THE EFFICACY OF INTRATHECAL MORPHINE FOR POSTOPERATIVE ANALGESIA AFTER VALVE SURGERY

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Abstract
Objective: To evaluate the effects of preoperative intrathecal morphine dose of 0.3 mg on postoperative pain, extubation time and pulmonary function in patients undergoing valve repair or replacement. **Materials and Method:** Sixty patients were allocated into two groups, receiving either 0.3 mg of morphine intrathecally prior to anaesthesia and intravenous patient-controlled analgesia with morphine postoperatively, or only postoperative intravenous patient-controlled analgesia. Visual analog scale at rest and on profound inspiration, morphine consumption during the first 48 postoperative hours, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) preoperatively and the first and second postoperative day were measured. Extubation time, adverse effects (pruritus, postoperative nausea and vomiting, respiratory depression) were recorded. Patient characteristics, preoperative risk score, intraoperative and anesthetic data did not differ significantly between groups. **Results:** The total dose of sufentanil used was 88.3 ± 15.9 µg in the control group and 87.1 ± 15.5 µg in the morphine group ($p > 0.05$). Pain scores at rest during the first postoperative 16 hours and pain score on profound inspiration after extubation in the intrathecal group were significantly lower than those in the control group ($p < 0.05$). Intravenous morphine consumption in the intrathecal group was lower until the 30th hour and reduced cumulative intravenous morphine consumption by more than 45% in comparison to the control group (12.8 ± 7.5 vs. 24.2 ± 10.1 mg). There was no significant difference in FVC, FEV1, mechanical and extubation time and the incidence of pruritus, nausea and vomiting between two groups. **Conclusion:** Preoperative intrathecal administration of 0.3 mg morphine in patients undergoing valve surgery improved analgesia and reduced morphine consumption in the first 30 h, without delaying extubation time or improving the FEV1 and FVC.

Key words: *Intrathecal morphine, cardiac surgery, postoperative pain*

1. BACKGROUND

The world's demand for open heart surgery as well as in Viet Nam is huge. Fast-track cardiac surgery was applied to reduce complications of mechanical ventilation, to shorten the intensive care time and hospital stay to meet the need of the increasing number of open heart surgery, to reduce the cost of treatment. Early extubation was an essential part of this protocol. It was born based on balance anesthesia and selecting opioid with short duration of action, so providing adequate analgesia in the early postoperative period is important [8].

The effective pain management after heart surgery not only reduces the harmful effects on the cardiovascular, respiratory, immune system and coagulation but also helps patients recover faster, and is an indispensable mental care. Effective treatment of acute pain may reduce the incidence of chronic pain, improve quality of life [6], [11]. Obtaining the optimal postoperative analgesia after cardiac surgery is a challenge to the anesthesiologists.

The discovery of opioid receptors in the dorsal horn opened a new pain control method. The impact of postoperative regional analgesia on major outcome in non-cardiac surgery has been studied. Regional analgesic techniques are gaining popularity in cardiac surgery and have been implemented in some fast-track protocols for cardiac anesthesia. Epidural analgesia has

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been shown to decrease the stress response to surgery, improve postoperative respiratory function and provide excellent postoperative pain relief following cardiac surgery. However, during surgery that requires high doses of heparin, epidural analgesia is associated with the risks of the formation of an epidural haematoma. Intrathecal opioid administration is associated with a reduced risk of epidural haematoma, and is simpler and more reliable than epidural analgesia. Small dose of intrathecal opioid provide adequate analgesia, reducing the risks of intravenous analgesic use, such as respiratory depression, pruritus, nausea and vomiting. However, this technique is not routinely applied in cardiac surgery due to the risk of hematoma formation, although, it may be not real. The high doses of intrathecal morphine used have frequently resulted in delayed extubation. Finally, the effects of intrathecal morphine on postoperative pulmonary dysfunction and extubation time were controversial.

