Randomized Trial

Intrathecal Morphine Improves Hemodynamic Parameters and Analgesia in Patients Undergoing Aortic Valve Replacement Surgery: A Prospective, Double-Blind, Randomized Trial

Hamed Elgendy, MD, PhD[1,2] and Hatem A. R. Helmy, MD[3]

From: [1]HAMAD Medical Corporation, Doha, Qatar; [2]Anesthesia Dept. Assiut University Hospitals, Egypt; [3]Cardiology Dept. Assiut University Hospitals, Egypt

Address Correspondence: Hamed M. Elgendy, MD, PhD
HAMAD Medical Corporation, Post Box 3050, Doha, Qatar
E-mail: helgendy70@gmail.com

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Background: Intrathecal morphine (ITM) has been used in hopes of providing good postoperative analgesia in cardiac surgery. Little is known about its use in isolated aortic valve replacement surgery.

Objectives: To evaluate the effects of 7 μ/kg ITM administration in aortic valve replacement in regards to hemodynamics, pain score, and postoperative complications when compared to general anesthesia alone.

Study Design: A randomized, double-blind trial.

Setting: Academic medical center.

Methods: Forty-four patients, who underwent aortic valve replacement, were randomly assigned to receive ITM, before the induction of general anesthesia (ITM group, n = 22) or no intrathecal injection i.e., general anesthesia alone (control group, n = 22). Induction of anesthesia was done with fentanyl, propofol, and isoflurane. Pain scores, determined by visual analog scale (VAS), were recorded immediately after extubation, at the first, sixth, twelfth, eighteenth, and twenty-fourth hour after extubation. Hemodynamics, heart rate, mean arterial pressure, central venous pressure, pulmonary capillary wedge pressure, and cardiac index were recorded intra-operatively and up to 24 hours post-operatively.

Results: VAS scores were lower in the ITM group at each measured time than control group ($P < 0.01$). The cumulative fentanyl consumption during the first 24 hours after extubation was significantly reduced by 35% in the ITM group (951 μg /first 24 hours) as compared to the control group (1463.6 μg /first 24 hours), ($P < 0.001$). The mean time to first request for rescue analgesia was significantly prolonged in the ITM group (20.11 ± 4.24 hours, $P < 0.001$) compared with the control group (0.60 ± 0.44 hours). The mean tramadol consumption dose was significantly reduced in the ITM group (279.33 ± 61.35 mg), compared with the control group (895 ± 106.42 mg), ($P < 0.001$).

Hemodynamic parameters exhibited a significant decrease in HR and MAP in the ITM group, but no significant difference was found in regards to CVP, PCWP, and CI. Glyceryl trinitrate consumption in the first 24 hours was significantly reduced by 43% in the ITM group (28.3 mg /first 24 hours) when compared to the control group (145.5 mg /first 24 hours), ($P < 0.001$).
Extubation time (4.5 ± 7.5 vs. 5.3 ± 1.0 hours, $P < 0.05$) and intensive care unit length of stay (3.7 ± 1.0 vs. 5.6 ± 1.6 days, $P < 0.01$) were shorter in the ITM group.

Limitations: Small sample size.

Conclusions: In valvular heart disease patients undergoing aortic replacement surgery, ITM is a good adjunct to general anesthesia as a safe and effective analgesic alternative. It provides better hemodynamic control, earlier tracheal extubation, and shorter ICU stay.

Key words: Intrathecal, morphine, fentanyl, analgesia, aortic, cardiac, surgery

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Fast-track protocols allowing early tracheal extubation have been applied to cardiac surgery to reduce costs and improve outcomes (1,2). Inadequate postoperative pain control is not only hazardous to the cardiac patients but also can increase hospital care cost and diminish patients' satisfaction. Moreover, It provides an appropriate alternative to intravenous (IV) opioids during major surgery (3).

An intravenous infusion of remifentanil provides excellent hemodynamic stability during cardiac surgery and is now frequently administered to allow fast emergence from anesthesia and early extubation. However, remifentanil is not available in every institution where control of postoperative pain is required.

The single-shot intrathecal morphine (ITM) injection could be attractive as it is easy, feasible, reliable, avoids epidural catheter insertion, and is more economical (4). Another crucial advantage is to avoid irregular and inadequate pain control in the early, and most painful, part of the postoperative period (5).

