Original Research Paper Medical Science

A Comparative Study Between Morphine, Dexmedetomidine And Ketamine as an Adjunct to Levobupivacaine in Paravertebral Block During Modified Radical Mastectomy

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ABSTRACT

Background: To compare the effects of morphine, dexmedetomidine and ketamine administered in paravertebral block as adjunct to levobupivacaine conduct a prospective, randomised, controlled single blind, clinical study.

Methods: A total of 120 breast cancer patients aged between 18-60 years of ASA I-II scheduled for elective modified radical mastectomy were comprises to four groups (30 in each): paravertebral block with 0.25% levobupivacaine (19 ml) with 1ml normal saline (group C), with 1 ml (5 mg) morphine (group M), with 1 ml (25 µg) dexmedetomidine (group D) and with 1ml (25 mg) ketamine (group K). All patients were given premedication on the night before surgery with ranitidine 150 mg and alprazolam 0.25 mg orally.

Results: The heart rate and MAP were almost stable in the intra-operative period. The SpO2 remained 97-100% in the intraoperative period among all the groups. VAS was significantly ($p<0.05$) different among the groups at 8 hours to 20 hours. The first requirement of rescue analgesia was significantly ($p=0.0001$) among the groups postoperatively. Total consumption of antemetic was among 16.3% of the patients in group M only. Hypotension was found among 6.6% in group D only and respiratory depression in 6.6% of group M patients.

Conclusion: Our results suggest that the dexmedetomidine (25 µg) with levobupivacaine (0.25%) for paravertebral block, during modified radical mastectomy, prolongs the duration of analgesia and decreased the rescue analgesia with significantly reduced the incidence of postoperative adverse effects.

KEYWORDS Dexmedetomidine, Breast cancer, Paravertebral block, Mastectomy, Haemodynamic

Introduction

Pain is one of the most dreaded side effects of surgery for the patient during as well as after surgery. Pain has various physiological side effects such as increased myocardial oxygen, demand poor ventilatory function, high sympathetic tone, decreased urine output, paralytic ileus etc as well as psychological disturbances like anxiety, sleep disturbances, altered behaviour and psychosis. Poorly controlled acute pain can lead to chronic pain syndrome which is very distressing to the patient therefore control of pain is an important element in perioperative period and requires exhausting effort from the attending anaesthesiologist.

Thoracic paravertebral block (TPVB) provides high quality analgesia and great advantage for the patients undergoing many different surgeries. At the same time, relieves the acute post-

operative painand may prevent development of chronic pain (Richardson et al, 2011). The traditional pain management had been reported to cause inadequate pain control (Poleshuck et al., 2006).

The administration of levobupivacaine in paravertebral block was characterized by rapid absorption after bolus injection and progressive accumulation after continuous infusion with maximum plasma concentrations at 24 hours (Burlacu et al., 2007).

Morphine is the principal alkaloid of opium. Morphine acts as a mu agonist, binding to receptors in the brain, spinal cord and other tissues. Local anaesthetic drug with adjuvants like fentanyl, morphine and clonidine have been studied and they improve the quality of the blockade (Barlacu et al., 2006).

Dexmedetomidine, an imidazole compound, is the pharmacologically active Dextro isomer of medetomidine that displays selective dose dependent α_2-adrenoceptor agonism. Addition of Dexmedetomidine in Combination with Local anaesthetic agent significantly prolong the duration of analgesia in paravertebral block (Sandip et al., 2014).

Ketamine, a phencyclidine derivative provides dissociative anaesthesia and profound analgesia with superficial sleep. The ketamine molecule contains an asymmetrical carbon atom with two optical isomers (enantiomers). The S (+) isomer is about three times more potent and longer acting as an anaesthetic than the R (-) isomers. Epidural ketamine provides postoperative analgesia. The cardiovascular effects usually did not associate with the use of ketamine were not observed, nor was there any evidence of sensory, motor or sympathetic block (Waxman et al., 1980).

