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A Comparative Study of Intrathecal Morphine and Clonidine as Adjuvant to Hyperbaric Bupivacaine in Infraumbilical Surgical Procedures Under Spinal Anaesthesia

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ABSTRACT

Spinal anesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical and easy to administer. However, postoperative pain control is a major problem because spinal anesthesia using only local anesthetics is associated with relatively short duration of action and thus early analgesic intervention is needed in the postoperative period. Comparison of efficacy of intrathecal low dose morphine and clonidine as adjuvant to hyperbaric bupivacaine to provide postoperative analgesia in infra umbilical surgeries. This prospective, randomized, double blinded comparative study was conducted in ramakrishna mission seva pratishthan, vivekananda institute of medical sciences, Kolkata after obtaining clearance from Institutional ethical and scientific committee. Study duration was August 2020-2021. All patients were randomly allocated into two groups (group BM-BC) with 40 patients in each group. Total 80 patients taken and divided in two groups. Group-BM 40 patients and group-BC 40 patients. In group-BC, 27 (67.5%) patients had no mephentermine injection, 8 (20.0%) patients had 1 mephentermine injection and 5 (20.0%) patients had 2 such. In group-BM, 37(92.5%) had no mephentermine injection and 3 (7.5%) patients had 2 such. Association of number of mephentermine injection vs groups was statistically significant (p = 0.0121). In group-BC, the mean time of 1st rescue analgesic of patients was 329.0250±51.0191. In group-BM, the mean time of 1st rescue analgesic of patients was 884.4750±188.9127. Distribution of mean time of 1st rescue analgesic with group was statistically significant (p<0.0001). Overall, intrathecal morphine did not increase respiratory depression. Intrathecal morphine was associated with a mild increase in vomiting but clonidine was associated with a mild increase in hypotension. To conclude, intrathecal morphine decreases pain intensity at rest and on movement up to 24 hrs after major surgery. Morphine-sparing is more pronounced after abdominal, gynecological and orthopedic surgery. Respiratory depression remains a major safety concern.

INTRODUCTION

Spinal anesthesia is the most commonly used technique for lower abdominal surgeries as it is very economical and easy to administer. However, postoperative pain control is a major problem because spinal anesthesia using only local anesthetics is associated with relatively short duration of action and thus early analgesic intervention is needed in the postoperative period[1,2].

Currently, hyperbaric bupivacaine is one of the most commonly used local anesthetic agents. Use of adjuncts like opioids and clonidine along with intrathecal hyperbaric bupivacaine is one of the methods to prolong this post-operative analgesia. Since 1979, intrathecal morphine, in low dose, has been used for post-operative pain management, in spinal anaesthesia for procedures like caesarean section, tubal ligation, other gynaecological surgeries, haemorrhoidectomy, transurethral prostatectomy and several orthopaedic procedures. It has provided effective and safe analgesia successfully[3]. However various incidences of adverse effects like nausea, vomiting, pruritus, respiratory depression have been reported which limits its usefulness[4].

Alpha adrenergic agonist clonidine has a variety of actions, which includes its ability to potentiate and prolong sensory blockade. Its advantage is that it does not produce side effects like pruritus or respiratory depressions, when used intrathecally but at its usual dose, that is, 1-2 mcg kg^{-1} is associated with bradycardia, relative hypotension and sedation[5].

Low doses of morphine and clonidine as intrathecal adjuvants can lower these side-effects without compromising their efficacy totally. In a recent comparative study done by Menacherry *et al* in 2018 they found out that the patients who received intrathecal hyperbaric bupivacaine with clonidine (60 mcg) proved to be a better adjuvant than clonidine (45 mcg) in prolonging sensory and motor blockade intraoperatively and effective post-operative analgesia. In a review article by DeSousa[7]. They studied the key aspects of intrathecal morphine for postoperative analgesia for various doses and different procedures as well as the side effects of morphine and it's prevention. In a recent study by Dutta *et al*.[8]. They found that intrathecal clonidine with bupivacaine prolongs the duration of sensory and motor blockade and also prolongs the duration of postoperative analgesia when compared to magnesium or controls. In another recent study by Kumar *et al*.[9]. They found that intrathecal dexmedetomidine as compared to intrathecal morphine as an adjuvant into intrathecal bupivacaine prolonged the time of first rescue analgesic without any significant adverse effec. Though there is insufficient data to compare the post-operative analgesic effects of these drugs in routine infra umbilical surgical procedures. This study is intended to compare the efficacy of post-operative analgesia between low doses of intrathecal morphine and clonidine with hyperbaric bupivacaine. The aim of the study is to note down the side effects produced in the study and to compare and treat accordingly.