ITM morphine has been shown to produce improved analgesia following cardiac surgery, compared with intravenous morphine (6,7). However, the high doses of ITM morphine used have frequently resulted in delayed extubation.

In aortic aneurysm surgery, low-dose ITM is safe, effective, and feasible (5,8). Moreover, it reduces the risk of major nonsurgical complications (9) . However, relatively little has been known about the effects of ITM on the hemodynamics of isolated aortic valve surgery patients.

In our institution, we have difficulty controlling patients' stress response, which induces unwanted tachycardia, especially after aortic valve replacement surgery even when using a higher dose of intravenous fentanyl and nitroglycerine. Thus, we tried to modulate the analgesic regimen after aortic surgery using ITM and investigate its impact on hemodynamic parameters and efficiency of analgesia in the first postoperative day.

Therefore, we conducted a prospective randomized double-blind study in patients undergoing aortic valve replacement surgery to assess the effects of preoperative ITM administration of 7 μg/ kg morphine on postoperative analgesia, hemodynamic stress response, and recovery profile following fentanyl-propofol-based and isoflurane anesthesia in comparison with general anesthesia alone.

Methods

Following local institutional ethics committee approval at Assiut University Hospitals, Assiut University, Egypt and obtaining written informed consent, 44 adult patients [American Society of Anesthesiologists (ASA) physical status II: III] scheduled for elective aortic valve replacement were included in this randomized double-blind controlled study.

Exclusion criteria were age > 45 years, body mass index > 35 kg/m^2, emergency surgery, previous cardiac surgery, patients with known contraindications for intrathecal (IT) analgesia such as allergies to the study drugs, patient refusal, low back pain, infection at the injection site, bleeding diathesis, and patients receiving preoperative heparin, coumadin derivatives, aspirin less than 7 days before operation, and non-steroidal anti-inflammatory drugs less than 3 days before operation. Left ventricular ejection fraction < 40%, use of inotropic drugs, evidence of chronic obstructive pulmonary disease, and treatment with clonidine or steroids were also excluded. All routine cardiac medications were continued until the morning of surgery.

Electrocardiogram (ECG), echo and chest radiograph, renal and liver function tests, complete blood picture, complete coagulation profile including prothrombin time and concentration (PT), partial thromboplastin time (PTT), international normalized ratio (INR), and bleeding time, were required before participation into the study. Based on full history, clinical examination, and investigation findings, the anesthesiologist and the cardiac surgeon first decided which patients were suitable to undergo aortic valve replacement surgery.

Using an online research randomizer (www.randomizer.org), patients were randomly allocated into 2 groups of 22 patients each to receive either ITM (ITM group) before induction of general anesthesia, 7 μg/ kg preservative-free morphine dissolved in 5 mL normal saline. All patients were placed in the sitting position and the skin at the level of the inter-space L3-L4 or L4-L5 was anesthetized using 3 mL lidocaine 1% through a 25-gauge needle. It administration was done through a 27-gauge spinal needle with pencil point tip (Sprotte Standard Needle, Pajunk, Geisingen, Germany). If the anesthesiologist was unable to obtain clear cerebrospinal fluid and administer the ITM, the patient was withdrawn from the study. For ethical considerations, patients in the control group had only local anesthesia of the skin. A bandage was placed on the puncture point in the back to ensure that all study health professionals were blinded to the patient allocation group. The anesthesiologist who performed the anesthetic was not involved in data collection and hence the double-blind nature of the study.

Preoperatively, the visual analog pain scale (VAS) score was described to the patients, ranging from 0 to100 (with 0 = no pain and 100 = the worst pain imaginable). All patients received their usual medication on the operation day, followed by pre-medication with intramuscular morphine 0.1 mg/kg and midazolam 0.05 mg/kg one hour before surgery.

Anesthesia was induced and maintained using propofol (1 – 2.5 mg/kg) (Diprifusor, Vial Medical, Fresenius, Schelle, Belgium) and an induction an IV dose of fentanyl 5 µ/kg to maintain mean arterial pressure (MAP) and heart rate (HR) to within 15% of preoperative values and tracheal intubation was facilitated with rocuronium bromide 1 mg/kg intravenously. In both groups, isoflurane was titrated 0.5% – 2% to maintain hemodynamic homeostasis and the cardiac anesthesia technique was standardized in both groups.

