An Optimal Dose Study of Intrathecal Morphine in Gynecological Patients

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Abstract

Background and objectives : Post-operative pain after gynecological surgery can be controlled by intrathecal administration of opioids and local anesthetics. Effective intrathecal analgesia can be achieved from low dose narcotics with less adverse effects, prolonged duration and reduced narcotics requirement. Therefore, we undertook a prospective randomized study to find out optimal dose of intrathecal morphine for long lasting post-operative analgesia with less adverse effect in this group of patients.

Method : Spinal anesthesia was induced in 343 patients, the American Society of Anesthesiologists (ASA) I-III, age between 15-65 years, who were enrolled into double-blind randomized study to three different groups. Each patients will receive a mixture of 0.5 per cent bupivacaine and morphine to the total volume of 4 ml. Intrathecally. Group I, II and III will receive preservative-free morphine 0.2, 0.25 and 0.3 mg, respectively. At 1, 2, 3, 6, 24, 48 and 60 h after surgery, assessment of pain (Verbal Numeric Pain Score: 0-10), pruritus, sedation, nausea, vomiting and the time to the first dose of analgesics requirement were recorded. Patients' satisfactions were also recorded at the last visit.

Results : Time to first dose of narcotics or nubain were not different between groups ($p = 0.13$). Although 64.91 per cent, 66.67 per cent and 76.52 per cent of patients from group I, II and III, respectively did not require narcotics treatment but the difference was not statistically significant ($p = 0.121$). However, the percentage of patients with moderate to severe pruritus (treatment desirable) were 30.7 per cent, 30.7 per cent and 39.1 per cent in group I, II and III respectively ($p = 0.296$).

Conclusion : Intrathecal morphine 0.2 mg produced adequate analgesia and less side effect. Increasing dose of intrathecal morphine showed no more efficacy and also increased the number of pruritic patient who required treatment.

Key word : Intrathecal Morphine, Post-Operative Analgesia, Gynecology, Adverse Effects

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Intrathecal opioids have been shown to provide effective analgesia in a variety of surgical settings since the introduction of this technique into clinical practice in 1979[1]. The advantage of spinally administered opioid is that the prolonged analgesia can be provided using a single injection at the time of surgery without the need for cumbersome and expensive pumps or multiple intravenous or intramuscular injections in the post-operative period.

For lower abdominal or lower limb surgery, it has been a common practice to administer an opioid with a local anesthetic drug during spinal anesthesia which will improve the operative analgesia and provide extended post-operative pain relief[2,3]. Sarma and Bostrom[4] compared the effect of intrathecal morphine in post hysterectomy patients in different doses (0, 0.1, 0.3, and 0.5mg). They found that the analgesia was inadequate in the group of patients who received 0.1 mg of morphine while 0.3-0.5 mg doses provided analgesic effects without statistically significant difference. The intrathecal morphine dose of 0.3 mg seemed to be the optimal dose from this study but the side effects were still high even although no serious adverse effects occurred.

As intrathecal morphine has been administered in various doses[4-6], determining the optimal dose should be considered. In study, the authors prospectively investigated the analgesic effect of 0.2, 0.25 and 0.3 mg doses of intrathecal morphine to determine a dose that prolonged analgesic effect with a minimal incidence of side effects.

MATERIAL AND METHOD

The study was approved by the ethical committee and written informed consent was obtained from all patients. Three hundred and forty three patients, ASA physical status I-III, scheduled for elective gynecological surgery under intrathecal anesthesia, were enrolled in this prospective, randomized study by using computerized generated random numbers. Double-blinding was achieved by injecting the patients who did not know the contents of the subarachnoid injection and by ensuring that the anesthesiologist performing the intrathecal injections did not participate in the post-operative care and evaluation of the patients.

Patients were excluded if they had a contraindication to regional anesthesia, an allergy to opioids, or a history of treatment with drugs other than simple oral analgesics and a significant coexisting disease.