MATERIALS AND METHODS

Study area: Vivekananda Institute of Medical Sciences and Ramakrishna Mission Seva Pratishthan, Kolkata after obtaining clearance from Institutional ethical and scientific committee.

Study design: It is a prospective, randomized, double blinded comparative study.

Study period: From August 2020-2021.

Sample size: 80 patients.

Inclusion criteria:

- Patient belonging to ASA grade I and grade II
- Age between 20-60 years of either sex
- Scheduled for elective infra umbilical surgeries

Exclusion criteria:

- Patient refusal
- Patients taking alpha blockers or betablockers
- Patients with labile hypertension
- Patients with known contraindications to spinal anaesthesia
- Allergic to any of the drugs used in the study
- Duration of surgery more than 120min

Methods of randomization: Randomization was done by using a computer-generated random number table. All patients were randomly allocated into two groups (Group BM-BC) with 40 patients in each group:

- Group BM patients received 3 mL of 0.5% hyperbaric Bupivacaine with 100 mcg of preservative free morphine, total volume made up to 4 mL with normal saline
- Group BC patients received 3 mL of 0.5% hyperbaric bupivacaine with 50 mcg of preservative free clonidine, total volume made up to 4 mL with normal saline

RESULTS

We observed that In group-BC, 2 (5.0%) patients were done appendix surgery, 4 (10.0%) patients were done DHS surgery, 1 (2.5%) patients were done Femur surgery, 1 (2.5%) patients were done Hemiarthroplasty surgery, 11 (27.5%) patients were done Hernia Surgery, 1 (2.5%) patients were done Ovarian cyst surgery,

2 (5.0%) patients were done PFN Surgery, 8 (20.0%) patients were done TAH+BSO Surgery, 2 (5.0%) patients were done TIBIA Surgery, 2 (5.0%) patients were done TKR Surgery and 6 (15.0%) patients were done VH+PFR Surgery. In group-BM, 3 (7.5%) patients were done appendix Surgery, 1 (2.5%) patients were done Bimalleolus Surgery, 6 (15.0%) patients were done DHS Surgery, 1 (2.5%) patients were done FEMUR Surgery, 1 (2.5%) patients were done Hemiarthroplasty Surgery, 9 (22.5%) patients were done Hernia Surgery, 1 (2.5%) patients were done Hernioplasty Surgery, 1 (2.5%) patients were done Neck Femur Surgery, 1 (2.5%) patients were done Ovarian Cyst Surgery, 2 (5.0%) patients were done PFN Surgery, 4 (10.0%) patients were done TAH+BSO Surgery, 1 (2.5%) patients were done TIBIA Surgery, 2 (5.0%) patients were done TKR Surgery and 7 (17.5%) patients were done VH+PFR Surgery. Association of Type of Surgery vs Group was not statistically significant (p = 0.9612).

It was found that in group-BC, 23 (57.5%) patients had ASA 1 and 17 (42.5%) patients had ASA 2. In group-BM, 22 (55.0%) patients had ASA 1 and 18 (45.0%) patients had ASA 2 which was not statistically significant (p = 0.8216). In our study no patients from both groups (group-BC and group-BM) had Respiratory Depression, Pruritus, Dry Mouth, Shivering and Bradycardia.

