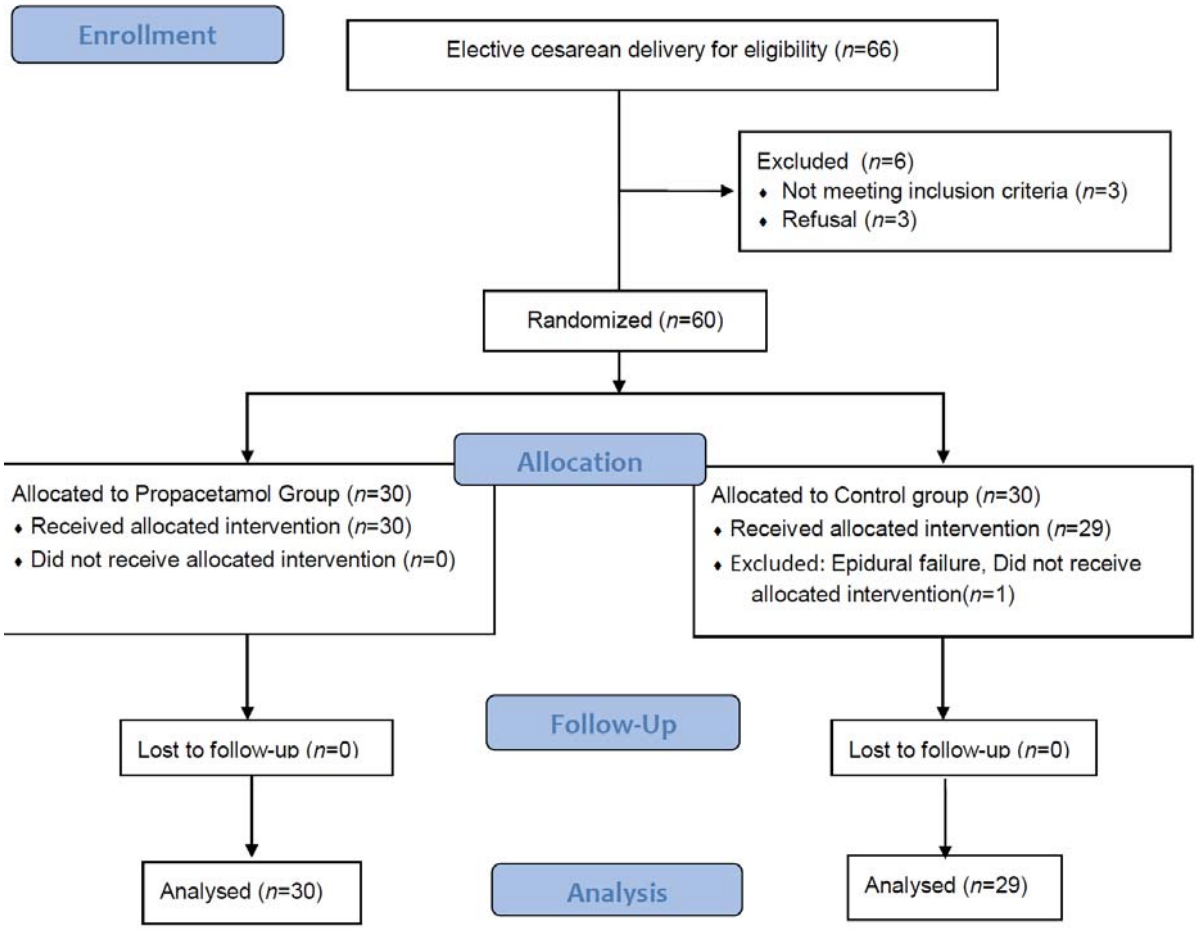


Table 2. Analgesic consumption of patient controlled epidural analgesia (PCEA)

	R Group P (*n*=30)	GroupC (*n*=29)	*P* value
PCEA dose (ml)			
2 hour post-op	10.5±2.5	10.2±2.4	0.69
6 hours post-op	25.3±6.6	24.4±6.4	0.62
24hours post-op	48.6±16.9	45.8±12.9	0.47
48hours post-op	56.6±21.2	54.1±15.3	0.60
Rescue analgesic (*n*)	10(32.2%)	7(24.1%)	0.49

The PCEA formula contains bupivacaine 1mg/ml and fentanyl 1mcg/ml.