In best of our knowledge, no clinical studies have examined the comparative effects of morphine, dexmedetomidine and ketamine as an adjunct to isobaric levobupivacaine in thoracic paravertebral block during modified radical mastectomy. We, therefore, proposed to conduct a prospective, randomised, controlled single blind, clinical study to compare the effects of morphine, dexmedetomidine and ketamine administered in paravertebral block as adjunct to levobupivacaine**.**

Materials and methods

This was a prospective, randomized; controlled single blind study was conducted in a King George's Medical University, Lucknow, India from January 2014 to November 2015. This study was approved by Institutional Ethical Committee and written informed consent was obtained from each individual. The diagnosed cases of carcinoma breast, ASA grade I & II, adults aged between 18-60 years and scheduled for elective modified radical mastectomy were included in the study. Patients with contraindications of paravertebral block, having heart block, psychiatric illness, bleeding disorder, allergy to amide type local anaesthetics, infection at the thoracic paravertebral injection site, body mass index > 35kg/sq-m, previous ipsilateral thoracic surgery, total pleurectomy, localized tumor, empyema and abnormal thoracic anatomy were excluded from the study.

A total 120 patients were included in the study and randomized into 4 groups (30 each). The randomization was done by using computer generated random numbers.

Group C: 0.25% levobupivacaine (19 ml) with 1ml saline

Group M: 0.25% levobupivacaine (19 ml) with 1 ml (5 mg) morphine

Group D: 0.25% levobupivacaine (19 ml) with 1ml (25 µg) dexmedetomidine

Group K: 0.25% levobupivacaine (19 ml) with 1ml (25 mg) ketamine

All patients were given premedication on the night before surgery with ranitidine 150 mg, and alprazolam 0.25 mg orally. All of them were properly informed regarding the procedure of giving paravertebral block and were preloaded with 10-15 ml/kg of Ringer Lactate. The heart rate, mean arterial pressure and SpO_2 were intra-operatively monitored. Visual analogue scale score, Ramsay sedation score, Numerical rating score, total cosumption of rescue analgesia, total consumption of antiemetic, complications and patient's satisfaction score were also noted.

All patients were positioned in sitting position and C_7 cervical spine identified and marked T_4 – T_7 vertebra respectively. Under aseptic precautions, at 2.5 cm lateral to the cephalad edge of the T4spinous process, the skin, subcutaneous tissue and the periosteum of the transverse process of the T4 vertebra was infiltrated with 3 ml of Lignocaine 2%. A 25G 10 cm insulated needle was introduced at 90 degree to the skin, at the site of local anaesthetic infiltration. The needle was advanced till it touches the transverse process of the vertebra, noting the depth. The needle was withdrawn and then advanced slightly caudal to walk off the transverse process for a distance of 1.0 to 1.5 cm. The study drug (20 ml), as per the group allocation, was injected in small aliquots of 5 ml with repeated aspiration in between. Any complication or difficulty during the performance of PVB will also be noted.

Thereafter, general anaesthesia was premedicated with emset 4 mg and glycopyrrolate 0.2 mg, then induced the patients with intravenous fentanyl 2 µg/kg and propofol 2 mg/kg. Orotracheal intubation was facilitated by Sch 2 mg/kg and ventilation will be controlled. Anaesthesia was maintained with vecuoronium, oxygen and nitrous oxide, and inhalationalagents. Mean arterial pressure (MAP) was maintained within 20% of the preoperative baseline. IV emset 4mg was administered once the patient is induced. No other analgesic was administered intra-operatively. IV mepheteramine 6 mg was administered as needed to keep MAP more than 60 mmHg, bradycardia manage by injection atropine 0.02mg/kg BW. At the end of surgery, residual neuromuscular blockade was reversed with 50 µg/kgneostigmine + 10 µg/kg glycopyrrolate and patient was extubated on spontaneous respiration and return of consciousness.

Statistical analysis

The data are presented in mean±SD and percentages. The Chi-square test was used to compare the categorical/dichotomous variables among the groups. The continuous variables were compared among the groups by one way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. The p-value<0.05 was considered significant. All the analysis was carried out by using SPSS 16.0 version (Chicago, Inc., USA).

