

การให้ morphine 0.15 มก. ทางไขสันหลัง สามารถมีประสิทธิภาพเทียบเท่ากับขนาด 0.2 มก. ในการระงับปวดหลังผ่าตัดคลอดหรือไม่

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Can 0.15 mg. Intrathecal Morphine be as Effective as 0.2 mg in Post Cesarean Pain Control?

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ความเป็นมา: การให้ morphine ร่วมกับยาชาทางไขสันหลัง 0.2 มก. สามารถระงับความปวดได้ดีหลังผ่าตัดคลอด แต่การให้ morphine ทางไขสันหลังนั้นมีผลข้างเคียงมากขึ้นตามขนาดยาที่ได้รับ

วัตถุประสงค์: เพื่อศึกษาประสิทธิภาพของการให้ยา morphine ทางไขสันหลังขนาด 0.15 มก. เปรียบเทียบกับขนาด 0.2 มก. ในการลดปวดหลังผ่าตัดคลอด และอุบัติการณ์ของผลข้างเคียงของขนาดยาทั้งสอง

วิธีการศึกษา: ทำการศึกษาแบบ randomized control trial ในผู้ป่วยที่ตั้งครรภ์ครบกำหนดมารับการผ่าตัดคลอดที่โรงพยาบาลรามาธิบดี โดยผู้ป่วยจะได้รับการสุ่มแยกเป็น 2 กลุ่ม คือ กลุ่มศึกษา จะได้ morphine 0.15 มก. และกลุ่มควบคุมจะได้ morphine 0.2 มก. ร่วมกับยาชา hyperbaric bupivacaine 10 มก. ผู้วิจัยทำการบันทึกข้อมูลปริมาณยา tramadol ที่ผู้ป่วยได้รับเพื่อบรรเทาอาการปวดหลังผ่าตัด 24 ชม. เป็นผลการศึกษาหลัก และอาการแทรกซ้อนที่สำคัญ เช่น คลื่นไส้ อาเจียน คัน ค่ะแน่นความปวด และระดับความพึงพอใจ

ผลการศึกษา: จากผู้ป่วยทั้งหมด 128 ราย ไม่พบความแตกต่างของปริมาณการใช้ tramadol จำนวนผู้ป่วยที่ต้องการยาระงับปวดเพิ่มเติม ระยะเวลาในการขอยา tramadol ครั้งแรก สัดส่วนผู้ป่วยที่มีระดับความปวดปานกลางถึงปวด

Background: 0.2 mg. intrathecal morphine for post cesarean section provides good analgesia. However, side effects increase with higher dosage.

Objective: To compare the effectiveness and side effects of 0.15 mg. and 0.2 mg. intrathecal morphine.

Method: A prospective randomized study of term parturients undergoing cesarean section was done. Patients were randomized into 2 groups: group I (study group) and group II (control group) received 0.15 or 0.2 mg intrathecal morphine with 10 mg heavy bupivacaine for spinal anesthesia respectively. Tramadol was used as a rescue drug postoperatively upon request. The amount of tramadol used in the first 24 hours was compared as the primary endpoint. Other common side effects such as nausea, vomiting, pruritus, pain score and satisfaction score were also recorded.

Results: Data from 128 patients was analyzed. There was no difference in the amount of tramadol use, number of patients who require rescue drug, time to first dose of tramadol and percentage of patients with moderate to severe pain score between the two groups. There was a trend of less severity and episode of nausea and vomiting (20.63% vs 34.92%; $p=0.09$) and higher satisfaction score (4-5 vs 3-5; $p=0.08$) in the 0.15 group. Incidences of

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มาก และอาการคัน ของทั้งสองกลุ่ม แต่มีแนวโน้มว่าผู้ป่วยที่ได้ morphine 0.15 มก. จะเกิดคลื่นไส้ อาเจียนน้อยกว่า (20.63% vs 34.92%; $p = 0.09$) และมีคะแนนความพึงพอใจสูงกว่า (4-5 vs 3-5; $p = 0.08$) กลุ่มที่ได้ morphine 0.2 มก. **สรุป:** การได้รับยา morphine 0.15 มก. ทางไขสันหลังลดอาการปวดได้เพียงพอ มีแนวโน้มในการเกิดอาการคลื่นไส้ อาเจียนน้อย และมีความพึงพอใจมากกว่ากลุ่มที่ได้ morphine 0.02 มก.

คำสำคัญ: การได้รับยา morphine ทางไขสันหลัง, ผ่าตัดคลอด, ระวังอาการปวดหลังผ่าตัดคลอด

pruritus were not different between the two groups.

Conclusion: The dose of 0.15 mg. intrathecal morphine provides adequate post cesarean analgesia, with a trend toward less nausea, vomiting and higher satisfaction score.

Keywords: intrathecal morphine , cesarean section, post cesarean pain control

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Introduction

Spinal anesthesia is widely accepted choice for cesarean section and intrathecal morphine has been used successfully for postoperative pain relief. The reason that spinal anesthesia with hyperbaric bupivacaine and morphine appears ideally for perioperative pain control in cesarean section is its simplicity, with only on dural puncture, and safety when compared with epidural anesthesia.