The anesthetic management of all patients was standardized. Patients were allocated to three groups: group I = 0.2 mg, group II = 0.25 mg, and

group III = 0.3 mg of morphine. Spinal anesthesia was undertaken with a 27 Gauge Quincke needle using a mixture of 0.5 per cent heavy bupivacaine 3.7-3.8 ml plus the solution of morphine which was prepared by an anesthetic nurse and 10 mg/ml of preservative free morphine was diluted to 1 mg/ml in normal saline using an aseptic technique and added up to 4 ml. Noninvasive blood pressure, heart rate, and oxygen saturation were continuously monitored during anesthesia. Assessment was started one hour after the subarachnoid injection, conducted by an investigator unaware of the constituents.

Post-operative pain was treated first with 5 mg intravenous nalbuphine every 4 h as needed. On patient request, nausea and vomiting was treated with 10 mg IV metoclopramide every 4 h and 1 mg of IV droperidol as needed for symptoms unrelieved by metoclopramide. Pruritus was treated with 3 mg of IV nalbuphine every 4 h and patients were offered 10 mg of IV chlorpheniramine every 6 h as needed. Other oral analgesic drugs were given when oral intake was allowed.

At Post Anesthesia Care Unit (PACU), the sedation, nausea, vomiting and pruritus scores were recorded every hours for the first three hour and then at 6,12, 24, 36, 48 and 60 h. Routine post-operative care was performed as usual after transferring patients back to the ward. Grading of sedation, nausea, vomiting and pruritus score is shown in Table 1. Episodes of nausea, vomiting, or pruritus requiring treatment were noted. Verbal numeric pain scores were graded on a 0-10 verbal scale (0 = no pain, 10 = the worst possible pain). The time of the patient's ability to sit on the bed and first ambulation was recorded. Within 60 h post-operatively, each patient was asked about satisfaction of post-operative analgesia, which was scored on 0-10 verbal scale, where 0 represented "unsatisfied" and 10 represented "very much satisfied".

Data were analysed by using the SPSS statistics package (version 9). Continuous data were analysed by ANOVA. Categorial data were analysed by chi-square test. Ordinal data were analysed by Kruskal-Wallis test. Survival analysis of time to first dose of analgesic, time to ability to sit on the bed and time to ambulation by Log-rank test (Kaplan-Meier). 95 per cent confidence interval as appropriate. P-value < 0.05 was considered statistically significant.

RESULTS

There were no significant differences between the three groups in age, weight, or height as shown in Table 2. Mean survival time of first dose analgesic, time to ability to sit on the bed and time to

Table 1. Grading scores for sedation, nausea, vomiting and pruritus.

Score	0	1	2	3
Sedation	Awake	Response to verbal commands	Response to shaking	Cannot wake up
Nausea	None	Mild, no treatment	Moderate, needed treatment	
Vomiting	None	Transient once, no treatment	Repeated, neede treatment	
Pruritus	None	Mild, no treatment	Moderate, needed treatment	Severe, need treatment

Table 2. Demographic data and type of skin incision.

	Intrathecal morphine dose		
	0.2 mg	0.25 mg	0.3 mg
N	114	114	115
Age (years)	41.37 ± 6.91	41.91 ± 8.32	41.78 ± 7.32
Weight (Kg)	57.07 ± 8.44	56.21 ± 9.26	56.65 ± 12.79
Height (cm)	156.10 ± 5.52	154.30 ± 12.16	153.91 ± 15.39
Incision (Transverse/Vertical)	69/45	66/48	72/43

Value are mean ± SD, number.
No significant differences in the data between the groups.

ambulation are shown in Table 3. The survival curve of mean analgesic time is shown as Fig. 1. Number of patients in each group who did not require narcotic treatment is demonstrated in Table 4. During the first 24 hours, pain requiring treatment and side effects, such as sedation, nausea, vomiting and pruritus, were not significantly different as shown in Table 5. Patients' satisfaction scores of post-operative analgesia in group I, II and III was 6, 6 and 7, respectively ($p = 0.11$).