After surgery, patients were transferred to the intensive care unit (ICU). The medical and nursing staffs in the ICU were unaware of the allocation group. The criteria for extubation included responding to verbal command, hemodynamic stability with minimal inotropic support, adequate pulmonary function (respiratory rate between 12 – 20 breath/minute, $PaCO_2$ < 50 mm Hg, PaO_2 > 75 mm Hg on FiO_2 < 40%, pH > 7.3), normothermia, adequate urine output, and absence of active bleeding (chest tube drainage < 50 mL/hour).

Mechanical ventilation was maintained until normothermia, hemodynamic stability, and accepted bleeding through the chest drains was achieved. Patients were extubated within a few hours of ICU arrival and received a titrated dose of fentanyl (0.5 – 1 µg/kg/hour) until the VAS was < 30. The propofol infusion was stopped, and the fentanyl was decreased in increments of 0.25 µ/kg/hour to allow the patient to wake up.

Following extubation, shivering was treated using 1.5 mg/kg of tramadol in both groups. The postoperative fentanyl dose titrated from 0.25 to 2 µg /kg/hour and sometimes supplemental doses of 25 – 50 µg of fentanyl administered in addition to additional tramadol analgesia according to the patient needs.

All patients received supplemental oxygen via a face mask following extubation to maintain oxygen saturation > 95%. Patients were discharged from the ICU when the following criteria were met: correct orientation, hemodynamic stability without the use of intravenous vasoactive drugs, SpO_2 > 95% with nasal oxygen < 4 L/minutes, and urine output > 0.5 – 1 mL/kg/hour. Postoperatively, hemodynamics were recorded at one hour and every six hours in the first 24 hours after extubation.

All pressures where we used pulmonary artery catheter (Swan-Ganz™ Catheters - Edwards Lifesciences, Irvine, CA, USA), MARQUETT, SOLAR 8000, patient monitor, U.K. Cardiac output (CO), cardiac index (CI) were measured using thermodilution method and CO computer of (SPECTRAMED)- HEMODYNAMIC PROFILE COMPUTER MODEL-SP1445 were measured at the following time points post operatively, 1, 6, 12, 18, and 24 hours after extubation.

Pain scores were measured one hour after tracheal extubation and every 6 hours during the first 24 hours. All the following postoperative parameters must be recorded: fentanyl and glyceryl-trinitrate (GTN) consumption were recorded in first 24 hours, a rescue supplemental analgesia of IV tramal which was given if needed or VAS was ≥ 30, first time to ask for supplemental analgesia, fluid intake and output postoperatively, and blood, plasma transfusion and mediastinal drainage volume.

Side effects related to lumbar puncture and ITM were recorded: nausea, vomiting, pruritus, headache, and urinary retention. Respiratory depression was defined as a respiratory rate < 10 breaths/minute. Central or peripheral neurological deficits were prospectively researched. A peri-operative myocardial infarction (MI) was documented when a new Q wave, new left bundle branch block, or new ST and T wave changes on postoperative ECG were observed in addition to elevated cardiac enzymes. Cardiac arrhythmias were also recorded. Extubation time, ICU, and hospital lengths of stay, and time to fulfill ICU discharge criteria were recorded. Postoperative complications were noted daily until hospital discharge.

Statistical Analysis

Our primary outcome measure was to calculate the total analgesic doses consumed in the first postoperative day. Secondary outcome measures were hemodynamic control, VAS scores, time to first request for rescue analgesics, doses of supplemental analgesics, and incidence of postoperative complications.

The statistical work of this study was done by a package of computer programs (SPSS version 16 for Windows i.e., Statistical Package for the Social Science) and Microsoft Excel version 7.0. Data are expressed as mean ± SD. Paired T-test was applied for significant differences in the same group. Student T-test was applied for significant differences between groups. P < 0.05 was considered statistically significant. Our aim is to obtain 20% decrease in analgesic requirements in a

sample population of 250 when using ITM. A calculated sample size of 22 would have an 80% power of detecting a difference at a 0.05 level of significance using a confidence interval of 95%.

Results

Patient characteristics and operative data showed an insignificant statistical difference in both groups (Table 1).