Morphine is less lipophilic, has slow onset of action, reaching the maximum analgesic effect of the chest after lumbar injection in 4-7 hours, duration of effect lasts up to more than 24 hours so its use is suitable for reducing postoperative pain. The meta-analysis study showed that morphine dose more than 0.3 mg had not increased the analgesic effects but increased undesirable effects [3]. There are some studies with limited subjects, no study has been done on this issue. We conducted this study to evaluate the effects of preoperative intrathecal morphine dose of 0.3 mg on postoperative pain, extubation time and pulmonary function in patients undergoing valve repair or replacement.

2. MATERIALS AND METHODS

The ethical committee of the hospital approved this prospective randomized control trial, written informed consent was obtained from 60 patients scheduled for primary elective valve repair or replacement via median sternotomy. Patients who were under 18 or over 60 years, had an ASA physical status IV, a neurological disorder, chronic diseases such as chronic lung diseases, liver failure, kidney failure, systolic pulmonary artery pressure more than 70 mmHg, were receiving therapy for chronic pain, an abnormal spinal anatomy, a local infection or sepsis at the site of lumbar puncture, left ventricular ejection fraction under 50%, had abnormal coagulation tests were excluded.

After enrollment, the patients were randomly allocated into two groups, receiving either 0.3 mg of preservative-free morphine intrathecally prior to anaesthesia and intravenous patient-controlled analgesia (PCA) with morphine postoperatively or only postoperative intravenous patient-controlled analgesia.

On the day before surgery, patients received instructions on how to use a patient-controlled analgesia device (PCA pump, B-Braun), visual analog scale (VAS) and spirometer (Flowscreen Pro®). Patients received 50 mg of hydroxyzine orally the night before surgery and the same dose one hour before being transferred to the operating room. In the operating room, patients were monitored by continuous ECG and ST-analysis, pulse oximetry, and an invasive arterial line inserted in the right radial artery under local anesthesia and peripheral intravenous line. In the morphine group, 0.3 mg morphine, diluted in 3 ml of normal saline was administered using a 27-gauge spinal needle in the L2-L3 space prior to induction of general anesthesia. If intrathecal puncture was not successful after two attempts or bloody staps occurred, the patient was excluded from the study. After pre-oxygenation, general anesthesia was induced in both groups with 0.3 mg/kg of etomidate, 0.1 mg/kg of vecuronium bromide, and 0.5 µg/kg of sufentanil first as a bolus, followed by a continuous infusion at 0.2 µg/kg/h. Mechanical ventilation was initiated with a tidal volume of 10 ml/kg, respiratory frequency of 12 cycles per minute, oxygen inspired fraction of 50%. A nasoesophageal thermometer, bladder catheter, and central venous catheter were inserted after anesthesia induction.

Anesthesia was maintained with either an adjustment of the isoflurane concentration or a bolus of sufentanil 0.2 µg/kg to maintain systolic blood pressure and heart rate within 20% of preoperative values. During cardiopulmonary bypass (CPB), hypnosis was maintained with

a propofol infusion at the rate of 4 mg/kg/h. Sufentanil infusion was terminated at the moment of skin closure. After arrival in the intensive care unit, a patient-controlled analgesia pump programmed for a 1 mg bolus of morphine with an administration interval locked at 7 minutes and free demand was installed.

Tracheal extubation was performed when patients were fully awake and responsive to verbal commands, as well as when the peripheral oximetry was greater than 94% on FiO_2 35%, spontaneous respiratory frequency was greater than 10 breaths per minute, temperature was greater than 36°C, and the patient was hemodynamically stable (low dose of cathecholamine), thoracic drainage less than 100 ml/h.

Pain scores at rest were measured using a 10 cm visual analog scale (0 = no pain, 10 = worst pain imaginable) at 4, 8, 12, 16, 20, 24, 30, 36, 42, 48 hours postoperatively and morphine consumption was also evaluated at the same times listed above. Pain scores on profound inspiration were measured after extubation and the first and second postoperative day.

Spirometry using a (Flowscreen Pro®, Germany) was performed preoperatively, in the first and second postoperative days to measure forced vital capacity (FVC), forced expiratory volume in the first second (FEV1).

