



Prospective Study of Intrathecal Morphine versus Patient Controlled Analgesia in Cardiac Patients

Haris Bilal¹, Nnanyelu Nzeakor¹, Karim Morcos¹ and Dumbor L Ngaage^{1*}

Abstract

Purpose: To compare efficacy and safety of Intrathecal Morphine (ITM) versus Intravenous Patient-controlled Analgesia (PCA) for cardiac surgery.

Methods: We prospectively studied 133 patients who received 0.1 - 0.6 mg of intrathecal morphine into L2-L5 space before induction (ITM) and 123 who had 1 mg intravenous patient controlled boluses with 5 minutes lock-out intervals post-sternotomy, between August and December 2010. Efficacy of pain control (Visual analogue score, additional analgesia requirement and intractable pain) and safety indicators (postoperative catecholamine requirement, first 24-hour fluid balance and time-to-extubation) were compared.

Results: Both groups were matched except PCA group had more females (27.6% vs 16.5%, $p=.03$). Fewer ITM compared to PCA patients (17% vs 47%, $p<.0001$) reported high pain scores first 24 h postoperatively, but additional analgesia requirement and mean times-to-extubation were similar. The catecholamine requirement was significantly greater in ITM group (92% vs. 80%, $p=.006$). After controlling for sex and other co-variables in multivariate analysis, PCA (odds ratio [OR] 4.26, 95% confidence interval [CI] 2.28-7.97) was associated with high pain score, while ITM (OR 3.39, 95% CI 1.50-7.69) was a predictor for postoperative catecholamine requirement.

Conclusion: Intrathecal morphine provides effective early post-sternotomy pain control but increases catecholamine and fluid requirement, so should be used cautiously.

Keywords

Intrathecal morphine; Patient-controlled analgesia; Post-sternotomy pain; Haemodynamics; Cardiac surgery

Introduction

Median sternotomy, the most common access used for cardiac surgery, is usually associated with severe early postoperative pain. Aggressive sternotomy pain control facilitates recovery, early mobilisation and decreases post-operative morbidity with direct implications for clinical resource utilisation and cost. Strategies to achieve effective early postoperative pain control after cardiac surgery have been reported to include; the use of opioids delivered

as intravenous infusion [1], intravenous patient-controlled analgesia [2], epidural infusion [3], epidural patient-controlled analgesia [4], single intrathecal bolus [5], and intermittent subcutaneous boluses [6]. Local anaesthetic agents have been injected into the surgical site [7], or thoracic epidural space as boluses [8] and/or infusion [9]. The ease of access and flexibility of managing opioid intravenous infusions and/or intravenous patient-controlled analgesia support their most frequent use, even though previous studies have consistently demonstrated a superior pain control by ITM after cardiac surgery [10]. Concerns about non-nociceptive complications that has been described as the "four classic" side-effects namely; pruritus, nausea and vomiting, urinary retention and respiratory depression [11,12], is a major deterrence to ITM.

At the study institution, intrathecal morphine (ITM) is commonly used for cardiac patients because of its efficacy in early post-sternotomy pain control. Anecdotally, however, we have observed haemodynamic differences between patients treated and those not treated with ITM. Whereas a non-cardiac series has demonstrated significant cardiovascular effects of ITM [13], the two cardiac studies that examined this potential complication were hindered by small sample size so the effect size was undermined and reached statistical significance only in one study [14]. More so, these studies only reported changes in biochemical profiles. We therefore, designed this single centre prospective observational study to compare the efficacy and safety of ITM versus intravenous patient-controlled analgesia (PCA) for post-sternotomy pain in cardiac surgery patients, with a focus on adverse haemodynamic effects.

Materials and Methods

Patients

Consecutive patients undergoing cardiac surgery through a median sternotomy from August 2010 to December 2010 were enrolled in this prospective study. The local Ethics committee approved the study.

All patients undergoing non-emergent cardiac were eligible and received unbiased information about the two options for early postoperative pain management during their visit for preoperative assessment. This was further discussed with the patient a day before surgery and a decision was then made about the post-operative pain control strategy. In select patients, a particular option was recommended based on their co-morbidities. For example, PCA may be recommended for patients receiving anti-platelet therapy until the time of surgery and ITM for patients with severe chronic obstructive pulmonary disease.

The general anaesthetic technique and peri-operative management protocols were standardized and similar for all the patients and included induction with midazolam and morphine or fentanyl, and maintenance during surgery with isoflurane.