However, intrathecal morphine carries many unsatisfied side effects; nausea, vomiting, pruritus with incidence of 21.5%, 14.8% and 59.5% respectively¹. Serious risk of respiratory depression is very rare due to low clinical dose used nowadays.

Recently, the dose of 0.2 mg intrathecal morphine is believed to be the most suitable dose for post cesarean pain control in our practice in Thailand, despite high incidence of side effects. But in some other centers, they preferred the 0.15 mg. morphine and claimed that it could provide adequate pain control with less side effects.

So we hypothesized that 0.15 mg. intrathecal morphine can be effective in post cesarean pain control in comparison with 0.2 mg. together with less side effects.

Methods

The study was approved by Ramathibodi ethic committee. The study enrolled of 134 full term

parturients, without maternal or fetal compromised condition, scheduled for elective cesarean section. We also included emergency cases whom did not received any analgesic drugs within 6 hours before cesarean section. The patient's written informed consent was obtained before participation in this study. Then the patients were randomly classified into two groups of 67 each. All patients were evaluated by anesthesiologists before being anesthetized. The patients' vital signs were monitored with non invasively automatic oscillotonometric device, ECG and pulse oximetry when they arrived at the operating room.

In the study group, 0.15 mg. preservative-free morphine sulphate in 0.15 mL solution was added to the hyperbaric bupivacaine just before the intrathecal injection, whereas in the control group, 0.2 mg. morphine in 0.2 mL solution was added. The dose of hyperbaric bupivacaine was the same, that is 10 mg. in 2 mL solution. Both groups were infused with 800-1000 mL of Acetar from the beginning of intrathecal injection. Hypotensive patients were treated with 5-10 mg. ephedrine intravenously to maintain systolic blood pressure within normal range, and not less than 95 mmHg.

In the first 24 hours after surgery, breakthrough pain was treated with tramadol 25-50 mg. IV, pruritus was treated with intravenous chlorpheniramine 10 mg. and nausea or vomiting was treated with intravenous ondansetron 4 mg. All of the medications were given

as requested by patients. The amount of rescue drugs was recorded, including time to first dose of tramadol, pain score at 6, 12, 18 and 24 hours post intrathecal morphine together with any adverse side effects. Satisfaction score was evaluated by a member of investigator team. Satisfaction score 5 is the maximum and 1 is the minimum satisfaction score.

Power analysis was done according to a previous study of Girgin NK et al². In patients receiving 0.2 intrathecal morphine, the morphine-equivalents were required 25±16 mg post-operatively. The authors expected a maximum increase of morphine requirement of 30% in 0.15 mg intrathecal morphine group and calculated the sample size for non-inferiority analysis (two-sided α 0.05, 80% power); N/group was 56.

Accordingly, the adequate sample size was recommended to be 56 per group. The authors then added 20% to prevent any loss of data during the study, so 67 patients per group were scheduled. All data were

recorded and analyzed in SPSS 18.0 program. Mean, standard deviation, median, range, frequency and percentage were used to express the results. Normal distribution was determined using QQ plots and the Kolmogorov-Smirnov test. Continuous variables were compared between two study groups using independent t-test or Mann-Whitney test as appropriate. The incidences of post-operative pain and other categorical variables were compared using chi-square or Fisher's exact test. The p-value of less than 0.05 was considered statistically significant.

Results

One hundred and thirty four patients were allocated into 2 groups, 6 patients were excluded from the study; 4 from 0.15 mg. group and 2 from 0.2 mg. group. All of them were due to inadequate blockade of the spinal anesthesia. There was no difference among the groups with respect to demographic data or parity. (Table 1)

Table 1 Demographic data

	Group MO 0.15 (n=63)	Group MO 0.2 (n=65)	p-value
Age (yr), mean±SD	32.37±5.04	33.46±5.35	0.235
Weight (kg), mean±SD	70.95±10.28	71.11±10.21	0.932
Height (cm), mean±SD	158.65±5.34	158.22±4.81	0.628
Primigravida (n)	30 (47.62%)	27 (41.54%)	0.489
Multigravida (n)	33 (52.38%)	38 (58.46%)	
GA, median (min-max)	38 (35-41)	38 (35-41)	0.275
ASA II, n	63	65	>0.999
C/S due to			
Repeat	18 (28.57%)	22 (33.85%)	0.52
CPD	20 (31.75%)	11 (16.92%)	0.05
Breech	5 (7.94%)	8 (12.31%)	0.413
Elderly	6 (9.52%)	3 (4.62%)	0.278
GDM	5 (7.94%)	5 (7.69%)	>0.999
Pfannenstiel incision	61 (96.83%)	63 (96.92%)	

Data are n (%) unless otherwise indicated.

The result for postoperative tramadol use was shown in Table 2. There was no difference between two groups in respect to numbers of patients who needed tramadol and amount of tramadol consumed. The time to first postoperative administration of tramadol was

similar between groups. Numbers of patients with moderate to severe pain score were not different as shown in Table 3. Forty percent of the patients in both groups received parecoxib for pain treatment.