Results

The mean age of the patients was 44.20 (±9.37) years in group C, 49.17 (±7.87) years in group M, 47.50 (±8.95) years in group D and 45.87 (±8.79) in group K. The ASA grade I was 53.3% in group C, 56.7% in group M, 43.3% in group D and 56.7% in group K. The height, weight and BMI were observed to similar among the groups. There were no significant differences (p>0.05) between the four groups in demographic data, ASA classification, height, weight and BMI (Table 1).

The heart rate was similar at 0 min among all the groups (p>0.05). The heart rate was not significantly different between groups, intra-operatively and postoperatively (Fig.1). Moreover the mean arterial blood pressure (MAP) was also not significantly different between groups, intra-operatively and postoperatively (Fig.2). The SpO_2 was similar at 0 min among all the groups. The SpO2 remained 97–100% in the intraoperative period among all the groups. There was no significant difference among the groups (Fig. 3).

The VAS was similar at 0 hours, 2 hours and 4 hours in postoperative period among all the groups. There was significant

(p=0.003) difference in VAS from 6 hours to 20 hours in postoperative period among the groups. A significant (p<0.05) difference was observed among the groups at 8 hours to 20 hours (Table 2).

The RSS was similar at all the time intervals among all the groups in postoperative period. The NRS was similar at 0, 2 and 4 hours among the groups in postoperative period.

The first requirement of rescue analgesia was significant difference in groups, postoperatively (Table 3). The first requirement of analgesia was significantly (p=0.001) higher in group D (7.70±1.74) than group C (4.43±1.43) and group M (7.33±2.21). Moreover, 24 hours requirement of rescue analgesia was also significantly different among the groups, postoperatively (Table 3). The first requirement of rescue analgesia in postoperative period was significantly (p=0.001) lower in group D (1.43±0.50) than group C (2.07±0.64) and group M (1.63±0.55). Total consumption of antemetic was among 16.3% of the patients in group M only (Table 3). Hypotension was found among 6.6% in group D only and respiratory depression in 6.6% of group M patients. Itching was in 3.3% of group M and group D. The patient's satisfaction was higher in group D (93.3%) than group C (73.3%), & M (86.7%) and group K (80%).

Discussion

Regional anaesthesia using paravertebral block (PVB) is an ideal alternative to general anaesthesia for breast cancer surgery. The mechanism of action of paravertebral analgesia is by direct penetration of local anaesthetic into the intercostal nerve, including its dorsal ramus, the rami communicantes and the sympathetic chain. Benefits of paravertebral block include a reduction in postoperative nausea and vomiting, prolonged postoperative pain relief and potential for early discharge (Richardson and Sabanathan 1995). This study we evaluate the efficacy and safety of paravertebral block using levobupivacaine with various adjuvants like morphine, dexmedetomidine and ketaminein conjunction with general anaesthesia for postoperative pain management in modified radical mastectomy and to find that which adjuvant is best.

In present study, the heart rate and mean arterial pressure was almost stable with the time intervals. There were not significantly different among the groups but hypotension occur in 2 cases of group D, which was managed. In dexmedetomidine group had better haemodynamic stability during intraoperative and postoperative period than group M, group K and group C. Pusch et al. (1999) observed that after single injection unilateral PVB given at the level of T4, as a sole anaesthetic technique for breast cancer, none of patient had any episode of hypotension and the hemodynamic parameter were comparable between the two groups. Saito et al. (2001) observed the sympathetic changes following unilateral PVB with lidocaine at T_{11} spine and demonstrated that PVB provide a reliable, unilateral, somatosensory and sympathetic block without producing hypotension and tachycardia associated with neuraxial blocks. Rachna et al. (2012) observed that the dexmedetomidine (30 µg) with 0.25% bupivacaine had better haemodynamic stability for brachial plexus block.

We assessed VAS score in postoperative period in all patients and observed that the VAS was similar at 0 hours, 2 hours, and at 4 hours in postoperative period among all the groups. . However, VAS was significantly different between the groups at 6 hours to 20 hours. Group D had lesser VAS scores than groups C, M and K, and the least VAS score in group D. This finding is in consonance with the other studies done so far in this field (Klein et al., 2000; Terheggen et al., 2002; Kairaluoma et al., 2004; Burlacu et al., 2006; Kairaluoma et al., 2006; Moller et al., 2007; Ahmed et al., 2011). Sandip et al. (2014), in their study on 60 patient also observed that the dexmedetomidine with 0.25% ropivacaine (18 ml) with) was significantly prolongs the duration of analgesia in PVB, and VAS.