Patients in the ITM group received a single dose of 0.1 to 0.6 mg of morphine delivered into the intrathecal space between the 2nd and 5th lumbar vertebrae using a small spinal needle size 25G, before induction of general anaesthesia. For the PCA group, morphine was

*Corresponding author: Dumbor L Ngaage, Essex Cardiothoracic Centre, Basildon University Hospital, Nethermayne Road, Basildon, Essex SS16 5NL, United Kingdom, Tel: 0845 1553111 Ext 4103; Fax: 01268 394333; E-mail: dngaage@yahoo.com

Received: March 02, 2013 Accepted: April 09, 2013 Published: April 15, 2013

set up to deliver 1 mg boluses on demand with a 5-minute lockout interval; no base rate was infused.

All the patients received regular baseline non-opioid analgesia in the form of intravenous Acetaminophen 1g every 6 hours.

Preoperative variables, intraoperative details and postoperative parameters were collected with specifically designed study questionnaires.

Postoperative pain control

In order to determine the efficacy of postoperative pain control we assessed; a) the severity of postoperative pain within the first 24 h after surgery using a visual analogue score (VAS), b) the use of additional analgesia, and c) the involvement of a specialist pain management team for intractable pain during the postoperative hospital stay. The patient was requested by the designated nursing staff providing a 1:1 care to rate the severity of postoperative pain using the VAS grading of:

- 0 – for no pain on movement
- 1 – mild pain on movement
- 2 – moderate pain on movement
- 3 – severe pain on movement

This assessment was done for each patient hourly post-extubation for the first four hours and then four-hourly afterwards. Scores of 2 and 3 were considered as significant postoperative pain and indicative of poor pain control.

Safety indicators

We recorded the postoperative requirement of catecholamines like Noradrenaline, Adrenaline, Dopamine and Dobutamine.

We also recorded the time-to-extubation, total fluid balance in first 24 hours after surgery, cardiac and pulmonary complications, and the length of stay in the intensive care unit.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 14.0 for windows, (SPSS inc 2005, Chicago, IL) and a two-sided p value <.05 was considered significant. Dichotomous variables, reported as percentages were compared between the groups with the chi-square test, while continuous variables presented as mean \pm SD were compared between groups using the student *t* test. All the preoperative and operative variables in table 1, including ITM versus PCA, were screened in separate univariate analyses to detect their association with significant postoperative pain, and the use of vasopressor. Variables that demonstrated potential effects ($p < .1$) were then included in backward multifactorial logistic regression models. The independent effect of ITM or PCA and other variables are reported as odds ratio (OR) and 95% confidence interval (CI).

Results

Baseline and operative characteristics

There were no significant differences in the baseline demographic and clinical characteristics between the 123 PCA and 133 ITM patients, except for gender distribution; PCA group had more female patients (Table 1).

The types of operative procedures were similar between the groups. The predominant operation for both groups was coronary artery bypass grafting, and the left internal mammary artery was harvested in equal proportions of patients in both groups.

Efficacy of pain control

A substantially higher proportion of PCA patients reported significant postoperative pain (VAS scores 2 and 3) in the first 24 hours after surgery. However, the use of additional analgesia during this period for the PCA (n=9, 7.3%) and ITM groups (n=9, 6.8%) were similar ($p=.88$). After the first 24-hour period, equivalent numbers of PCA (n=43, 35.0%) and ITM patients (n=47, 35.3%) received morphine-based preparations, and this was also true for referral to specialist pain management team for intractable pain (PCA n=5, 4.1% versus ITM, n=6, 4.5%, $p=.86$).

After controlling for gender differences and other potential confounders in a multivariate analysis, the use of PCA (OR 4.26, 95% CI 2.28 – 7.97, $p < .0001$) was a predictor for poor early post-sternotomy pain control (Table 2). Increasing patient age was associated with a decrease in the odds of significant early post-sternotomy pain.

Safety indicators

A remarkably higher postoperative requirement for catecholamines in the first 24 hours postoperatively was observed among the ITM patients (n=122, 91.7%) compared to PCA group (n=98, 79.7%, $p=.006$). Vasopressor therapy with Noradrenaline was by far the most frequent catecholamine used. Also, ITM patients had more positive fluid balance in the first 24 hours postoperatively than PCA group. By multivariate analysis, ITM (OR 3.39, 95% CI 1.50 – 7.69, $p=.003$) exhibited a strong direct link with the use of catecholamines in the first 24 hours after surgery (Table 2).

There were no significant differences in the mean duration of ventilation for both groups; 7.1 ± 7.7 hours for ITM and 7.6 ± 4.5 hours for PCA patients ($p=.55$), and in the distribution of other cardiac and pulmonary complications (Table 1). There were no neurological complications or operative (in-hospital and/or 30-day) deaths in the study cohort.