Mechanical, extubation time and adverse effects (pruritus, nausea and vomiting, respiratory depression, headache, epidural hematome) were recorded.

The sample size was based on anticipated consumption of postoperative systemic morphine. In the previous study at our institution, a similar anesthesia protocol without intrathecal morphine indicated that at least 23 patients per group allowed detection of a 25% reduction in morphine consumption, at an alpha level of 0.05 and with a 90% power (morphine consumption during the first 48 h was 29.3 ± 7.6 mg). Continuous variables are presented as mean ± SD. The pain scores, postoperative morphine consumption, pulmonary function were evaluated using Student's t-tests, categorical data were compared using Fisher's exact test. A p-value < 0.05 was considered significant.

3. RESULTS

Patient characteristics, preoperative risk score, intraoperative and anesthetic data did not differ significantly between two groups (table 1). Mean anesthesia duration and CPB time were similar in both groups (237.4 ± 242.7 vs. 243.8 ± 51.3 minutes and 85.6 ± 49.4 vs. 87.7 ± 51.2 minutes, respectively). The total dose of sufentanil used was 88.3 ± 15.9 µg in the control group and 87.1 ± 15.5 µg in the morphine group (p > 0.05).

Table 1. Patient characteristics, operative and anesthetic data

	IM (n = 30)	Control (n = 30)	p
Age; year	38.1 ± 12.8	35.4 ± 11.5	> 0.05
Sex; M/F	12/18	13/17	> 0.05
Weight; kg	49.8 ± 7.3	49.1 ± 6.9	> 0.05
Height; cm	158.9 ± 7.3	158.1 ± 6.6	> 0.05
Euroscore	2.8 ± 0.7	2.7 ± 0.9	> 0.05
CBP time; min	85.6 ± 49.4	87.7 ± 51.2	> 0.05
Aortic cross-clamp; min	62.3 ± 40.9	64.5 ±39.8	> 0.05
Duration of anesthesia; min	237.4 ± 242.7	243.8 ± 51.3	> 0.05
Sufentanil; µg	87.1 ± 15.5	88.3 ± 15.9	> 0.05

Values are expressed as number of patients or mean ± SD.

IM, intrathecal morphine; M/F, male/female

Pain scores at rest during the first postoperative 16 hours (figure 1) and pain score on profound inspiration (figure 2) in the intrathecal group after extubation were significantly lower than those in the control group ($p < 0.05$).

Postoperative morphine consumption at different intervals (figure 3) during the first postoperative 30 hours in the intrathecal group was significantly lower and the cumulative morphine consumption reduced by more than 45% (table 2) in comparison to the control group (12.8 ± 7.5 vs. 24.2 ± 10.1 mg).

Table 2. Cumulative intravenous morphine consumption (mg)

	IM (n = 30)	Control (n = 30)	p
H4	1.6 ± 1.9	5.4 ± 2.7	> 0.05
H8	2.6 ± 2.4	8.4 ± 4.6	> 0.05
H12	3.6 ± 3.5	11.6 ± 6.1	> 0.05
H16	4.8 ± 4.1	14.5 ± 8.1	> 0.05
H20	7.6 ± 5.2	16.7 ± 8.2	> 0.05
H24	9.8 ± 6.8	20.6 ± 9.4	> 0.05
H30	12.8 ± 7.5	24.2 ± 10.1	> 0.05
H36	13.7 ± 9.7	26.4 ± 9.8	> 0.05
H42	14.8 ± 8.9	28.5 ± 10.7	> 0.05
H48	16.8 ± 9.6	31.5 ± 10.9	> 0.05

H, hour

The FVC, FEV1 decreased in both groups. There was no significant difference in FVC, FEV1 after extubation and on the first and second postoperative day (table 3).

The intrathecal morphine did not shorten mechanical and extubation time (4.62 ± 2.29 vs. 4.88 ± 2.55 and 6.39 ± 2.80 vs. 6.51 ± 2.93 hours, respectively).

