

The Effect of Combined Intrathecal Morphine and Clonidine on Stress Response, Extubation Time and Postoperative Analgesia after Cardiac Surgery

Mona Mohamed Mogahed^{*}, Jehan Mohammad Ezzat Hamed and Mohamed Shafik Elkahwagy

Faculty of Medicine, Tanta University, Egypt

^{*}Corresponding author: Mona Mohamed Mogahed, Faculty of Medicine, Tanta University, Tanta, Egypt, Tel: 0201145130150; Fax: 020403292202; E-mail: monamogahedfr@hotmail.com

Received date: June 10, 2017; Accepted date: July 03, 2017; Published date: July 07, 2017

Copyright: © 2017 Mogahed MM, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: Pain is a major complication after cardiac surgery, if it is poorly controlled, it will lead to more complication as respiratory depression, myocardial ischemia, delayed extubation, and more ICU stay, with the more analgesic consumption and patients suffering. Intrathecal morphine produces intense and prolonged analgesia and can be useful adjunct for controlling postoperative pain and facilitating early extubation after cardiac surgery. The addition of intrathecal clonidine to morphine allows the dose of intrathecal morphine to be reduced and reduces the risk of respiratory depression while maintaining good analgesia and allows early extubation. This randomized controlled study was carried out on 40 patients undergoing open cardiac surgery and was divided into two groups; group (I): is the control group (n=40) and group (II): is the morphine clonidine group (n=40), patients received intrathecal morphine 4 mcg/kg and clonidine 1 mic/kg. The aim of this study was to evaluate the effects of combined intrathecal morphine and clonidine on stress response, time of extubation, and postoperative analgesia after cardiac surgery. The results of our study revealed that, there was no statistical significant changes in CVP (central venous pressure), Sao₂ (Oxygen saturation) and lactate level in both group, but there was a decrease in HR after induction and before bypass in the intrathecal morphine clonidine group compared with the control one, also there was a significant reduction in MAP after induction, before bypass and after bypass in morphine clonidine group vs. control group. Cortisol level was decreased after sternotomy, after ICU admission and after extubation in the morphine group vs. control group. Time to extubation, vas, and morphine consumption in 24 h were all decreased in the morphine group compared with the control one, with no significant differences in post-operative complication in both studied groups.

Conclusion: In patients with well-preserved ventricular and respiratory function scheduled for fast-track cardiac surgery, the use of combined intrathecal morphine 250 µg and clonidine provides good postoperative analgesia and early extubation without side effects.

Keywords: Intrathecal; Morphine; Clonidine; Cardiac surgery

Introduction

The intensity of sternotomy incision pain after cardiac surgery, is often severe, and is worsened by coughing, deep breathing, moving or turning in bed and mobilization [1-4].

Severe pain leads to impairment of pulmonary function, and severe respiratory [5,6] and other [7] complications which is the leading cause of postcardiac surgical morbidity [8,9]. Early extubation should be the goal after cardiac surgery, as it may reduce postoperative complications and decrease ICU stay and costs [10].

Adequate control of pain leads to early extubation and rapid transfer to the ward and is mostly applied to patients who have well-preserved pulmonary and ventricular function [11]. The addition of intrathecal clonidine to morphine allow the dose of intrathecal morphine to be reduced and reduces the risk of respiratory depression while maintaining good analgesia and allows early extubation [12]. Intrathecal and epidural anesthesia have been shown to decrease stress response to surgery, improve postoperative respiratory function, and provide excellent postoperative pain relief after cardiac surgery [13].

Regional anesthetic techniques are gaining popularity in cardiac surgery and have been implemented as an integral part of some fast-track cardiac anesthesia [14].

This study investigated the effect of pre-operative intrathecal 250 µg morphine administration of combined with clonidine in patients undergoing cardiac surgery on opioid consumption and duration of controlled ventilation.

Patients and Methods

This study was carried out on forty patients (submitted to cardiac surgery CABG or valve replacement). An informed consent was taken from all patients. The patients were randomly allocated into 2 groups:

Group I (40 patients): control group.

Group II (40 patients): received intrathecal morphine and clonidine preoperatively.

Inclusion criteria: Patients undergoing cardiac surgery CABG or valve replacement with age between 25 and 60 years old.