Discussion

This prospective study, like other cardiac [5,12,15,16] and non-cardiac surgery series [10], demonstrates the efficacy of ITM for early post-sternotomy pain control. The risk of poor postoperative pain in the first 24 hours after cardiac surgery is greater with PCA than with ITM. In fact, patients were four times more likely to have significant postoperative pain if PCA was used as the pain control strategy compared to ITM. It is worthy of note, however, that although a greater number of patients who received PCA reported significant postoperative pain in the first 24 hours, their requirement for additional analgesia was similar to the patients with ITM. It could therefore be argued that an inappropriate use of PCA may be contributory. Improper timing in PCA boluses may lead to catch-up rather than pre-emptive analgesia, which in ITM is guaranteed. Also, the lingering effect of general anaesthesia may predispose a drowsy patient to poor compliance with PCA usage. In a meta-analysis [10] ITM was found to provide even more effective postoperative pain relief resulting in significant reduction in the requirement for additional analgesia. However, that study raised some concern about

Table 1: Comparison of baseline and operative characteristics of the study groups.

Variable	Intrathecal morphine	Pain controlled analgesia	P value
	n=133 (%)	n=123 (%)	
Demographics			
Mean age (years)	66.4 ± 10.7	65.1 ± 12.7	0.37
Female	22 (16.5)	34 (27.6)	0.03
Mean body mass index (kg/m ²)	27.9 ± 5.3	26.9 ± 4.4	0.09
Clinical presentation			
Angina class III/IV	40 (30.1)	36 (29.3)	0.65
New York Heart Association Class III/IV	44 (33.3)	36 (29.3)	0.82
Left ventricular ejection fraction			
0.30 – 0.50	8 (6.0)	15 (12.2)	0.22
<0.30	5 (3.8)	5 (4.1)	
Previous cardiac surgery	3 (2.3)	7 (5.7)	0.16
Co-morbidities			
Hypertension	92 (69.2)	78 (63.4)	0.33
Renal impairment	1 (0.8)	4 (3.3)	0.15
Stroke	16 (12.0)	14 (11.4)	0.87
Diabetes	32 (24.1)	23 (18.7)	0.3
Chronic obstructive pulmonary disease	24 (18.0)	22 (17.9)	0.97
Peripheral vascular disease	13 (9.8)	16 (13.0)	0.42
Operations			
Coronary artery bypass grafting	75 (56.4)	76 (61.8)	0.27
Heart valve surgery	28 (21.1)	19 (15.4)	
Combined coronary and valve surgery	23 (17.3)	21 (17.1)	
Other	7 (5.3)	7 (5.7)	
Operative details			
Mean cardiopulmonary bypass time	95.9 ± 53.2	95.2 ± 65.9	0.93
Mean cross-clamp time (minutes)	64.9 ± 41.6	60.9 ± 47.7	0.47
Left internal mammary artery used	124 (93.2)	116 (94.3)	0.72
Mean blood loss in first 24hrs (mls)	535.4 ± 347.1	553.3 ± 376.7	0.69
Postoperative outcomes			
Reoperation for bleeding/tamponade	5 (3.8)	2 (1.6)	0.3
Atrial fibrillation	35 (26.5)	36 (29.5)	0.6
Any pulmonary complication	15 (11.4)	14 (11.5)	0.98
Duration of ventilation (hours)	7.1 ± 7.7	7.6 ± 4.5	0.55
Vasopressor use	122 (91.7)	98 (79.7)	0.006
Highest pain score			<.0001
0	59 (44.4)	6 (4.9)	
1	51 (38.3)	59 (48.0)	
2	18 (13.5)	49 (39.8)	
3	5 (3.8)	9 (7.3)	
Day 0 additional analgesia	9 (6.8)	9 (7.3)	0.88
Intractable pain management	6 (4.5)	5 (4.1)	0.86
Day 0 mean fluid balance (mls)	1630.6 ± 942.1	1364.5 ± 714.4	0.01
Mean stay in intensive care unit (days)	2.2 ± 1.8	2.8 ± 2.8	0.06

Table 2: Risk factors for a) poor post-sternotomy pain control and b) postoperative vasopressor requirement.