The VAS scores were significantly lower in the ITM group compared to the control group at all time measurements ($P < 0.001$) (Fig. 1).

The cumulative fentanyl consumption during the first 24 hours after extubation was significantly reduced by 35% in the ITM group (951 µg /first 24 hours) as compared to the control group (1463.6 µg /first 24 hours) ($P < 0.001$). None of our patients in either group showed chronic pain preoperatively, as shown in Table 1.

The mean time to first request for rescue analgesia was significantly prolonged in the ITM group (20.11 ± 4.24 hours, $P < 0.001$) compared with the control group (0.60 ± 0.44 hours). The mean tramadol consumption dose was significantly reduced in the ITM group (279.33 ± 61.35 mg) compared with the control group (895 ± 106.42 mg) ($P < 0.001$) (Table 2).

Glyceryl trinitrate consumption (GTN) in the first 24 hours was significantly reduced by 43% in the ITM group (28.3 mg/first 24 hours) when compared to the control group (145.5 mg /first 24 hours) ($P < 0.001$).

Both intra-operative and postoperative heart rate and mean arterial pressure were significantly lower in the ITM group when compared to the control group

Table 1. *Patient characteristics and operative data.*

	ITM n = 22	Control n = 22
Age (y)	26.5 ± 6.9	25.9 ± 6.5
Gender (M/F)	11/11	10/12
Preoperative VAS	0/22	0/22
Weight (kg)	56 ± 7.9	64.4 ± 11.4
Height (cm)	159.8 ± 5.8	171.5 ± 6.2
Ejection fraction	63.4 ± 10.8	63.6 ± 4.2
CBT/min	99.8 ± 5.5	98.3 ± 7.1
ACCT/min	74.0 ± 7.4	78.8 ± 6.1

Values expressed as number, percentages, and means ± SD
Abbreviations: ITM = intrathecal morphine, VAS = visual analog scale, CPBT = cardiopulmonary bypass time, ACCT/min = aortic cross clamping time/min

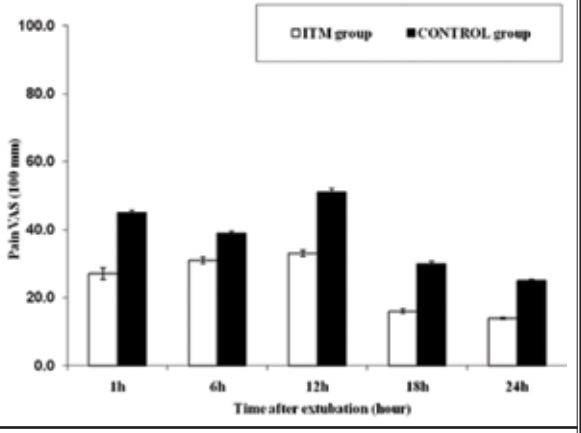

Fig. 1. *Effects of preoperative intrathecal administration of 7 µg/kg morphine on pain scores.*
Pain scores were measured on 100 mm visual analog scale. Data are expressed as mean ± SD ($P < 0.001$) as compared to the control group.

Table 2. *Postoperative parameters.*

Parameter	ITM	Control	*P* value
Time to first awakening/h	1.5 ± 29.3	1.6 ± 31.3	0.8
Time to extubation/h	4.5 ± 75.3	5.3 ± 1.0	0.04
ICU stay	3.7 ± 1.0	5.6 ± 1.6	0.002
Hospital LOS	8 ± 12	10 ± 9	0.12
GTN consumption /mg /1st 24 h	28.3 ± 17.5	145.5 ± 52.2	0.001
First request rescue analgesia/h	20.11 ± 4.24	0.60 ± 0.44 h	< 0.001
Tramadol consumption/mg/1st 24 h	279.33 ± 61.35	895 ± 106.42 mg	< 0.001
Fentanyl consumption/µg /1st 24 h	951.0 ± 190.9	1463.6 ± 130.6	0.001
Fluid intake/mL/ 1st 24 h	4179.2 ± 1029.7	4340.9 ± 772.6	0.673
Fluid output/ mL/1st 24 h	4745.8 ± 1133.1	5140.9 ± 1449.6	0.478
Postoperative blood transfusion/ mL	1404.2 ± 720.6	1727.3 ± 261.1	0.168
Postoperative plasma transfusion/U	4.2 ± 1.0	3.8 ± 0.8	0.362
Total mediastinal drainage/mL	1112.5 ± 393.2	1013.6 ± 156.7	0.434

NOTE. Data expressed as mean ± SD. $P < 0.05$ considered to be significant.
Abbreviation: LOS = length of stay, GTN = glyceryl-trinitrate.

