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INTRATHECAL BUTORPHANOL AS AN ADJUVANT TO PREVENT THE SIDE EFFECTS OF INTRATHECAL MORPHINE AND BUPIVACAINE COMBINATION!

Anaesthesiology

Dr. Gurjinder Singh Senior Resident, Department of anaesthesia &Intensive Care, VMMC &Safdarjung, Hospital, NewDelhi.

Dr.Anita Vig Professor, Department of Anaesthesia &Intensive Care, Govt. Medical College, Jammu.

Dr.Renu Wakhloo Associate Professor, Department of Anaesthesia &Intensive Care, Govt Medical College, Jammu.

Dr.Akshaya Kumar Das* Senior Resident,VMMC & Safdarjung Hospital, NewDelhi. *Corresponding Author

ABSTRACT

BACKGROUND: Intrathecal opioids have its own side-effects like nausea vomiting, hypotension, pruritus and rarely respiratory depression. We have conducted this study to evaluate the effect of Intrathecal Butorphanol to minimize the side effects of Bupivacaine –morphine combination.

MATERIAL AND METHODS: In this randomised control study,100 patients of either sex ranging in the age group between 18 to 60 years belonging to ASA grade I &II, scheduled for hip and lower limb surgeries were selected. The study population was randomly allocated to three groups with 50 patients each group I, II. Group I received Bupivacaine (2.5ml) + Morphine (0.5ml) 100 µg + Normal Saline (0.5ml) whereas Group II received Bupivacaine (2.5ml) + Morphine (0.5ml) 100 µg + Butorphanol (0.5ml) 25 µg for spinal anaesthesia. Parameters observed were incidence of nausea, vomiting, urinary retention., respiratory depression, sensory level regression and time to need for first rescue analgesia.

RESULTS: The time taken to segmental regression to S1 dermatome and motor regression to Bromage scale 0 was significantly longer in Group II i.e. 157.2 ± 7.91 minutes and 142.6 ± 7.76 minutes respectively as compared to Group-I (BUPIVACAINE +MORPHINE). The incidence of side effects like pruritus, nausea and vomiting, urinary retention, hypotension and bradycardia were lesser with patients received intrathecal Bupivacaine +Morphine+ Butorphanol($p<0.05$).

CONCLUSION: Butorphanol can be used as a suitable alternative to prevent the side-effects of intrathecal morphine and prolongs the duration of sensorimotor block.

KEYWORDS

Morphine, Bupivacaine, Butorphenol, Intrathecal Opioids

INTRODUCTION

Spinal anaesthesia is one of the methods of anaesthesia for procedures carried out on lower abdominal, sub-umbilical, lower limbs, pelvis, genitals and perineum. Various local anaesthetic agents have been used in spinal anaesthesia since their introduction. Various drugs have been tried as adjuvant to local anesthetic like opioids, ketamine, neostigmine, midazolam and α_2- adrenergic agonists like clonidine, dexmedetomidine.

The first report on the use of intrathecal opioids for acute pain relief was in 1979 by Wang and colleagues who used morphine as adjuvant[1]. Morphine is the forerunner of adjuvants to local anesthetic solution for achieving a good sensory and motor block. The side effects of intrathecal /epidural opiates though dose dependent, may sometimes manifest in annoying symptoms like pruritus, urinary retention, nausea and early or late respiratory depression [2] and needs prolong hospital stay &monitoring[3].

Butorphanol is a synthetic opioid that exhibits partial agonist-antagonist activity at the mu-opioid receptors and agonistic activity at the Kappa-opioid receptors [4]. It is hypothesized that generalized pruritus may be result from an imbalance of both the mu and kappa opioid systems and kappa-agonists like Butorphanol have been shown to inhibit pruritus in both animals and human beings after intrathecal morphine administration [5]. The pruritus preventing effect of intrathecal Butorphanol was already proven by different studies [5-7].

we planned to conduct one study to evaluate the effects Butorphanol for prevention of side effect of intrathecal morphine and duration of sensorimotor block & analgesia.

MATERIALS AND METHODS

After obtaining approval from Hospital Ethical Committee, the present study was undertaken in the Department of Anesthesiology and Intensive Care, Govt. Medical College Jammu.150 patients of either sex ranging in the age group between 18 to 60 years belonging to ASA grade I &II, scheduled for hip and lower limb surgeries were selected for the study after taking prior informed consent.

Patients with a history of allergy to any of the study drug history of opioid abuse, impaired cardiac, renal, hepatic and biliary function, patients on tranquilizers, hypnotics, sedatives and other CNS depressant drugs, pregnant women, posted for day care Surgical procedures, preoperative urinary bladder catheterization, history of obstructive sleep apnea or any contraindication to spinal anesthesia were excluded from the study.

Groups

Patients were randomly allocated to one of the two study groups, each group comprising of 50 patients. Randomization was performed using computer generated random number table.

Group I :(n=50)– Bupivacaine (2.5ml) + Morphine (0.5ml) 100 µg + Normal Saline (0.5ml).

Group II (n=50)-Bupivacaine (2.5ml) + Morphine (0.5ml) 100 µg + Butorphanol (0.5ml) 25 µg

The total volume of the drug was kept 3.5 ml in all the groups.