Exclusion criteria: Emergency surgery: combined valve replacement and CABG surgery, redo CABG, patients with left ventricular ejection fraction less than 40%, patients with platelets count less than

100000/dL, patients with significant renal impairment, Patients with significant neurological impairment, patients with liver disease, patients with bleeding disorder, current anticoagulant therapy, patients with chronic cardiac or respiratory failure and patients who received corticosteroids within 24 h preoperatively. All patients underwent routine examinations as determined by age, sex and type of surgery. Clinical examination was performed to assess the ASA physical status of the patients and to exclude any contraindication. Electrocardiogram (ECG), Chest radiograph, echocardiography, liver function, Hb and Ht, renal function, prothrombin time and activity, partial thromboplastin time and complete blood picture.

All patients were premedicated with midazolam 15-20 µg/kg intravenously to facilitate the placement of the central line and arterial cannula.

The patients in group (II) were placed in sitting position and the back of the patients were sterilized with povidone-iodine (betadine). The skin was anesthetized with 3 ml of 1% lidocaine, lumbar puncture was done at L2-L3 or L3-L4 interspace with a 25-gauge needle. The patients received 4 µg/kg morphine with 1 µg/kg clonidine intrathecally one hour before induction of anesthesia. General anesthesia was induced by fentanyl 7-10 µg/kg, etomidate 0.25 mg/kg, cisatracurium 0.2 mg/kg to facilitate intubation and maintained by isoflurane 0.25-1%, cisatracurium 0.03 mg/kg, fentanyl 5-10 mcg/kg and propofol 0.1-0.2 mg/kg.

Non-invasive and invasive blood pressure, heart rate, oxygen saturation, tidal carbon dioxide and electrocardiogram (ECG). CVP, arterial blood gases and urine output.

In the ICU before extubation, pain was controlled by PCA morphine 1 mg at a lockout period of 10 min with a maximum dose of 28 mg/4 h.

Measurements: Heart rate (HR), Mean arterial pressure (MAP), Central venous pressure, Oxygen saturation, Acid-base changes (pH, Pco₂, HCO₃).

The above parameters were recorded before induction of anesthesia, after induction of anesthesia, before bypass, after bypass, before shift to ICU. On arrival to ICU. These measurements were recorded every 2 h until the patients extubated, then 15, 30, 60 min and then hourly for 4 h after extubation.

Plasma lactate level (mg/dL), plasma cortisol was measured preoperatively, poststernotomy, on admission to ICU, after extubation, after 8, 24, 48 h after ICU admission.

After extubation pain was assessed by visual analogue score (VAS) 0 no pain to 10 (worst pain imaginable) every 30 min for 1st 4 h in ICU; then every one hour for the next 4 h; then every 2 h for 20 h and finally after 24 h. When VAS equal or more than 4 morphine 2 mg was given IV.

Total dose of intravenous morphine was recorded in 1st 24 h in both group. Sedation was assessed by Ramsay sedation score.

In the ICU, Patients were extubated when they have the following criteria:

Patients awake and obey commands.

SpO₂>92% on ≤ 50% oxygen, Maximum inspiratory pressure ≥ -25 cm H₂O, Core temperature >36°C, Chest tube drainage 100 ml/h for 2 consecutive h.

Postoperative hypertension (SBP 140 mmHg) was treated with nitroglycerin infusion, Postoperative hypotension (SBP 75 mmHg) was treated by vasoactive drugs.

Side effects of intrathecal morphine were recorded such as pruritus, nausea, vomiting and respiratory depression if respiratory rate <10/min. Time from admission to ICU up to extubation was recorded.