In this study, all the groups were compared for doses of paracetamol consumption. Group D was found to have a significantly lower consumption of paracetamol (mean 1.43 ± 0.50) during the postoperative period than other groups, the least requirement of rescue analgesia in group D. In the study by Coveney et al. (1998), only 14 out of 112 patients receiving PVB (12.5%) required postoperative analgesia as compared to72 out of the 89 (80.9%) patients who received general anaesthesia (p<0.0001).

In present study, all groups not required antiemetic except groups M. Klein et al. (2004) observed that GA group have significantly greater consumption of antiemetics than group PVB. Kairaluoma et al (2004) also observed that patients receiving PVB with GA required lesser number of antiemetic doses (15) in comparison to patients receiving GA only 38. Various studies on paravertebral blocks have quoted different rates of complications. No complications were reported by Greengrass et al. (1996) and Moller et al (2007). Coveney et al (1998) has reported complication in 2.6% of patient with two cases experiencing epidural extension while one patient developed pneumothorax. Terheggen et al (2002) reported one case with epidural block and one patient with pleural puncture. Kairaluoma et al (2004) had reported a single incidence of accidental intravascular injection of bupivacaine. Kanchan et al (2013) reported that none of patient had any complication in the first 24 hr in postoperative period.

In the present study, no complications related to the procedure technique were noted in all the Groups. There was no evidence of pneumothorax, hematoma, total spinal anaesthesia, local anaesthetic toxicity. Hence, paravertebral block can be considered as a safe adjunct to general anaesthesia.

In present study Group D had best patient satisfaction and early recovery than Group K, M, and C. Suzanne et al (2013) observed that use of preoperative PVB in patient undergoing mastectomy plus immediate reconstruction significantly decreased patient length of stay. K AK et al. (2013) observed that thoracic PVB with levobupivacaine increased patient satisfaction for those who underwent percutaneous nephrolithotomy. Kanchan et al. (2013) observed that both bupivacaine 0.5% and ropivacaine 0.5% provide good patient satisfaction score after a multilevel thoracic PVB.

Conclusion

We conclude that Dexmedetomidine as an adjunct to levobupivacaine in paravertebral block results better postoperative analgesia with significantly less incidence of postoperative nausea and vomiting as well as haemodynamic stability in comparison to morphine and ketamine. The procedure also proved to be safe as no complication was encountered in the paravertebral block.

Conflict of interest: None

Table 1: Baseline characteristics of patients

	Group C (n=30)	Group M (n=30)	Group D (n=30)	Group K (n=30)	p-value
Age (mean±SD), years	44.20 ±9.37	49.17 ±7.87	47.50 ±8.95	45.87±8.79	0.15[a]
ASA grade					
I	16 (53.3%)	17 (56.7%)	13 (43.3%)	17 (56.7%)	0.23[b]
II	14 (46.7%)	13 (43.3%)	17 (56.7%)	13 (43.3%)	
Height (mean±SD), cm	157.17 ±7.14	153.30 ±5.88	156.83 ±8.10	155.17±7.65	0.15 [a]
Weight (mean±SD), kg	62.53 ±6.17	60.00 ±5.38	61.30 ±4.58	60.00±5.39	0.21 [a]
BMI (mean±SD)	25.43 ±3.15	25.62 ±2.87	25.12 ±3.38	25.11±3.44	0.91 [a]