In group-BC, 2 (5.0%) patients were vomiting. In group-BM, 10 (25.0%) patients were vomiting. Association of vomiting vs Group was statistically significant (p = 0.0122). In group-BC, 13 (32.5%) patients had Hypotension. In group-BM, 3(7.5%) patients had Hypotension. Association of Hypotension vs Group was statistically significant (p = 0.0051).

Our study showed that in group-BC, the mean weight (mean±SD.) of patients was 65.2375±4.1407 kg. In group-BM, the mean Weight (mean±s.d.) of patients was 65.3825±4.3210 kg. This was not statistically significant (p = 0.8786). It was found that the mean Duration of Surgery (mean±s.d.) of patients was higher in group-BC [88.0750±23.2483 min] compared to group. BM patients [85.8750±24.3702 min] which was not statistically significant (p = 0.6807).

Our study showed that distribution of mean Sedation Scale (B) (p = 0.0863), Sedation Scale 2 hrs (p = 0.0615), Sedation Scale 3 hrs (p = 0.0917), Sedation Scale 4 hrs (p = 0.6013), Sedation Scale 6 hrs (p = 0.5620), Sedation Scale 8 hrs (p = 0.3204) and Sedation Scale at 10 hrs (p = 0.3204) with both Groups was not statistically significant. Distribution of mean Sedation Scale 1 hrs (p<0.0001) and Sedation Scale at 5 hrs (p<0.0001) with both Groups was statistically significant.

In group-BC, the mean time of 1st rescue analgesic (mean±SD) of patients was 329.0250±51.0191. In group-BM, the mean Time of 1st rescue analgesic (mean±s.d.) of patients was 884.4750±188.9127. Distribution of mean Time of 1st rescue analgesic with Group was statistically significant (p<0.0001).

In group-BC, 27 (67.5%) patients had no M6, 8 (20.0%) patients had 1 M6 and 5 (20.0%) patients had 2 M6. In group-BM, 37 (92.5%) had no M6 and 3 (7.5%) patients had 2 M6 Association of No of M6 vs Group was statistically significant (p = 0.0121). In group-BC, the mean no of paracetamol inj (1 g) (mean±SD) of patients was 2.0750±0.5723. In group-BM, the mean no of paracetamol inj (1 gm) (mean±SD) of patients was 1.1000±0.3789. Distribution of mean no of paracetamol inj (1 g) with Group was statistically significant (p<0.0001) (Table 1-3).

Table 1: Association between vomiting and hypotension: group

Vomiting	Group-BC	Group-BM	Total	Chi-square value	p-value
No	38.0	30.0	68.0	6.2745	0.0122
Row (%)	55.9	44.1	100.0		
Col (%)	95.0	75.0	85.0		
Yes (%)	2.0	10.0	12.0		
Row (%)	16.7	83.3	100.0		
Col (%)	5.0	25.0	15.0		
Total	40.0	40.0	80.0		
Row (%)	50.0	50.0	100.0		
Col (%)	100.0	100.0	100.0		
Hypotension					
No	27.0	37.0	64.0		
Row (%)	42.2	57.8	100.0		
Col (%)	67.5	92.5	80.0		
Yes	13.0	3.0	16.0	7.8125	0.0051
Row (%)	81.3	18.8	100.0		
Col (%)	32.5	7.5	20.0		
Total	40.0	40.0	80.0		
Row (%)	50.0	50.0	100.0		
Col (%)	100.0	100.0	100.0		

Table 2: Distribution of mean time of 1st rescue analgesic and no of paracetamol inj (1 g): group

	Groups	No.	Mean	SD	Minimum	Maximum	Median	p-value
Time of 1st rescue analgesic	Group-BC	40	329.0250	51.0191	230.0000	410.0000	330.0000	<0.0001
	Group-BM	40	884.4750	188.9127	600.0000	1440.0000	900.0000	
No of paracetamol inj (1 g)	Group-BC	40	2.0750	0.5723	1.0000	3.0000	2.0000	<0.000
	Group-BM	40	1.1000	.3789	0.0000	2.0000	1.0000	