DISCUSSION

Pain is an extremely complex process that involves the interaction of an array of neurotransmitters and neuromodulators at all levels of the neuraxis. A long duration of severe pain may change the processing of pain; for instance, by involving pain memory. Identification of various receptors and processes that are involved in the transmission of pain at the spinal level has led to the use of many drugs and technique in pain management[7]. These include the

Table 3. Time in hours between initial intrathecal injection and the need for supplemental narcotics.

	Group I	Group II	Group III	P value
Time to first dose analgesic (h)	44.95 ± 0.89 (41.03, 48.86)	45.96 ± 1.95 (42.15, 49.78)	50.22 ± 1.70 (46.88 < 53.55)	0.13
Time to sitting on bed (h)	29.31 ± 0.89 (27.56, 31.05)	29.77 ± 4.93 (27.95, 31.59)	27.90 ± 0.74 (26.44, 29.35)	0.54
Time to ambulation (h)	23.16 ± 0.43 (22.31, 24.01)	22.54 ± 0.36 (21.83 ± 23.24)	22.26 ± 0.43 (21.42, 23.10)	0.24

Values are expressed as mean ± SD (95% CI)

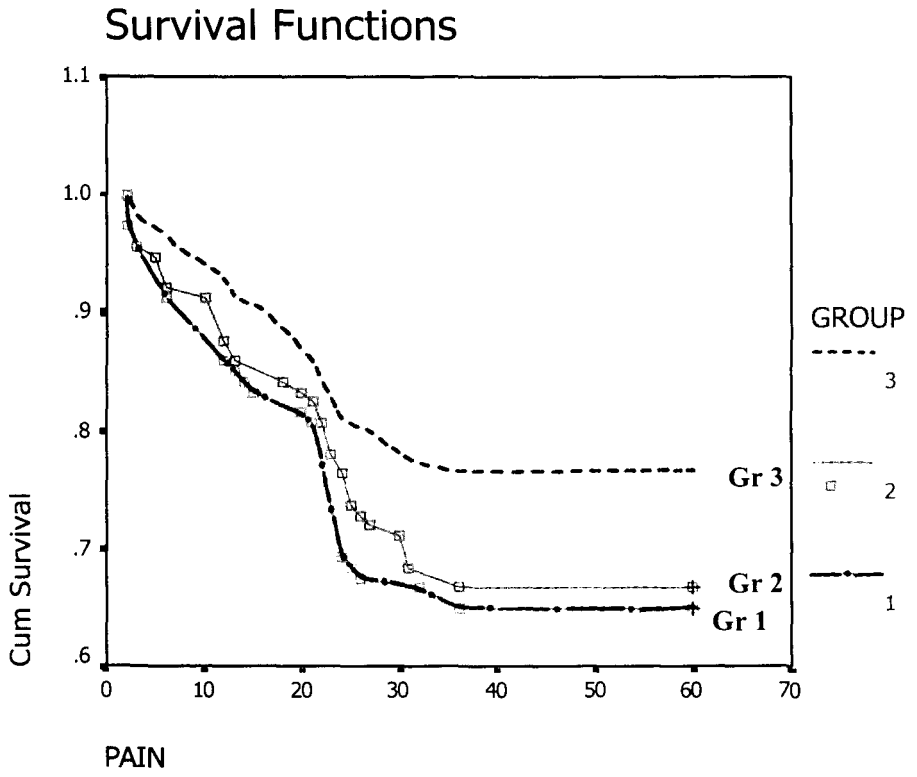

Fig. 1. Mean survival time to first dose of narcotic used in each group (p = 0.13).

Table 4. Number of patients in each group who did not require narcotic treatment in that period of time.

	Group I		Group II		Group III		P-value
	N	%	N	%	N	%	
Narcotic in 24 h	22	19.3	25	21.9	20	17.5	
24 h narcotic free	92	80.7	89	78.1	95	83.3	0.685
36 h narcotic free	76	66.7	78	68.4	89	78.1	0.159
48 h narcotic free	74	64.9	76	66.7	88	77.2	0.121
60 h narcotic free	74	64.9	76	66.7	88	77.2	0.121

Table 5. Number of patients with side effects and required treatment within 24 hours.