[a]ANOVA test, [b]Chi-square test

Table 2: Comparison of VAS score among the groups

Time period (hours)	Group C (n=30) Mean (±SD)	Group M (n=30) Mean (±SD)	Group D (n=30) Mean (±SD)	Group K (n=30) Mean (±SD)	p-value[1]
0	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	>0.05
2	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	>0.05
4	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	1.00 (0.00)	>0.05
6	4.27 (0.45)	1.00 (0.45)	1.00 (0.37)	1.27 (0.45)	0.003*
8	4.43 (0.63)	2.43 (2.43)	1.00 (1.23)	3.78 (0.63)	0.002*
10	1.99 (1.49)	3.70 (3.79)	1.00 (1.02)	3.99 (0.99)	0.0001*
12	1.29 (0.53)	4.27 (0.99)	0.99 (0.72)	4.67 (1.53)	0.003*
14	4.45 (0.53)	1.43 (1.99)	4.30 (0.54)	2.56 (1.54)	0.001*
16	4.53 (0.73)	1.00 (1.94)	4.33 (0.71)	1.89 (1.81)	0.001*
18	1.00 (0.68)	4.40 (3.99)	1.63 (0.93)	1.00 (2.48)	0.0001*
20	1.00 (0.21)	1.43 (1.01)	2.80 (0.41)	1.00 (2.12)	0.02*
22	1.00 (0.33)	1.33 (1.89)	1.80 (1.06)	2.00 (1.45)	0.08
24	1.00 (0.54)	1.00 (1.01)	1.00 (0.79)	1.00 (1.91)	0.77

[1]ANOVA test, *= <0.05 (Significant), >0.05=Not significant

Table 3: Time of first requirement of rescue analgesia

	Group C (n=30)	Group M (n=30)	Group D (n=30)	Group K (n=30)	p-value
Time of first requirement of rescue analgesia	4.43 ±1.43[a,b]	7.33 ±2.21[b]	7.70 ±1.74[a,c]	5.40 ±1.92[b,c]	0.0001*
24 hour consumption of rescue analgesia (paracetamol)	2.07 ±0.64[a]	1.63 ±0.55 [a]	1.43 ±0.50 [a,b]	1.88 ±0.75 [b]	0.001*
Total consumption of antemetic (ondansatron) in postoperative period	0 (0.0%)	4 (16.3%)	0 (0.0%)	0 (0.0%)	-

[1]ANOVA test, *= <0.05 (Significant), [a,b,c]p=0.001 (Post hoc comparison test)

Fig. 1: Heart rate (beat/min)

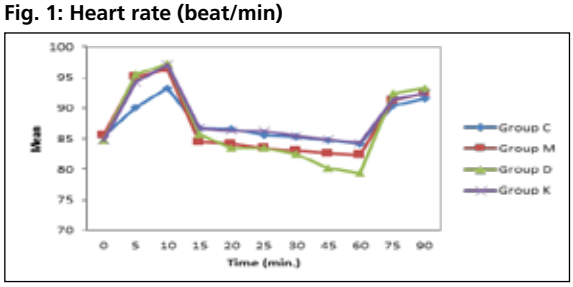
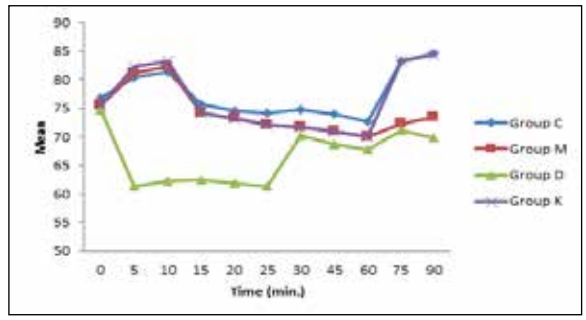


Fig. 2: Mean Arterial Blood Pressure (mmHg) Summary



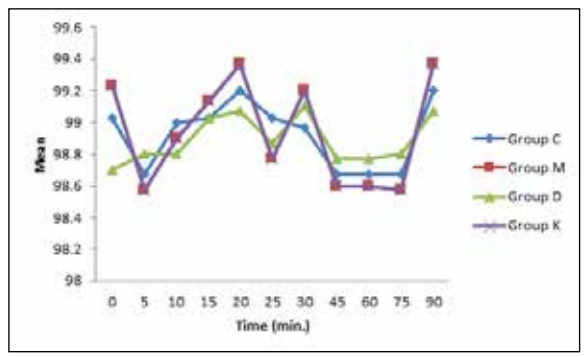


Fig. 3: Oxygen saturation (SpO2)

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