Patients receiving intrathecal morphine 0.15 mg. had a trend toward fewer episodes of nausea with *p* value of 0.09. (Table 4) The antiemetic drug use of those who had symptoms were not different between. The incidence of pruritus was similar between groups.

Patients in the 0.15 mg. group had slightly higher satisfaction score. (*p*=0.08)

There was no reported episode of respiratory depression. No patient in this study received naloxone.

Table 2 Results for postoperative tramadol used

	Group MO 0.15 (n=63)	Group MO 0.2 (n=65)	<i>p</i> -value
Tramadol use, n (%)	33 (52.38)	30 (46.15)	0.481
Tramadol mg. in 24 hr. (if used)	25 (10-75)	50 (10-75)	0.382
Time to 1 st tramadol (if used) (hr.)	12 (2-22)	13.5 (2-24)	0.799

Data are median (min-max) unless otherwise indicated

Table 3 Pain score between the 2 groups:

Hour	Group MO 0.15 (n=63)	Group MO 0.2 (n=65)	<i>p</i> -value
PO moderate to severe pain (hr.)			
6	18 (28.57%)	23 (35.38%)	0.409
12	21 (33.33%)	14 (21.54%)	0.134
18	28 (44.44%)	25 (38.46%)	0.492
24	24 (38.1%)	25 (38.46%)	0.966

Data are n (%).

Table 4 Results for side effects related to intrathecal morphine used and satisfaction score

	Group MO 0.15 (n=63)	Group MO 0.2 (n=65)	<i>p</i> -value
Nausea/vomiting, n (%)	13 (20.63)	22 (34.92)	0.094
ondansetron use (mg.)	4	4 (4-12)	0.329
pt. with severe nausea (n)	0	4	0.119
Pruritus, n (%)	48 (76.19)	52 (80)	0.602
CPM used (mg.)	10 (10-20)	10 (10-20)	0.757
NSAIDS used, n(%)	25 (39.68)	28 (43.08)	0.697
Satisfaction score	5 (4-5)	5 (3-5)	0.087

Data are median (min-max) unless otherwise indicated

Discussion

More than 10 years ago, a study of Rodanant, et al³ comparing the efficacy of 0.2, 0.25 and 0.3 mg. intrathecal morphine (ITM) for post gynecological operation pain control in 343 Thai patients and found no difference in postoperative pain outcomes and a trend toward less side effects with decreasing dose group. So 0.2 mg. ITM was the optimal dose in

conclusion. Since then, many studies had tried even lower dose. Girgin et al² did not find a statistical difference in pain outcomes in dose of 0.1-0.4 mg. but they only had 18-20 patients in each of five groups categorized in this study. Another study of Wong, et al⁴ had found a definite clinically significant advantage (less pain and fewer interventions for treating the pain) to using 0.2 mg. over 0.1 mg. Wong, et al's sample size

was substantially larger with 241 patients and had the power to demonstrate the difference of the outcome.

Our study showed that intrathecal morphine 0.15 mg. was adequate for post cesarean pain control in comparison to 0.2 mg. Number of patients needed rescue analgesia was not different. The amount of opioids used per patient was even non-significantly higher in the 0.2 mg. group. Time to first rescue drug was also similar. 12 hr. pain score was slightly higher in the 0.15 mg. group with p -value of 0.134.

Side effects of the two groups also did not differ significantly. However, there was a trend toward lower episode of nausea and vomiting (20.63% vs. 34.92%) with lower dose intrathecal morphine ($p=0.094$). No patient in the 0.15 group had severe nausea and vomiting comparing to 4 patients in the 0.2 group had these symptoms.

The incidence of pruritus was 76.19% and 80% in the 0.15 and 0.2 mg, respectively. ($p=0.602$). Another interesting outcome that almost reached significant level of difference is satisfaction score ($p=0.087$). Patients in the 0.2 mg. group gave lower satisfaction score. There were 3 from 65 patients in 0.2 mg group giving satisfaction score 3 but no patient in 0.15 mg group giving satisfaction score 3 or lower. We observed that those who gave lower score had more severity of side effects (both nausea, vomiting and pruritus).

There are 3 limitations of the study. First, the randomization was not concealed; however, baseline characteristics were not different. Second, anesthesiologists who gave spinal anesthesia and evaluators who asked about satisfaction score were not blinded; nevertheless, patients did not know how much morphine they received. Lastly, the analysis of this study was not intention to treat analysis. We performed per-protocol analysis instead of intention to treat analysis.

An important bias in our study was that most Thai people were very shy and polite. Most patients gave highest satisfaction score despite of pain or side effects. We suggest other way to collect these outcomes in the future study.

Conclusion

0.15 mg dose of intrathecal morphine provided adequate post cesarean analgesia in comparison to 0.2 mg dose. 0.15 mg dose also resulted in a trend of less severity and less episode of nausea and vomiting. Moreover, patients in 0.15 group gave higher satisfaction score. We suggest to use 0.15 mg. intrathecal morphine for post cesarean pain control in the future practice.

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