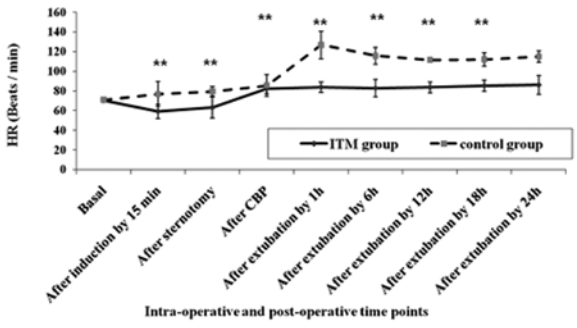

Fig. 2. *Intra-operative and post-operative HR in ITM group and control group.*
Abbreviations: CPBc= cardiopulmonary bypass, **($P < 0.001$)

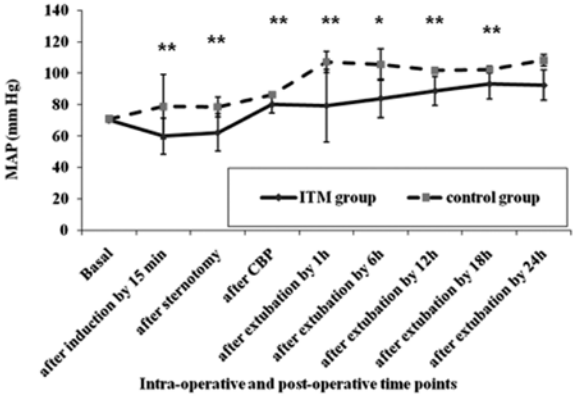

Fig. 3. *Intra-operative and post-operative MAP in ITM group and control group.*
Abbreviations: CPB = Cardiopulmonary bypass, ** ($P < 0.001$)

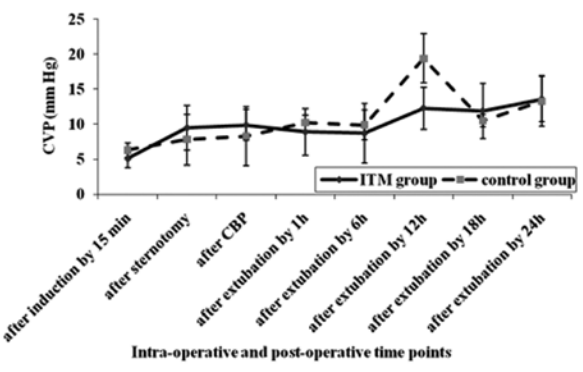

Fig. 4. *Intra-operative and post-operative CVP in ITM group and control group.*
Abbreviations: CPB = Cardiopulmonary bypass.

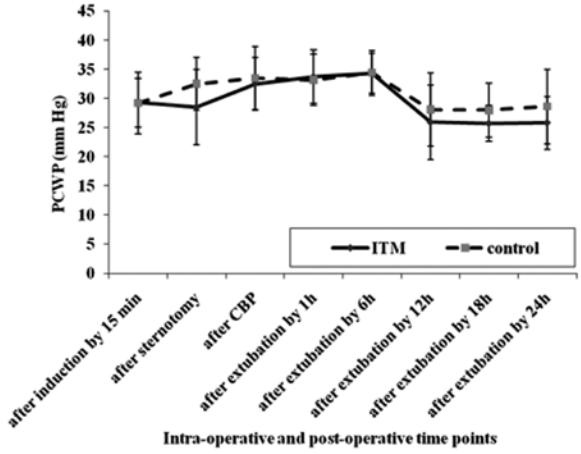

Fig. 5. *Intra-operative and post-operative PCWP in ITM group and control group.*
Abbreviations: CPB = Cardiopulmonary bypass.