Figure 2

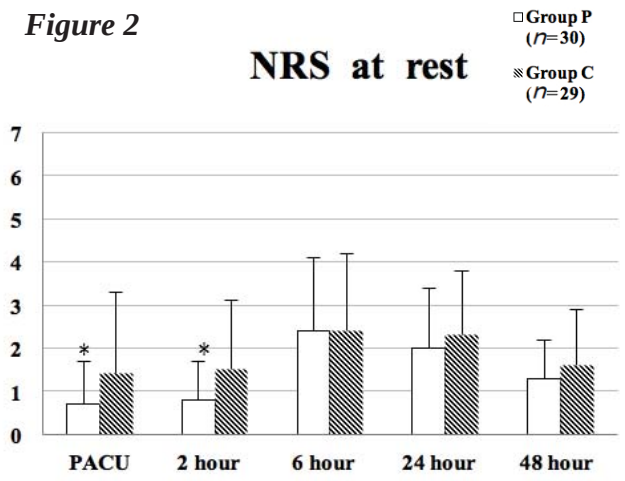


Table 3 Postoperative adverse events and satisfaction during PCEA

	R Group P (*n*=30)	Group C (*n*=29)	*P* value
Muscle power	(0/1/2/3)	(0/1/2/3)	
Arrival PACU (*n*)	5/6/5/14	4/10/8/7	0.25
2 hour post-op (*n*)	2/2/9/17	2/4/12/11	0.50
6 hours post-op (*n*)	0/0/2/28	0/1/5/23	0.43
24hours post-op (*n*)	0/0/0/30	0/0/2/27	0.54
48hours post-op (*n*)	0/0/0/30	0/0/0/29	1.0
Adverse events			
PONV (*n*)	1(3.3%)	2(6.9%)	0.54
Dizziness (*n*)	6(18.8%)	2(6.9%)	0.14
Headache (*n*)	0(0%)	1(3.4%)	0.30
Pruritis (*n*)	1(3.3%)	0(0%)	0.32
Numbness (*n*)	26(86.7%)	26(89.6%)	0.50
Foley catheter > 48h (*n*)	6(20%)	8(27.6%)	0.49
Satisfaction	3.07±0.37	2.93±0.52	0.26

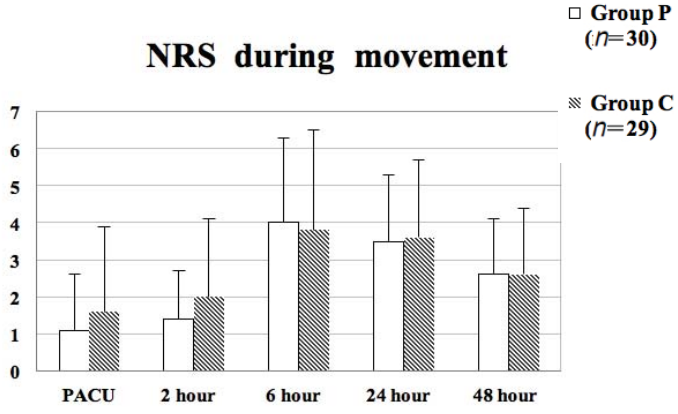
Muscle power grading as: 3=No motor block, 2= Inability to raise extended leg, able to move knees and feet, 1= Inability to raise extended leg and move knee, able to move feet , 0=Complete motor block of the lower limbs.

PACU=Post-anesthesia care unit

PONV=postoperative nausea and vomiting

Satisfaction grading as: 1=unsatisfied, 2=fair, 3=satisfied, 4=very satisfied

Figure 3



Propacetamol 輔助硬膜外自控式止痛改善剖腹產早期術後疼痛控制

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背景：多模式止痛用於急性疼痛可提供更好的鎮痛效果，並減少鴉片類藥物的不良反應。Propacetamol 是乙醯胺酚的前藥，乙醯胺酚是用於急性疼痛的最廣泛使用的藥物。這項研究旨在研究 Propacetamol 在剖腹產後 48 小時內緩解疼痛的輔助效果。

方法：我們設計一項前瞻性，隨機，安慰劑對照試驗，探討剖腹產後單次劑量靜脈使用 propacetamol 作為產婦硬膜外自控式止痛的輔助效果。產婦分為實驗組（propacetamol ,P 組）或對照組（生理食鹽水 ,C 組），產婦於胎盤分娩後立即接受靜脈注射。主要結果為休息與活動的疼痛強度，疼痛強度以數字等級量表 (0-10 分) 評估，評估時間為到達恢復室與術後 2、6、24 和 48 小時。此外，還記錄了自控式止痛的總劑量，止痛藥拯救劑量，運動阻斷，不良反應和產婦滿意度。

結果：共有 60 名產婦納入，其中 59 名完成研究（實驗組 30 人，控制組 29 人）。在術後 2 小時內，實驗組的休息疼痛強度明顯低於控制組（p = 0.04）。兩組之間自控式止痛的總劑量和要求止痛藥拯救劑量的患者之間無顯著差異（p> 0.05）。兩組之間肌張力，不良反應和滿意度方面也沒有明顯差異 (P> 0.05)。

結論： 硬膜外自控式止痛合併使用 Propacetamol 在剖腹產後 2 小時內提供更好的疼痛緩解。

關鍵詞：多模式止痛、剖腹產術後疼痛、Propacetamol、硬膜外自控式止痛

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