Assuming that mean (SD) morphine consumption would be about 50 (25) mg per 24 h, we calculated that a sample of 40 patients would be enough to detect such a difference with a type I error of 0.05 and a type II error of 0.10. Results were collected, tabulated and statistically analyzed by an IBM compatible personal computer with SPSS statistical package version 20 (SPSS Inc. Released 2011. IBM SPSS statistics for windows, version 20.0, Armonk, NY: IBM Corp.). Two types of statistical analysis were done: a) Descriptive statistics: e.g. was expressed in: Number (No), percentage (%) mean (\bar{x}) and standard deviation (SD). b) Analytic statistics: e.g. Student's t-test is a test of significance used for comparison of quantitative variables between two groups of normally distributed data, while Mann Whitney's test was used for comparison of quantitative variables between two groups of not normally distributed data. 2 Chi-square test (χ^2) was used to study association between qualitative variables. Whenever any of the expected cells were less than five Fischer's Exact test with Yates correction was used. P value of <0.05 was considered statistically significant. Logistic regression was not done as prediction was not an aim of this work; however, the 2 groups were matched at the beginning of the study for gender, age and ASA (Table 1).

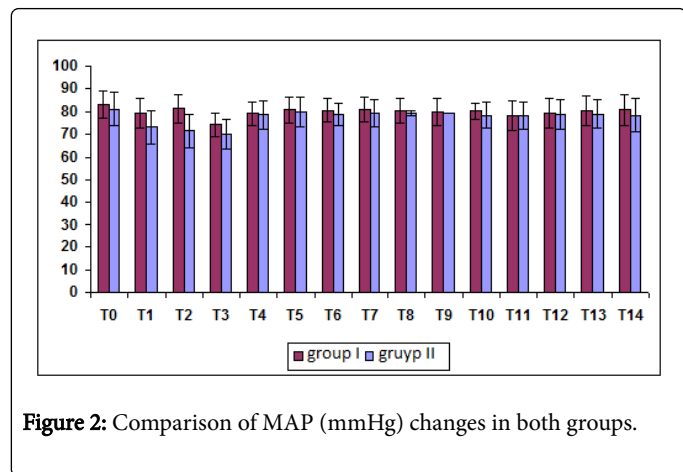
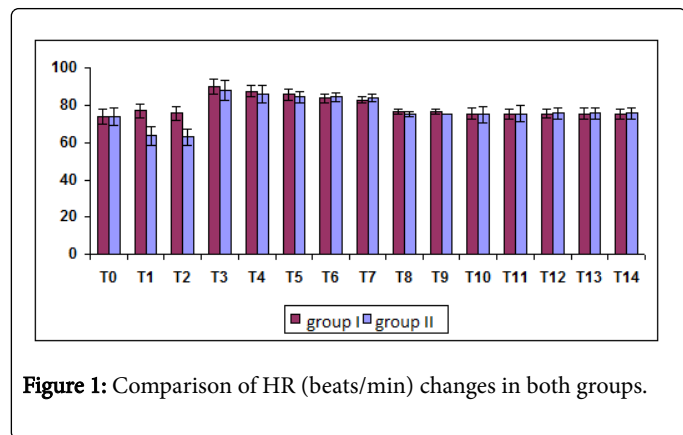
Demographic Data	Group I	Group II	T-test		
			t	P-value	
Age (years)	25	26	0.756	0.863	
	Range	59			58
	Mean	38.55			37.75
	SD	13.081			11.229
Weight (kg)	Range	60	60	0.853	0.956
		75	78		
	Mean	65.55	65.8		
	SD	4.98	5.083		
Height (cm)	Range	165	167	-0.214	0.896
		182	182		
	Mean	174.1	174.45		
	SD	5.119	5.246		
Sex M/F	11/9	12/8	P value -0.749		
*statistically significant difference at P<0.05.					

Table 1: Comparison of demographic data in both groups.