	Group I		Group II		Group III		P-value
	N	%	N	%	N	%	
Pruritus	35	30.7	35	30.7	45	39.1	0.296
Nausea	31	27.2	17	14.9	27	23.5	0.071
Vomiting	41	36.0	41	36.0	40	34.8	0.977
Sedation	5	4.4	9	7.9	7	6.1	0.543
Pain score > 5	55	48.2	49	43.0	46	40.0	0.445

use of preemptive analgesia and techniques such as intrathecal drug administration. Pre- or postincisional administration of either intrathecal morphine or bupivacaine reduced hyperalgesia on the day of surgery [8]. Slappendel, et al[9], found that presurgical intrathecal administration of bupivacaine and morphine can minimize post-operative pain and morphine requirement.

Severe post-operative pain can influence patient outcome after surgery[10]. Undertreatment of pain may impede short-term recovery and may even have a detrimental long-term effect on health [11]. Appropriate post-operative pain management contributes to earlier mobilization, shortened hospital stays, and reduced costs.

Intrathecal morphine has been known to be an effective post-operative analgesia in humans for almost two decades. Many studies have evaluated the effects of intrathecal morphine after various types of surgery[5,6,12,13]. Chadwick and Ready[14] retrospectively reported experience with intrathecal morphine after cesarean delivery with doses from 0.3-0.5 mg; although a non-significant "trend" toward longer analgesia was noted, no dose effect was found regarding the side effect Jiang et al[15] studied the doses of intrathecal morphine between 0 and 0.125 mg and found a linear relation between morphine doses and durations of analgesia. Side effects were not significantly dose-related, although pruritus was more common in the treatment groups than in the control group.

Various factors have complicated the interpretation of the results such as the administration of supplementary opioids or long acting sedative drugs, which may act synergistically with them[16]. Such drugs may prevent the accurate assessment of post-operative analgesia because of prolonged sedation and altered cognition. In the present study, the authors attempted to circumvent these problems by avoiding peri-operative administration of supplementary opioids and long acting sedation.

The present study revealed that mean analgesia time between the groups was not statistically significantly different ($p = 0.13$). The mean survival times were longer than 40 hours in all groups. The incidence of side effects from this study was similar to a previous study[17]. The side effects within 24 hours after intrathecal morphine injection, such as moderate to severe pruritus, sedation, nausea, vomiting and pain requiring treatment (pain score > 5) were also not significantly different between the groups.

Delayed respiratory depression is the most feared side effect of intrathecal opioids, however, its

true incidence is not known. In the present study, no serious respiratory depression was found which was consistent with previous studies (1,18,19). Cole et al (18) studied the respiratory effects of low dose spinal morphine following knee arthroplasty. They found no significant difference in the incidence of episodes of apnea between the treatment and placebo group. The pattern of respiratory dysfunction was similar to the use of IV morphine and there seems to be no need for intensive-care based recovery. Rawal et al(20) reported only a 0.36 per cent incidence of respiratory depression after intrathecal morphine in 1,100 patients. The reason why the incidence was so low may be due the clinical use which was minimized between 0.2-0.8 mg.

The time to first ambulation and ability to sit on the bed was not different between the groups. From the present study, the authors found that the time to first ambulation or even sitting on the bed was not solely related to being pain free, but mainly depended on the persistent use of a urinary catheter and the indwelling intravenous fluid. The patients would not move from the bed even though they were pain free. They needed more encouragment from the nursing staffs and attending physicians.

In summary; the major finding of the present study is that the optimal dose of intrathecal morphine in gynecological surgery is as low as 0.2 mg. This dose resulted in excellent pain relief and a low demand for systemic narcotics in the first 24 hours after surgery. The larger dose of 0.25 or 0.3 mg of intrathecal morphine did not produce better analgesia, moreover, the number of patients who suffered from pruritus was higher than other groups even though the incidence of itching was not significantly higher.