Table 3: Association between No of Injection Mephentermine (M6): Group

No of M6	Group-BC	Group-BM	Total	Chi-square value	p-value
No	27.0	37.0	64.0	8.8352	0.0121
Row (%)	42.2	57.8	100.0		
Col (%)	67.5	92.5	80.0		
1	8.0	3.0	11.0		
Row (%)	72.7	27.3	100.0		
Col (%)	20.0	7.5	13.8		
2	5.0	0.0	5.0		
Row (%)	100.0	0.0	100.0		
Col (%)	12.5	0.0	6.3		

DISCUSSIONS

This prospective, randomized, double blinded comparative study was conducted in Ramakrishna Mission Seva Pratishthan, Vivekananda Institute of Medical Sciences, Kolkata after obtaining clearance from Institutional Ethical and Scientific Committee. Study duration was August 2020-2021. All patients were randomly allocated into two groups (Group BM and BC) with 40 patients in each group. Total 80 patients taken and divided in two groups: Group-A 40 patients and Group-B 40 patients.

Pre-anaesthetic evaluation was done by taking history of coexisting disease and allergy, review of clinical findings and investigation reports on the evening before surgery. Heart rate, respiratory rate, MAP, SPO2, were recorded. Patients were explained about VAS pain scale for assessment where 0 depicted no pain and 10 the worst possible pain. All patients were fasted for 8 hrs for solid food.

Our study showed that, out of 80 patients, most of the patients were 31-40 years of age but this was statistically significant (p = 0.0496). The mean age was higher in group-BM [40.1000±9.4076 years] compared to group-BC patients [37.5000±7.1253 years] and it was not statistically significant (p = 0.1675).

It was found that in our study the male population was higher than the female population it was not statistically significant (p = 0.8160).

We observed that, higher number of patients had Hernia in group-BC compared to group-BM which was not statistically significant (p = 0.9612).

It was found that, majority number of patients had ASA 1 in group-BC compared to group-BM, which was not statistically significant (p = 0.8216).

Liu *et al*.[10] found that compared with placebo, intrathecal DEX significantly prolonged the durations of both sensory block (weighted mean difference [WMD] = 134.42 min, 95% CI, 109.71-159.13 min, p<0.001) and motor block (WMD = 114.27 min, 95% CI, 93.18-135.35 min, p<0.001). It also hastened the onset of sensory block (WMD = -0.80 min; 95% CI, -1.21 to -0.40, p<0.001) and motor block (WMD = -1.03 min, 95% CI, -1.51-0.56 min, p<0.001). Furthermore, it delayed the time to first analgesic request (WMD = 216.90 min, 95% CI, 178.90-254.90 min, p<0.001) and reduced the incidence of shivering (risk ratio [RR] = 0.39, 95% CI, 0.27-0.55, p<0.001). DEX was associated with increased risk of transient bradycardia (RR = 1.59, 95% CI, 1.07-2.37, p = 0.022) and hypotension (RR = 1.40, 95% CI, 1.04-1.89, p = 0.026) but did not increase the incidence of postoperative nausea and vomiting (RR = 0.87, 95% CI, 0.62-1.24, p = 0.45).

In our study, no patients from both groups (group-BC and group-BM) had Respiratory Depression, Pruritus, Dry Mouth, Shivering and Bradycardia.

Gehling and Tryba[3] found that total of 790 patients with intrathecal morphine and 524 patients who received placebo were analysed. Compared with placebo the lower dose of morphine resulted in an increase of nausea (RR 1.4, 95% CI 1.1-1.7), vomiting (RR 3.1, 95% CI 1.5-6.4) and pruritus (RR 1.8, 95% CI 1.4-2.2). The higher dose resulted in an increased risk ratio for pruritus (RR 5.0, 95% CI 2.9-8.6) but not nausea (RR 1.2, 95% CI 0.9-1.6) or vomiting (RR 1.3, 95% CI 0.9-1.9).