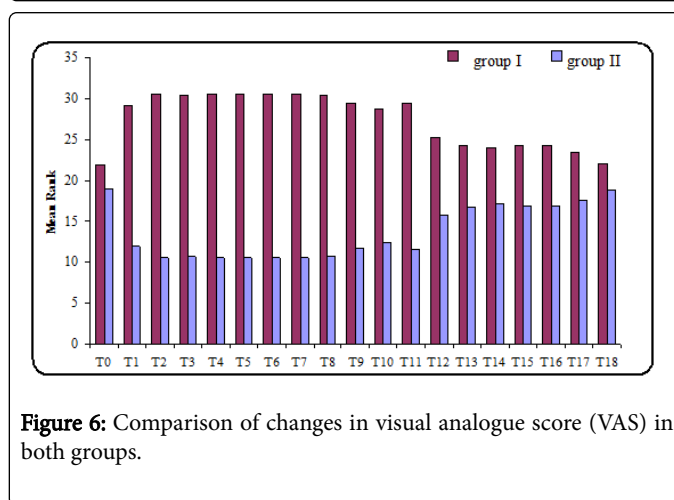
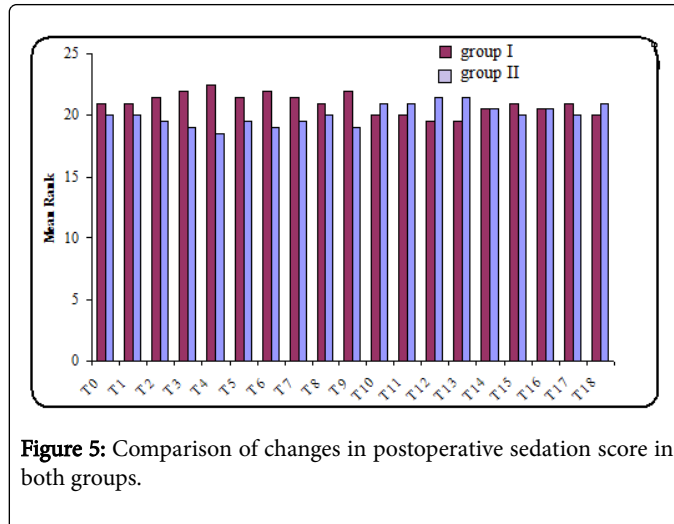
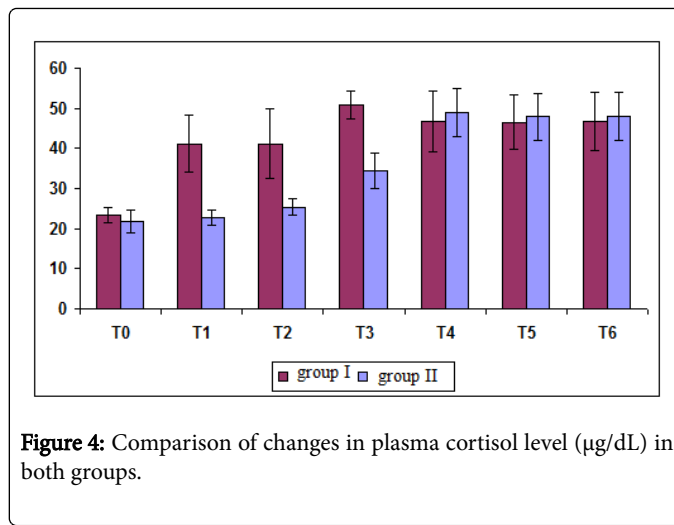
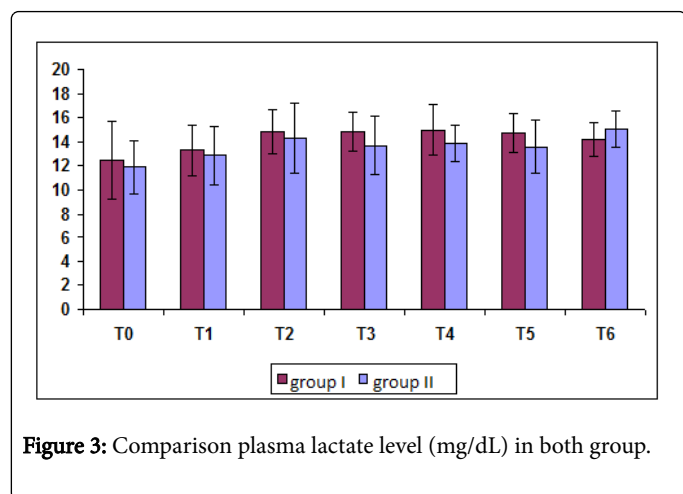
Results

There was a statistically significant decrease in HR in group II at time after induction (T1) and before bypass (T2) in comparison with group I (P<0.05) (Figure 1), While there was a statistically significant

decrease in MABP in group II at time after induction (T1), before bypass (T2) and after bypass (T3) in comparison with group I (P<0.05) (Figure 2).