($P < 0.001$) (Figs. 2 and 3). However, there were no significant differences in CVP (Fig. 4), pulmonary capillary wedge pressure (PCWP) (Fig. 5), and cardiac index (CI) (Fig. 6) between the 2 groups.

Recovery profile including extubation time and ICU length of stay were significantly reduced in the ITM group compared to the control group ($P < 0.05$); however, hospital stay was prolonged in the control group but statistically insignificant. In the first 24 hours postoperative, fluid intake and output of blood, plasma transfusion, and mediastinal drainage showed an insignificant difference between the 2 groups (Table 2).

Postoperative complications are listed in Table 3. None of the patients experienced bloody lumbar puncture, post-lumbar puncture headache, or respiratory depression.

Mild opioid-related side effects like nausea and vomiting were treated with ondansetron, 4 mg intravenously, and pruritus was treated with nalbuphine, 2.5 to 5 mg intravenously. Urinary retention cannot be assessed as all patients had urinary catheters for the first 48 hours postoperatively. Only one patient in the control group had a ventricular tachycardia and was managed properly with IV amiodarone.

Discussion

The present study revealed that ITM morphine 7 µg/kg, when combined with general anesthesia, resulted in improved hemodynamic control and better an-

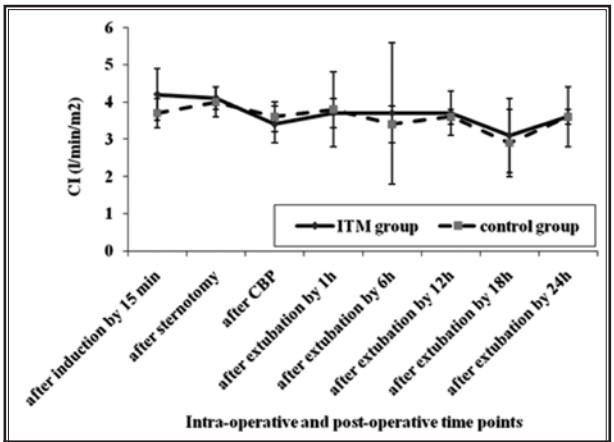

Fig. 6. *Intra-operative and post-operative CI in ITM group and control group.*
Abbreviations: CPB = Cardiopulmonary bypass.

Table 3. *Frequency of postoperative complications in the 2 studied groups.*

	ITM Group (n = 22)	Control Group (n = 22)
Opioid-related complications		
Nausea	5	4
Vomiting	3	2
Pruritus	5	2
Respiratory depression	0	0
Spinal anesthesia complications		
Post-spinal tap headache	0	0
Central neuroaxial hematoma	0	0
Cardiac complications		
Myocardial infarction	0	0
Ventricular tachycardia	0	1

NOTE. Values represent number of patients. Abbreviation: ITM = intrathecal morphine.

algesia after aortic valve replacement compared with general anesthesia alone.

The ITM group had significantly lower VAS pain scores after extubation and significantly reduced total IV fentanyl and tramadol requirements. Also, the study exhibited increased time for first rescue analgesia request and reduced GTN consumption in the first 24 hours in the ITM group when compared to the control group.

Earlier tracheal extubation and shorter ICU stay were recorded in the ITM group. Regarding postoperative complications, none of the patients experienced respiratory depression or neurological deficits; there were only opioid-related side effects, which were easily managed.

Inadequate analgesia during the postoperative period may lead to many adverse hemodynamic (tachycardia, hypertension, and vasoconstriction), metabolic, immunological, and hemostatic alterations (10,11). Therefore, effective analgesia during the immediate postoperative period following cardiac surgery has been shown to reduce the incidence and severity of myocardial ischemia (12).

Although ITM was tested before in aortic aneurysm surgery, we are concerned about the hemodynamic instability which can develop in the early postoperative period following aortic valve replacement surgery. The majority of our patients are young and experience more intense pain than older patients as is consistent with previous reports (13,14).