We found that, most of the patients from group-BM had Vomiting complications compared to group-BC patients which was statistically significant. In our study, most of the patents from group-BC had Hypotension, where only 3 patients from group-BM had Hypotension which was statistically significant. Our study showed that, mean Weight was lower in in group-BC compared to group-BM but this was not statistically significant.

It was found that the mean Duration of Surgery was higher in group-BC compared to group-BM patients which was not statistically significant.

In our study the difference of mean Heart Rate (HR) (B), Intra-op HR 30min, Intra-op HR 60 min, Intra-op HR 90 min and Intra-op HR 120 min with both Groups were not statistically significant. Only the difference of mean Intra-op HR 10 min and Intra-op HR 45min with both Groups were statistically significant. We found that the distribution of mean Intra-op Post-op HR 30 min, Intra-op Post-op HR 120 min, Intra-op Post-op HR 180 min, Intra-op Post-op HR 8 hrs, Intra-op Post-op HR 16 hrs and Intra-op Post-op HR 24 hrs with both Groups were not statistically significant. Distribution of mean Intra-op Post-op HR 60 min, Intra-op Post-op HR 90 min, Intra-op Post-op HR 150 min, Intra-op Post-op HR 4 hrs, Intra-op Post-op HR 12 hrs and Intra-op Post-op HR 20 hrs with both Groups were statistically significant.

It was found that distribution of mean SPO2 Baseline, Intra-op SPO2 10 min, Intra-op SPO2 30 min, Intra-op SPO2 45 min, Intra-op SPO2 60 min, Intra-op SPO2 90 min and Intra-op SPO2 120 min with both Groups were not statistically significant.

We observed that the distribution o f mean Post-op SPO2 30 min, Post-op SPO2 90 min, Post-op SPO2 180 min, Post-op SPO2 4hrs, Post-op SPO2 12hrs, Post-op SPO2 20 hrs and Post-op SPO2 24 hrs with both Groups were not statistically significant.

We found that the distribution of mean SBP Baseline, Intra-op SBP 10 min, Intra-op SBP 30 min, Intra-op SBP 45 min, Intra-op SBP 60 mins and Intra-op SBP 120 min with both Groups were not statistically significant but only distribution of mean Intra-op SBP 90 min with both Groups were statistically significant. We also found that the distribution of mean Post-op SBP 60 min, Post-op SBP 180 min, Post-op SBP 8 hrs, Post-op SBP 16 hrs, Post-op SBP 20 hrs and Post-op SBP 24 hrs with both Groups were not statistically significant. Distribution of mean Post-op SBP 10 min, Post-op SBP 30 min, Post-op SBP 90 min, Post-op SBP 120 min, Post- op SBP 150 min, Post-op SBP 4 hrs and Post-op SBP 12 hrs with both Groups were statistically significant.

In our study distribution of mean DBP Baseline, Intra-op DBP 10 min, Intra-op DBP 30 min, Intra-op DBP 45 min, Intra-op DBP 60 min, Intra-op DBP 90 min and Intra-op DBP 120 min with both Groups were not statistically significant.

Our study showed that distribution of mean Post-op DBP 10 min, Post-op DBP 30 min, Post-op DBP 60 min, Post-op DBP 90 min, Post- op DBP 120 min, Post-op DBP 150 min, Post-op DBP 180 min, Post-op DBP 4 hrs, Post-op DBP 8 hrs, Post-op DBP 12 hrs, Post-op DBP 16 hrs, Post-op DBP 20 hrs and Post-op DBP 24 hrs with both Groups were not statistically significant.

We found that the distribution of mean MAP Baseline, Intra-op MAP 10, Intra-op MAP 30, Intra-op MAP 45, Intra-op MAP 60, Intra-op MAP 90 and Intra-op MAP 120 with both Groups were not statistically significant.

Our study showed that distribution of mean Post-op MAP 10 min, Post-op MAP 30 min, Post-op MAP 90 min, Post-op MAP 120 min and Post-op MAP 150 min with both Groups were statistically significant. Distribution of mean Post-op MAP 60 min, Post-op MAP 180 min, Post-op MAP 4 hrs, Post-op MAP 8 hrs, Post-op MAP 12 hrs, Post-op MAP 16 hrs, Post-op MAP 20 hrs and Post-op MAP 24 hrs with both Groups were not statistically significant.