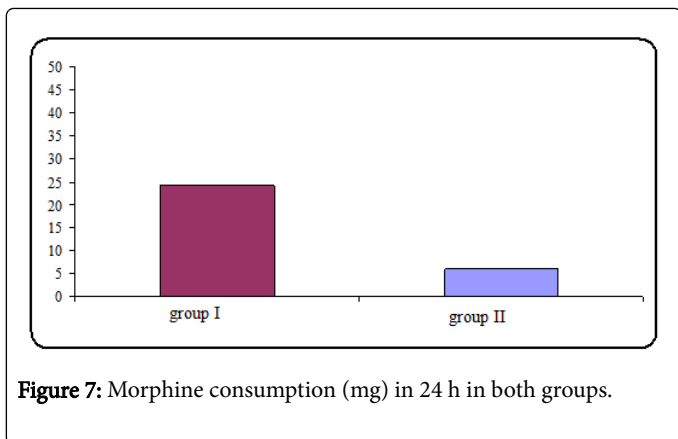


No statistically significant difference in both groups as regards to plasma lactate level (mg/dl) (P>0.05) (Figure 3), However, there was a statistically significant lower plasma cortisol level (µg/dl) in group II at time of poststernotomy (T1), on admission to ICU (T2) and following tracheal extubation (T3) in comparison with group I (P<0.05) (Figure 4).

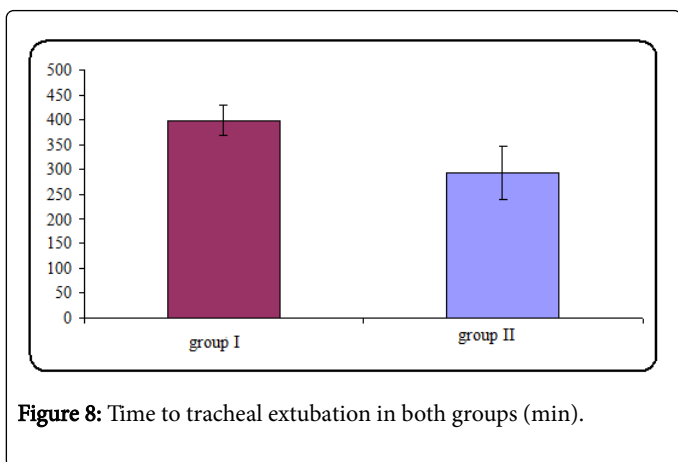


Sedation score in both groups showed no statistically significant difference between both groups (p>0.05) (Figure 5) While the visual analogue score (VAS) in both groups showed statistically significant higher pain score in group I after one h in ICU (T1) and onward to time 20 h in ICU (T17) in comparison with group II (P<0.05) (Figure 6).

The amount of morphine consumption in 24 h in both groups was statistically significant lower in group II with mean value was 6 ± 1.2 , in comparison to group I with mean value was 14 ± 1.2 ($p < 0.05$) (Figure 7).



The mean time of extubation in (group II) 293.2 ± 54.6 was statistically less significant in comparison to the mean time to extubation in group I 339.00 ± 29.6 ($P > 0.05$). (Figure 8). No significant difference in both groups as regards to frequencies of postoperative complication (Table 2).



Type of complications	Group I	Group II	P
	(n=20)	(n=20)	
Opioid related complications			
Nausea	6	7	0.99
Vomiting	3	4	0.99
Purities	0	2	0.99
Urinary retention	0	2	0.99
Respiratory depression	0	0	0.99
Spinal anesthesia complications			
Post-spinal tap headache	0	0	0.99
Central neuroaxial haematoma	0	0	0.99
Cardiac complications			

Postoperative myocardial infarctions	0	0	0.99
Atrial fibrillation	2	2	0.99
Ventricular tachycardia	1	1	0.99
Stroke	0	0	0.99
Death	0	0	0.99

*statistically significant difference at $P < 0.05$.

Table 2: Frequencies of post-operative complication in both groups.

Discussion

The quality of postoperative analgesia and its relationship has recently received much attention [15]. There are various methods for postoperative pain management ranging from regional blocks with local anesthetics to systemic administration of synthetic opioids [16]. Inadequate analgesia during the postoperative period may lead to many adverse hemodynamics (tachycardia, hypertension, vasoconstrictor-ion), respiratory (tachypnea, decreased tidal volume), metabolic (increased catabolism), immunologic (impaired immune response), and haemostatic (platelet activation) alteration. Aggressive control of postoperative pain has been shown to decrease morbidity and mortality in high risk patients after noncardiac surgery [17].