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การศึกษาขนาดมอร์ฟีนที่เหมาะสมในการฉีดเข้าช่องไขสันหลังในผู้ป่วยผ่าตัดทางนรีเวช

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วิธีการระงับความปวดภายหลังการผ่าตัดทางนรีเวช ด้วยการฉีดมอร์ฟีนเข้าช่องไขสันหลัง เป็นวิธีหนึ่งที่พบว่ามีประสิทธิภาพในการระงับความปวด ซึ่งขึ้นอยู่กับขนาดของมอร์ฟีนที่ใช้ อย่างไรก็ตาม อาการไม่พึงประสงค์ จากการฉีดมอร์ฟีนเข้าช่องไขสันหลัง ก็มีความสัมพันธ์กับขนาดของมอร์ฟีนเช่นกัน ดังนั้นการศึกษาขนาดที่เหมาะสมของมอร์ฟีนที่ใช้เพื่อให้ได้การระงับปวดที่นานพอ และมีผลข้างเคียงน้อยที่สุด จึงมีความสำคัญ การศึกษานี้เป็นการศึกษาแบบทดลองที่มีการปกปิดสองชั้น ในผู้ป่วย 343 ราย ที่มีสภาพทั่วไปตาม ASA status ที่ 1–3 อายุระหว่าง 15–65 ปี โดยทำการสุ่มตัวอย่างผู้ป่วย ให้ได้ 3 กลุ่ม ผู้ป่วยแต่ละรายจะได้รับการฉีด 0.5% bupivacaine ผสมรวมกับมอร์ฟีนขนาดต่าง ๆ กัน รวมเป็น 4 มิลลิลิตร ทางช่องไขสันหลัง โดยขนาดมอร์ฟีนที่ใช้ในกลุ่มที่ 1, 2 และ 3 เป็น 0.2, 0.25 และ 0.3 มิลลิกรัม ตามลำดับ ทำการบันทึกเวลาที่ปราศจากความปวด ระดับความปวด (โดยใช้ verbal numeric pain score 0–10) ความรุนแรงของอาการคัน อาการง่วงซึม อาการคลื่นไส้อาเจียน และจำนวนผู้ป่วยที่ได้รับยาระงับปวดเพิ่มเติมครั้งแรก ที่ชั่วโมงที่ 1, 2, 3, 6, 24, 48 และ 60 ชั่วโมงหลังการผ่าตัดสิ้นสุด นอกจากนี้ได้บันทึก ความพึงพอใจของผู้ป่วยต่อการระงับปวด จากการถามผู้ป่วยในการไปเยี่ยมครั้งสุดท้าย ผลการศึกษาพบว่า ระยะเวลาที่ปราศจากความปวด ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p = 0.13) จำนวนผู้ป่วยที่ไม่ได้รับยาระงับปวดเพิ่มเติม เมื่อคิดเป็นร้อยละ ในกลุ่มที่ 1, 2 และ 3 เท่ากับ ร้อยละ 64.91, 66.67 และ 76.52 ตามลำดับ และไม่มีความแตกต่างกันทางสถิติ (p = 0.121) จำนวนผู้ป่วยที่มีอาการคันในระดับปานกลางถึงรุนแรง (หรือต้องการการรักษา) เมื่อคิดเป็นร้อยละ เท่ากับ 30.7, 30.7 และ 39.1 ในกลุ่มที่ 1, 2 และ 3 ตามลำดับ และความแตกต่างนี้ไม่มีนัยสำคัญทางสถิติ (p = 0.296) โดยสรุป ขนาดของมอร์ฟีน 0.2 มิลลิกรัม ทางช่องไขสันหลัง ก่อให้เกิดการระงับปวดหลังผ่าตัดได้พอเพียงประกอบกับมีผลข้างเคียงน้อย การเพิ่มขนาดของมอร์ฟีนไม่พบว่าประสิทธิภาพในการระงับปวดเพิ่มขึ้น แต่กลับพบจำนวนผู้ป่วยที่มีอาการคันและต้องการการรักษาเพิ่มขึ้นอีกด้วย

คำสำคัญ : การฉีดมอร์ฟีนเข้าช่องไขสันหลัง, การระงับปวดหลังผ่าตัด, นรีเวชวิทยา, อาการไม่พึงประสงค์

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