The incidence of pruritus, nausea and vomiting was similar in the two groups (table 4). All intrathecal punctures were successful at the first or second attempt. No cases of spinal or epidural hematoma or respiratory depression after extubation were observed.

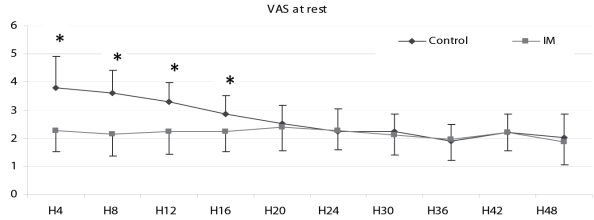

Figure 1. Pain score at rest
* $p < 0.05$

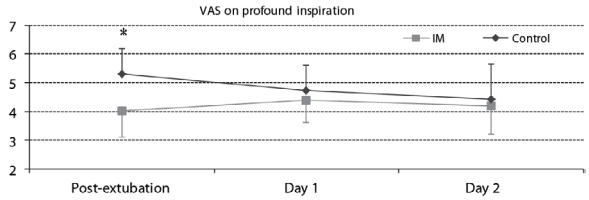

Figure 2. Pain score on profound inspiration
* $p < 0.05$

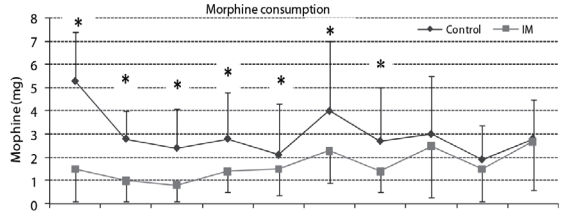

Figure 3. Postoperative morphine consumption at different intervals
* $p < 0.05$

Table 3. Lung spirometry

	FEV1; l			FVC; l		
	IM	Control	P	IM	Control	p
Pre-operative	2.08 ± 0.91	2.06 ± 0.72	> 0.05	2.31 ± 0.94	2.36 ± 0.72	> 0.05
Day 1	1.05 ± 0.38	1.15 ± 0.55	> 0.05	1.18 ± 0.41	1.27 ± 0.64	> 0.05
Day 2	1.53 ± 0.79	1.47 ± 0.43	> 0.05	1.79 ± 0.97	1.66 ± 0.47	> 0.05

Table 4. Mechanical ventilation and extubation time and undesirable effects

	IM (n = 30)	Control (n = 30)	p
Mechanical ventilation (hour)	4.62 ± 2.29	4.88 ± 2.55	> 0.05
Extubation time (hour)	6.39 ± 2.80	6.51 ± 2.93	> 0.05
Nausea (%)	7 (23.3)	8 (26.7)	> 0.05
Vomiting (%)	5 (16.7)	6 (20)	> 0.05
Pruritus (%)	3 (10)	2 (6.7)	> 0.05
Headache (%)	1 (3.3)	0	> 0.05

4. DISCUSSION

This study showed that preoperative intrathecal morphine dose of 0.3 mg provided lower pain scores at rest during the first postoperative 16 hours, pain score on profound inspiration after extubation, reduced intravenous morphine consumption until the 30th hour and reduced cumulative intravenous morphine consumption by more than 45% in comparison to the control group.

Research results are consistent with research of the other authors. Alhashemi et al [1] compared intrathecal morphine doses of 250 and 500 µg and placebo, and concluded that intrathecal analgesia decreased postoperative morphine requirements, but did not have a clinically relevant effect on extubation time after coronary artery bypass grafting surgery. This study suggests that 250 µg is the optimal dose of intrathecal morphine to provide significant postoperative analgesia without delaying tracheal extubation. Roediger et al [9] reported that 500 µg of morphine intrathecally prior to anaesthesia reduced by 40% of the total consumption of intravenous morphine by PCA and lower pain scores at rest during the first 24 h following extubation. Peak expiratory flow rate was greater and postoperative catecholamine release was significantly lower.