Driven by economic reasons, it is better in cardiac surgery to extubate patients during the immediate postoperative period [18]. However, in patients undergoing cardiac surgery, perioperative myocardial ischemia (diagnosed by electrocardiography and/or transesophageal echocardiography) is most commonly observed during this time (25%-38% incidence) and is likely related to outcome [19]. For this and other reasons, early extubation may be associated with risk and is not appropriate in certain patients [20]. When early extubation is planned, aggressive control of pain is essential to decrease morbidity and mortality [8,9].

In the present study the central venous pressure, oxygen saturation, arterial blood gases and plasma lactate level remained almost constant throughout the study period with no statistical significant differences in both groups, there was a decrease in heart rate (HR) after induction and before bypass in relation to the baseline values in the morphine group and this decrease was statistically significant when compared with the control group, the mean arterial pressure (MAP) showed a decrease after induction, before bypass and after bypass in morphine group, in comparison with the baseline values, whereas in control group, this decrease was limited to after bypass time. Intrathecal opioid has been shown to provide effective analgesia following non-cardiac surgery [21] and cardiac surgery [22].

Our study agrees with Chiari et al. [23] in a study on analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent, showed that mean arterial pressure decreased significantly from baseline in all groups after injection of 50 µg, 100 µg, 200 µg, intrathecal clonidine onset time of this decrease was dose dependent. Heart rate decreased after injection of 100 µg, 200 µg intrathecal clonidine. However Ferreira C et al. injected subarachnoid in patients undergoing cardiac surgery with cardiopulmonary bypass and showed that the use of clonidine at the spinal dose of 1 µg/kg [1] was not able to reduce the intensity of response to surgical trauma [24].

Our study showed that plasma levels of cortisol in morphine group were lower than in control group, on admission to ICU and at the time of tracheal extubation.

Roediger et al. [25,26] who studied the use of pre-operative intrathecal morphine for analgesia following coronary bypass surgery, showed that catecholamines plasma concentration were significantly lower in the intrathecal group, plasma and urinary cortisol concentration were similar in both groups.

Our study also in agreement with Chaney et al. [26] who studied the effect of large-dose intrathecal morphine for coronary artery bypass grafting and found that norepinephrine and epinephrine levels tended to be lower in intrathecal morphine group patients than those in placebo, the difference was not statistically significant.

As regard extubation time, our study showed that patients who were tracheally extubated during the postoperative period, mean time to extubation was less after intrathecal morphine+clonidine (Group M) compared with the control group (Group C).

Our results go in hand with the work of Dominique et al. [27] in a study to compare the effect of combined intrathecal morphine and sufentanil with low-dose iv sufentanil during propofol anesthesia for fast-track cardiac surgery. The results of that study showed that intrathecal sufentanil and morphine allowed shorter duration of intubation.

In contrast to our result, Chaney et al. [26] found no difference in extubation times with either 4.0 mg or 10 µg/kg of intrathecal morphine compared with placebo. A relatively high dose of intraoperative fentanyl (50 and 20 µg/kg) may have a significant contributing factor for delayed extubation in these studies.

Our results are agreed with the work done by Chaney et al. [26] who investigated the use of large-dose intrathecal morphine for cardiac surgery and its effects on postoperative analgesic requirements. Patients were randomized to receive either 4.0 mg of intrathecal morphine or intrathecal saline placebo. The results of this study showed that patients in the intrathecal morphine group required significant less postoperative intravenous morphine than in intrathecal saline placebo, and was not surprisingly that they found that the analgesia produced from the dose (4.0 mg) lasted approximately 48 h (morning of operative day to morning of postoperative day 2).

Zarate et al. [14] who evaluate the use of remifentanyl combined with intrathecal opioid on extubation time, analgesia, and intensive intrathecal morphine as an alternative to sufentanil during desflurane anesthesia. They concluded that intrathecal morphine provided superior pain control after cardiac surgery compared with a sufentanil general anesthetic technique.