Risk factors for poor pain control	Odds ratio	95% Confidence Interval	P value
Patient controlled analgesia	4.26	2.28 – 7.97	<.0001
Angina class III/IV	2.75	1.44 – 5.25	0.002
Cardiopulmonary bypass time (minutes)	1.02	1.00 – 1.03	0.02
Age in years	0.97	0.94 – 0.99	0.01
Risk factors for use of vasopressors			
Operations other than Coronary artery bypass grafting	3.66	1.23 – 10.84	0.02
Intrathecal morphine	3.39	1.50 – 7.69	0.003
Aortic cross-clamp times (minutes)	1.03	1.01 – 1.06	0.001
Angina class III/IV	0.37	0.17 – 0.82	0.01

the risk of respiratory depression and consequently, longer duration of ventilation. Opinions about the influence of ITM on extubation times in cardiac patients are divided. In our study ITM did not confer any disadvantage with regards to ventilation times and duration of hospitalisation.

The mechanism by which ITM achieves effective postoperative pain control is the stimulation of opioid receptors in the substantia gelatinosa of the posterior spinal cord [17].

ITM induces an intense pain control with a trade-off for a varying degree of vasoplegia resulting in increased requirement for vasopressor therapy and volume transfusion, which have been associated with high postoperative morbidity [18]. These setbacks have not been previously well described in cardiac patients. Chaney et al. [14] reported lower serum levels of Noradrenaline and Adrenaline after cardiac surgery in patients treated with ITM, but in their randomized trial of 60 patients, the decrease in catecholamine levels was not statistically significant. Breslow et al. [13] showed that ITM significantly diminished postoperative sympathetic nervous system activity as evidenced by reduced Noradrenaline levels after abdominal aortic operations, and Fleisher et al. [19] demonstrated an alteration of the sympathovagal balance in favour of peripheral vasoconstriction after epidural anaesthesia with bupivacaine compared to general anaesthesia after major urological procedures. So possibly, the combination of the intrathecal route and the morphine may contribute to these adverse haemodynamic effects in cardiac surgery patients.

Four classic non-nociceptive side-effects that has been associated with ITM are pruritus, nausea and vomiting, urinary retention and respiratory depression [11]. Meta-analyses [10,15] have shown that clinical outcomes in patients undergoing major surgery with ITM have been adversely impacted by these complications. There are reports of delays in extubation attributed to ITM in cardiac surgery patients [15]. It is not clear if the risk of developing side-effects with ITM for cardiac patients is dose-related. Jacobson et al. [20] investigated the dose-response effects of ITM for knee and hip replacement and concluded that while even small doses (0.3 mg and 1 mg) of morphine were associated with minor side effects, larger doses were associated with risk of respiratory depression. Aun et al. [5] compared 2 mg versus 4 mg of morphine in cardiac surgery patients and reported similar pain control efficacy with increased risk of vomiting and pruritus with the higher dose, but observed no difference in respiratory depression. However in that study, patients were electively ventilated after surgery and respiratory depression

was not assessed. Fitzpatrick et al. [16] compared 1 mg versus 2 mg in cardiac patients and reported comparable efficacy of pain relief but a slight increase in the risk of respiratory depression associated with the higher dose.

In addition to these classic side-effects, some authors [15] having drawn attention to the potential to cause harm with the administration of ITM, concluded that, the risks of ITM may outweigh its benefits.

Limitations

The inherent limitations of the study design include selection bias resulting in more female patients in the PCA group. However, the potential influences of confounding variables, including gender, were controlled by multivariate analysis. Also the ideal dose of ITM is not known. In the present study we used uniform dosing with higher doses for patients on preoperative analgesia for other painful conditions. Perhaps ITM doses that are finely titrated to the patients' body surface area or weight may lessen the haemodynamic effect of ITM.

Conclusion

Intrathecal morphine provides potent early postoperative pain relief after cardiac surgery using a median sternotomy. This, however, comes at a price of increased postoperative requirement of vasopressor therapy. The recognised classic side-effects, the potential risks of administration, and the haemodynamic trade-off for the early postoperative pain control associated with ITM demands caution in the use of ITM in cardiac patients and should discourage its routine use.

Further studies of the safety of ITM in cardiac surgery are needed.

References

- Rauf K, Vohra A, Fernandez-Jimenez P, O'Keeffe N, Forrest M (2005) Remifentanyl infusion in association with fentanyl-propofol anaesthesia in patients undergoing cardiac surgery: effects on morphine requirement and postoperative analgesia. *Br J Anaesth* 95: 611-615.
- Gurbet A, Goren S, Sahin S, Uckunkaya N, Korfali G (2004) Comparison of analgesic effects of morphine, fentanyl, and remifentanyl with intravenous patient-controlled analgesia after cardiac surgery. *J Cardiothorac Vasc Anesth* 18: 755-758.
- el-Baz N, Goldin M (1987) Continuous epidural infusion of morphine for pain relief after cardiac operations. *J Thorac Cardiovasc Surg* 93: 878-883.
- Hansdottir V, Philip J, Olsen MF, Eduard C, Houltz E, et al. (2006) Thoracic epidural versus intravenous patient-controlled analgesia after cardiac surgery: a randomized controlled trial on length of hospital stay and patient-perceived quality of recovery. *Anesthesiology* 104: 142-151.