Effective pain relief when patients waking up in the recovery room is very important. Nader et al. [7] showed that patients given intrathecal morphine 7 µg/kg and fentanyl 1.5 µg/kg had low VAS pain score (2 versus 7) when entering to the recovery room and 24 hours after surgery (3 versus 5) versus the control group ($p < 0.05$).

Pain score at rest at all time points was less than 3, in other words, intrathecal morphine provided effective analgesia. The clinical significance of intrathecal morphine is that it constitutes an important component of multimodal pain management.

In the present study, intrathecal instead of epidural morphine was used. Epidural analgesia by opioid combined with or without local anesthetic provided excellent analgesia for cardiac surgery. This technique is not popular because of higher risk of hematome formation, especially in patients under valve surgery who need postoperative anticoagulation. Normalization of coagulation before epidural catheter removal may counter anticoagulant strategy. In addition, Intrathecal approach is simpler, more reliable and intrathecal puncture was implemented before operation (normal coagulation).

Although intrathecal morphine had better analgesia than the control group, but there was no statistically significant difference between two groups in FVC, FEV1. This can be explained that the control group used morphine via PCA, it is also an effective pain relief method. Furthermore, postoperative pulmonary dysfunction is a complex process affected by many factors including reduced normal activity of the respiratory muscles due to anesthesia, surgery, spinal inhibitory reflex (spinal reflex inhibition) on neural activity of the diaphragmatic nerve and respiratory muscles. Effective pain relief after surgery is only one part of improved respiratory function, good heart function is also very important to improve respiratory function, oxygen exchange in the lungs and muscle activity [10]. In term of pulmonary function, the result of this study is consistent with those of Dos Santos using 400 µg of intrathecal morphine. The two groups exhibited similar results for FEV1, FEV1/FVC and PaO_2/FiO_2 ratio [2].

Choosing the optimal dose of intrathecal morphine is a consideration, due to respiratory depression and prolongation of mechanical ventilation when using high doses of intrathecal morphine, the authors used recently a lower dose

of morphine in early extubation anesthesia. The authors selected doses of 7 µg/kg or 0.5 mg [1], [7]. Meanwhile, Lena [5] concluded that a dose of 4 µg /kg is not effective enough to ease the pain for surgical cardiac patients. The current trend, doses of 6 - 10 µg/kg were used, for the purpose of easy preparation, the dose of 0.3 mg was administered. Extubation time between two groups did not differ (6.39 ± 2.80 versus 6.51 ± 2.93 hours). This time is consistent with the definition of early extubation, in 6 - 8 hours after surgery [4].

The most serious side effect of intrathecal opioid is respiratory depression. No episode of oxygen desaturation (SpO_2 less than 90%) or respiratory rate less than 10 per minute was observed in our patients, but all the patients received oxygen via mask in the intensive care unit. Respiratory depression, which is a result of the rostral redistribution to brainstem respiratory centers, is a complication of intrathecal morphine. The lack of respiratory depression must be considered within the context of the small number of treated patients. However, patients who had received intrathecal morphine were continuously monitored at postanesthesia cardiac care unit by trained personnels.

In our institution, the urinary catheter was usually drawn on the second day, at this time, urinary retention effects of opioids was off, the urinary retention incidence was low and did not differ between the groups. The study had its limitations. It did not conclude a true placebo group, an intrathecal injection of normal saline solution was not used because of the ethical reason.

In conlusion, preoperative intrathecal morphine dose of 0.3 mg provided low pain scores at rest during the first postoperative 16 hours, pain score on profound inspiration after extubation, reduced intravenous morphine consumption until the 30th hour and reduced cumulative intravenous morphine consumption by more than 45% without delaying extubation but did not improve lung function in patients undergoing valve surgery.

5. CONCLUSION

Preoperative intrathecal administration of 0.3 mg morphine in patients undergoing valve surgery improved analgesia and reduced morphine consumption in the first 30 h, without delaying extubation time or improving the FEV1 and FVC.

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