Therefore, we tried a moderate dose of ITM to examine its possible side effects. We studied only selective type of valve disease to check the hemodynamic stability of our technique; we found better hemodynamic control in HR and MAP, but no difference was found in CVP, PCWP, and CI between the 2 groups. On the other hand, in a previous report (15), the authors studied 40 patients including elective coronary bypass graft and aortic or mitral valve replacement patients, and found no intra-operative differences in MAP, MPAP, CVP, and CO values between the 2 groups. Also, recovery profile, ICU stay, and hospital discharge were similar in both groups. This discrepancy could be attributed to the other investigators using a mixture of patients not having the same pathology. This may explain the lack of difference observed in hemodynamics. Another possible cause is that they used a different fast track protocol with remifentanil infusion versus sufentanil infusion in addition to ITM 8 μg/kg, so there was no difference in recovery and length of stay.

Although ITM can provide excellent postoperative analgesia, concerns have been raised regarding the potential for ventilatory depression and delayed extubation when used as part of a fast-tracking program. We found earlier extubation time in the ITM group when compared to the control group. On the other hand, Chaney et al (16) demonstrated significant prolongations of the time until tracheal extubation in patients receiving ITM (10 μg/kg) combined with systemic fentanyl (20 μg/kg). These investigators concluded that long-acting ITM and IV opioid analgesics increased the risk of ventilatory depression after cardiac surgery.

However, others have reported that smaller intra-operative doses of IV fentanyl (2 – 4 µg/kg), followed by ITM (10 µg/kg) allowed extubation in the operating room after thoracotomy procedures without increasing the incidence of postoperative respiratory complications (17). Differences in drug dosage, study design, and various clinical protocols are the most common reasons for different extubation times between these studies.

This explains the difference when Fitzpatrick and Moriarty (18) used higher doses of both ITM and IV fentanyl but others reduced the dose in a thoracotomy study (17). Moreover, Jacobsohn and his co-workers (19) found that ITM did not delay early extubation in cardiac surgery but improved pulmonary functions. In minimally invasive cardiac surgery, ITM provides efficient postoperative analgesia, reduces IV opioid consumption, and does not defer early extubation (20). Therefore , we decided to reduce our dose.

A recent study showed that ITM and bupivacaine reduced the risk of postoperative delirium after coronary artery bypass grafting (CABG) in a population of opium dependent patients (21). Addition of intrathecal magnesium sulfate reduces postoperative opioids requirements without increasing their side effects (22). The most serious complication of IT injection is epidural or spinal hematoma, and the risks are higher when the injection is followed by systemic anticoagulation. None of the previous reports on the use of ITM for cardiac surgery have noted spinal or epidural hematoma (23-26) yet the estimated risk is 0.35%.

The exclusion criteria related to these possible complications were particularly strict (27) and the surgeons agreed to delay surgery for any patient with blood in the spinal tap fluid (although there were no such cases). For this study, systemic heparinization was delayed for at least 60 minutes after lumbar puncture. This delay may be clinically relevant with respect to formation of neuroaxial hematomas. No clinical evidence of central neuroaxial hematoma was found in any patients who received ITM. However, this relatively small number of patients precludes any strong conclusions about the safety of ITM administration in aortic valve replacement procedures.

We reported mild opioid-related side effects like nausea, vomiting, and pruritus, which were managed easily as consistent with a previous study (2).

At the molecular level, several experimental studies described the cellular benefits of ITM. Li and his colleagues (28) found that ITM preconditioning induces cardioprotection via activation of delta, kappa, and mu opioid receptors and (29) the same group explained that ITM remotely preconditions the heart via a neural pathway. A recent study showed a contribution of spinal neuronal nitric oxide synthase (NOS) signaling to ITM cardioprotection (30). More studies are required to prove the molecular benefits of ITM on the clinical level.

This study has some limitations. We studied relatively small number of patients because the incidence of rheumatic aortic valve disease is very small in comparison to mitral valve disease in our population. We did not use IV morphine as a form of maintenance analgesia to test the same intrathecal drug as we tried to avoid delayed extubation and prolonged recovery; instead we used IV fentanyl as a short acting IV analgesic with fewer systemic side effects.

Conclusion

In conclusion, ITM after aortic valve replacement surgery with general anesthesia had better hemodynamic and analgesic benefits than with general anesthesia alone. Moreover, its use has reduced extubation time and ICU stay.

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HE performed the data collection, participated in the study design and statistical analysis, and wrote the manuscript. HH participated in the study design, statistical analysis, and interpretation of data and writing of manuscript.

A portion of the results were presented at the 8th meeting of the Asian Society of cardiothoracic anesthesia, Tokyo, Japan.

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