We found that Distribution of mean Intra-op RR 10 Intra-op RR 30, Intra-op RR 45, Intra-op RR 60, Intra-op RR 90 and Intra-op RR 120 with both Groups were not statistically significant.

In our study distribution of mean Post-op RR 30 min, Post-op RR 60 min, Post-op RR 90 min, Post-op RR 120 min, Post-op RR 150 min, Post-op RR 180 min, Post-op RR 4 hrs, Post-op RR 8 hrs, Post-op RR 12 hrs, Post-op RR 16 hrs, Post-op RR 20 hrs and Post-op RR 24 hrs with both Groups was not statistically significant.

Meylan *et al*.[11] found that twenty-seven studies (15 cardiac-thoracic, nine abdominal and three spine surgery) were included, 645 patients received intrathecal morphine (dose-range, 100-4000 µg). Pain intensity at rest was decreased by 2 cm on the 10 cm visual analogue scale up to 4 hrs after operation and by about 1 cm at 12-24 hrs.

It was found that distribution of mean VAS at 0 with Group was not statistically significant. We found that, mean VAS at 1 hrs, VAS at 2 hrs, VAS at 3 hrs, VAS at 4 hrs, VAS at 5 hrs, VAS at 6 hrs, VAS at 8 hrs, VAS at 10 hrs, VAS at 12 hrs, VAS at 16 hrs, VAS at 20 hrs and VAS at 24 hrs with both Groups were statistically significant.

Strebel *et al*.[12] examined duration of pain relief from intrathecal clonidine administration until the first request for supplemental analgesia was significantly prolonged: 295±80 min (Group 1, control), 343±75 min in Group 2 (+16%), 381±117 min in Group 3 (+29%) and 445±136 min in Group 4 (+51%) (estimated parameter for dose 1.02 [95% confidence interval 0.59-1.45]). Relative hemodynamic stability was maintained and there were no between-group differences in the sedation score.

Our study showed that distribution of mean Sedation Scale (B), Sedation Scale 2 hrs , Sedation Scale 3 hrs, Sedation Scale 4 hrs, Sedation Scale 6 hrs, Sedation Scale 8 hrs and Sedation Scale at 10 hrs with both Groups was not statistically significant. Distribution of mean Sedation Scale 1 hrs and Sedation Scale at 5 hrs with both Groups was statistically significant.

Van Tuijl *et al*.[13] showed that a group of 106 women received spinal anaesthesia using either bupivacaine 0.5% (2.2 mL) heavy with 0.5 mL normal saline 0.9% (B) or bupivacaine 0.5% (2.2 mL) heavy with clonidine (75 µg) in 0.5 mL normal saline 0.9% (BC). The mean time to the first analgesic request in the BC group was 129 (SD 13.8) min, compared with 55 (14.2) min in the B group [mean difference (95% CI) -75 (-106 to -44) min]. In the BC group 22 (42%) patients had a complete motor block 1 hrs after surgery compared with 4 (8%) patients in the B group [RR (95% CI) 0.18 (0.07-0.49)].

We found that the mean Time of 1st rescue analgesic was significantly higher in group-BM compared to group-BC patients ($p<0.0001$).

It was found that most of the patients had 2 M6 in group-BC compared to group-BM but this was statistically significant ($p = 0.0121$).

In our study, mean no of paracetamol injection (1 g) was significantly higher in group-BC compared to group-BM patients. ($p<0.0001$).

CONCLUSION

Overall, intrathecal morphine did not increase respiratory depression. Intrathecal morphine was associated with a mild increase in vomiting but Clonidine was associated with a mild increase in hypotension. To conclude, intrathecal morphine decreases pain intensity at rest and on movement up

to 24 hrs after major surgery. Morphine-sparing is more pronounced after abdominal, gynecological and orthopaedic surgery. Respiratory depression remains a major safety concern.

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