Bowler et al. [28] who studied a combination of intrathecal morphine and remifentanyl (RITM) for fast-track cardiac anesthesia and surgery. Patients in the RITM group exhibited significantly lower visual pain scores during the first 2 h after surgery, sedation score were significantly lower in the RITM during the first 3 h after extubation and postoperative morphine requirements during the 24 h were significantly lower in RITM than in the control group.

In our results as regard the side effects of intrathecal morphine, the incidence of nausea and vomiting was similar in both groups. Nausea and vomiting were controlled with standard antiemetic therapy. The pruritus experienced by 2 of the patients in the intrathecal morphine

group was only mild and did not need treatment. Other cardiac postoperative complications were similar in both groups.

Our results are in accordance with Zarare et al. [14] who found that, the incidence of postoperative, opioid-related side effects (e.g., nausea and vomiting, pruritus, and urinary retention) were small, and no differences were noted between the two groups.

The safety of an intrathecal injection immediately prior systemic heparinization required for CPB; It has been recommended that the technique should not be used in patients who demonstrate known preoperative coagulopathy from any cause, surgery should be delayed 24 h if a bloody tap occurs, and the time from lumbar puncture to systemic heparinization should exceed 60 min [29]. An analysis estimates the risk of spinal hematoma in patients receiving spinal blockade for cardiac surgery is in the range of 1:220,000 to 1:3600, with 95% confidence [30].

Conclusion

1. In conclusion, pre-operative intrathecal morphine administration of 250 µg in patients undergoing cardiac surgery improved analgesia and reduced opioid consumption, without increasing incidence of opioid related-side effects.

2. 250 µg intrathecal morphine appears to be the optimal dose of intrathecal morphine to provide significant postoperative analgesia without delaying tracheal extubation.

3. Low-dose ITM offer an alternative anesthetic technique, which appears to have some benefits over general anesthesia alone for cardiac surgery.

4. The combination of intrathecal morphine and clonidine allow the dose of morphine to be reduced, reduces the risk of respiratory depression, gives effective control of postoperative pain in cardiac patients and reduce the duration of controlled ventilation.

5. In patients with well-preserved ventricular and respiratory function scheduled for fast-track cardiac surgery, the use of combined intrathecal morphine and clonidine provides superior postoperative analgesia and early extubation.

6. Intrathecal morphine partially ameliorated the stress response to cardiac surgery.

References

1. Mueller XM, Tinguely F, Tevaearai HT (2000) Pain location, distribution, and intensity after cardiac surgery. *Chest* 118: 391-396.
2. Milgrom LB, Brooks JA, Qi R (2004) Pain levels experienced with activities after cardiac surgery. *Am J Crit Care* 13: 116-125.
3. Lahtinen P, Kokki H, Hynynen M (2006) Pain after cardiac surgery: a prospective cohort study of 1-year incidence and intensity. *Anesthesiology* 105: 794-800.
4. Mazzeffi M, Khelemsky Y (2011) Poststernotomy pain: a clinical review. *J Cardiothorac Vasc Anesth* 25: 1163-1178.
5. Baumgarten MC, Garcia GK, Frantzeski MH (2009) Pain and pulmonary function in patients submitted to heart surgery via sternotomy. *Rev Bras Cir Cardiovasc* 24: 497-505.
6. Sasseron AB, Figueiredo LC, Trova K (2009) Does the pain disturb the respiratory function after open heart surgery? *Rev Bras Cir Cardiovasc* 24: 490-496.
7. Bigeleisen PE, Goehner N (2015) Novel approaches in pain management in cardiac surgery. *Curr Opin Anaesthesiol* 28: 89-94.