5. Aun C, Thomas D, St John-Jones L, Colvin MP, Savege TM, et al. (1985) Intrathecal morphine in cardiac surgery. *Eur J Anaesthesiol* 2: 419-426.
6. Munro AJ, Long GT, Sleigh JW (1998) Nurse-administered subcutaneous morphine is a satisfactory alternative to intravenous patient-controlled analgesia morphine after cardiac surgery. *Anesth Analg* 87: 11-15.
7. Chiu KM, Wu CC, Wang MJ, Lu CW, Shieh JS, et al. (2008) Local infusion of bupivacaine combined with intravenous patient-controlled analgesia provides better pain relief than intravenous patient-controlled analgesia alone in patients undergoing minimally invasive cardiac surgery. *J Thorac Cardiovasc Surg* 135: 1348-1352.
8. Hemmerling TM, Prieto I, Choinière JL, Basile F, Fortier JD (2004) Ultra-fast-track anesthesia in off-pump coronary artery bypass grafting: a prospective audit comparing opioid-based anesthesia vs thoracic epidural-based anesthesia. *Can J Anaesth* 51: 163-168.
9. Lundstrøm LH, Nygård E, Hviid LB, Pedersen FM, Ravn J, et al. (2005) The effect of thoracic epidural analgesia on the occurrence of late postoperative hypoxemia in patients undergoing elective coronary bypass surgery: a randomized controlled trial. *Chest* 128: 1564-1570.
10. Meylan N, Elia N, Lysakowski C, Tramèr MR (2009) Benefit and risk of intrathecal morphine without local anaesthetic in patients undergoing major surgery: meta-analysis of randomized trials. *Br J Anaesth* 102: 156-167.
11. Chaney MA (1995) Side effects of intrathecal and epidural opioids. *Can J Anaesth* 42: 891-903.
12. Gehling M, Tryba M (2009) Risks and side-effects of intrathecal morphine combined with spinal anaesthesia: a meta-analysis. *Anaesthesia* 64: 643-651.
13. Breslow MJ, Jordan DA, Christopherson R, Rosenfeld B, Miller CF, et al. (1989) Epidural morphine decreases postoperative hypertension by attenuating sympathetic nervous system hyperactivity. *JAMA* 261: 3577-3581.
14. Chaney MA, Smith KR, Barclay JC, Slogoff S (1996) Large-dose intrathecal morphine for coronary artery bypass grafting. *Anesth Analg* 83: 215-222.
15. Chaney MA, Nikolov MP, Blakeman BP, Bakhos M (1999) Intrathecal morphine for coronary artery bypass graft procedure and early extubation revisited. *J Cardiothorac Vasc Anesth* 13: 574-578.
16. Fitzpatrick GJ, Moriarty DC (1988) Intrathecal morphine in the management of pain following cardiac surgery. A comparison with morphine i.v. *Br J Anaesth* 60: 639-644.
17. Stoelting RK (1989) Intrathecal morphine—an underused combination for postoperative pain management. *Anesth Analg* 68: 707-709.
18. Fischer GW, Levin MA (2010) Vasoplegia during cardiac surgery: current concepts and management. *Semin Thorac Cardiovasc Surg* 22: 140-144.
19. Fleisher LA, Frank SM, Shir Y, Estafanous M, Kelly S, et al. (1994) Cardiac sympathovagal balance and peripheral sympathetic vasoconstriction: epidural versus general anesthesia. *Anesth Analg* 79: 165-171.
20. Jacobson L, Chabal C, Brody MC (1988) A dose-response study of intrathecal morphine: efficacy, duration, optimal dose, and side effects. *Anesth Analg* 67: 1082-1088.

Author Affiliation

Top

¹Lancashire Cardiac Centre, Blackpool Victoria Hospital, Whinney Heys Road, Blackpool, UK

Submit your next manuscript and get advantages of SciTechnol submissions

- ❖ 50 Journals
- ❖ 21 Day rapid review process
- ❖ 1000 Editorial team
- ❖ 2 Million readers
- ❖ More than 5000 
- ❖ Publication immediately after acceptance
- ❖ Quality and quick editorial, review processing

Submit your next manuscript at • www.scitechnol.com/submission