8. Filsoufi F, Rahmanian PB, Castillo JG (2008) Predictors and early and late outcomes of respiratory failure in contemporary cardiac surgery. *Chest* 133: 713-721.
9. Ubben JF, Lance MD, Buhre WF (2015) Clinical strategies to prevent pulmonary complications in cardiac surgery: an overview. *J Cardiothorac Vasc Anesth* 29: 481-490.
10. Badenes R, Lozano A, Belda FJ (2015) Postoperative pulmonary dysfunction and mechanical ventilation in cardiac surgery. *Crit Care Res Pract* 2015: 420513.
11. Scott NB, Turfrey DJ, Ray DA (2001) A prospective randomized study of the potential benefits of thoracic epidural anesthesia and analgesia in patients undergoing coronary artery bypass grafting. *Anesth Analg* 93: 523-525.
12. Ossipov MH, Harris S, Lloyd P, Messineo E (1990) An isobolographic analysis of the antinociceptive effect of systemically and intrathecally administered combinations of clonidine and opiates. *J Pharmacol Exp Ther* 255: 1107-1116.
13. Liem TH, Booi LH, Gielen MJ (1992) Coronary artery bypass grafting using two different anesthetic techniques: part 3 Adrenergic responses. *J Cardiothorac Vasc Anesth* 6: 162-167.
14. Zarate E, Latham P, White PF (2000) Fast-track cardiac anesthesia Use of remifentanyl combined with intrathecal morphine as an alternative to sufentanil during desflurane anesthesia. *Anesth Analg* 91: 283-287.
15. Liu S, Carpenter RL, Neal JM (1995) Epidural anesthesia and analgesia their role in postoperative outcome. *Anesthesiology* 82: 1474-1506.
16. Scott LJ, Perry CM (2000) Tramadol: a review of its use in perioperative pain. *Drugs* 60: 139-176.
17. Tuman KJ, McCarthy RJ, March RJ (1991) Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg* 73: 696-704.
18. Cheng DCH (1995) Pro. Early extubation after cardiac surgery decreases intensive care unit stay and cost. *J Cardiothorac Vasc Anesth* 9: 460-464.
19. Smith RC, Leung JM, Mangano DT (1991) Postoperative myocardial ischemia in patients undergoing coronary artery bypass graft surgery. *Anesthesiology* 74: 464-473.
20. Guenther CR (1995) Early extubation after cardiac surgery decreases intensive care unit stay and cost. Con: early extubation after cardiac surgery dose not decrease intensive care unit stay and cost. *J Cardiothorac Vasc Anesth* 9: 465-467.
21. Derrode N, Lebrun F, Levron JC (2003) Influence of perioperative opioid on postoperative pain after major abdominal surgery: sufentanil TCI versus remifentanyl TCI. A randomised, controlled study. *British Journal of Anaesthesia* 91: 842-849.
22. Fleron MH, Weiskopf RB, Bertrand MA (2003) Comparison of intrathecal opioid and intravenous analgesia for the incidence of cardiovascular, respiratory, and renal complications after abdominal aortic surgery. *Anesthesia and Analgesia* 97: 2-12.
23. Chiari A, Lober C, Eisenach JC (1999) Analgesic and hemodynamic effects of intrathecal clonidine as the sole analgesic agent during first stage of Labor: a dose response study. *anesthesiology* 91: 388-396.
24. Ferreira C, Tenório S (2014) Subarachnoid clonidine and trauma response in cardiac surgery with cardiopulmonary bypass. *Rev Bras Anestesiol* 64: 395-399.
25. Roediger L, Senard JJ, Larbuisson MR (2006) The use of pre-operative intrathecal morphine for analgesia following coronary artery bypass surgery. *Anesthesia* 61: 838-844.
26. Chaney MA, Smith KR, Barclay JC, Slogoff S (1996) Large dose intrathecal morphine for coronary artery bypass grafting. *Anesth Analg* 83: 215-222.
27. Dominique A, Schmidlin D (2002) Intrathecal sufentanil-morphine shortens the duration of intubation and improves analgesia in fast-track cardiac surgery. *Can J Anesth* 49: 711-717.
28. Lena P, Balarac N, Arnulf JJ (2005) Fast-track coronary artery bypass grafting surgery under general anesthesia with remifentanyl and spinal analgesia with morphine and clonidine. *J Cardiothorac Vasc Anesth* 19: 49-53.
29. Vandermeulen EP, Van Aken H, Vermeylen J (1994) Anticoagulants and spinal epidural anesthesia. *Anesth Analg* 79: 1165-1177.
30. Ho AM, Chung DC, Joynt GM (2000) Neuraxial blockade and haematoma in cardiac surgery Estimating the risk of a rare adverse event that has not (yet) occurred. *Chest* 117: 551-555.