Pre-anesthetic Preparation:

As per the hospital protocol every patient was kept fasting for 8 hours preoperatively. Each patient received oral ranitidine 150 mg night before surgery. Peripheral iv access was secured by 18 G i.v. cannula and bolus dose of Ringered lactate was transfused at a dose of 10 ml/kg. After shifting of the patients to OR, base line vital parameters were recorded. Anesthetic Technique: After all aseptic precautions, 25 G Quinke spinal needle was inserted in L_3 –L_4 or L_4– L_5 interspace and lumbar puncture was performed in sitting position. The study drugs were injected after ensuring free flow of CSF.

Sensory blockade

The onset of sensory block was checked every minute by bilateral pin prick method using a blunt 25G hypodermic needle till it reached T_{10} level which was taken as level to start surgery.

Motor blockade

Modified Bromage Scale was used to assess motor block after spinal anesthesia.

(0 = No motor power impairment and able to raise straight leg.,1 = Unable to raise straight leg but able to flex knee,2 = Unable to flex knee,3 = Unable to flex ankle and foot). Attainment of Bromage score 3 was used as a cutoff value to start the surgery.

Sedation

Grading of sedation was evaluated by using Ramsey Sedation Score. Sedation score was recorded just before the initiation and every 15 minutes during the surgery.

Parameters which were observed:

Sensory level, Bromage score and sedation score were noted in every 30 minutes in the recovery room. The regression of sensory block was determined by the time taken for two dermatomal regressions from the injection of study drug. Sensory regression to S_1 dermatome and motor regression to Modified Bromage 0 were also recorded.

Severity of Nausea and Vomiting & pruritus were measured by separate three point scales.

(0= no nausea and vomiting;1= mild nausea or vomiting not requiring treatment.;2= moderate nausea or vomiting requiring treatment ;3= severe vomiting requiring more than one dose of antiemetic or multiple anti emetics).

(0= No pruritus;1= mild to moderate facial pruritus that may or may not require treatment.;2= severe facial pruritus requiring treatment;3= pruritus involving extra facial region requiring treatment.)

Pruritus was treated with 4mg of dexamethasone intravenously.

Urinary Retention

Postoperative urinary retention (POUR) was assessed by history, physical examination and the need for bladder catheterization.

Duration of Analgesia

Linear Visual Analogue Scale (VAS) was used to measure postoperative pain severity with pain intensity ranging from 0 to 10. Duration of analgesia was taken as time period till VAS of 4 was noted. Rescue analgesia was provided by intravenous Paracetamol 1gm.

Hemodynamic parameters like heart rate, blood pressure, SPO2 were recorded in every 5 minutes for first half an hour and thereafter every 10 minutes till the end of surgery. Postoperatively these parameters were recorded in every 30 minutes for 1st 3 hours and thereafter every two hours up to 24 hours.

STATISTICALANALYSIS

The recorded data was entered in a spreadsheet (Microsoft Excel) and then analyzed in SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as Mean ±SD and categorical variables represented as frequencies and percentages. Graphically the data was presented by bar and line diagrams. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables.

1. P > 0.05 - Not significant
2. P < 0.05 - Significant

RESULTS

All the demographic variables like age, weight, height, gender distribution was comparable in all two groups with P >0.05(Table-1). Vital signs like Systolic Blood pressure (SBP), Diastolic blood Pressure(DBP), Mean blood Pressure, Oxygen saturation (SpO2) at all the observation time were comparable in two groups with P>0.05(Fig 1-5). Time taken to achieve T10 Sensory level and Bromage 3 motor grade were comparable in all the groups with P>0.05(Table-1).

VARIABLES	GROUP I	GROUP II	P VALUE
AGE	37.3±12.67	38.4±12.84	P=0.6673
WEIGHT	65.06 ±6.849	64.16±8.163	P= 0.551
HEIGHT	158.54 ±7.404	160.2±7.265	P=0.260
MALE %	60	66	—
FEMALE%	40	34	----
Time to reach the T10 level	7.1±1.8	7.5±1.18	P= 0.191
Time to reach Bromage 3 motor blockade	6.5±1.13	6.7±1.01	P= 0.353

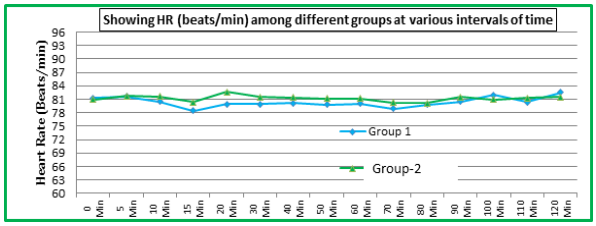
SENSORY, MOTOR BLOCK &DURATION OF ANALGESIA:

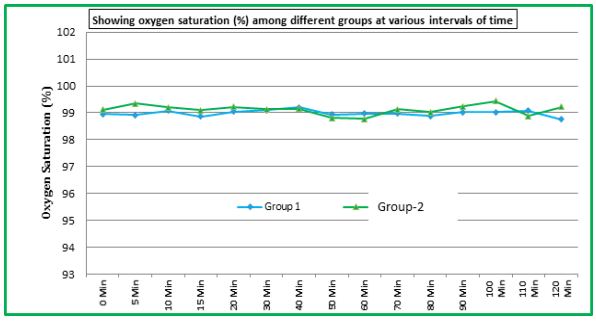
Results of our study showed that the time taken to segmental regression to S1 dermatome and motor regression to Bromage 0 in Group –II (Bupivacaine +Morphine+Bupronorphine) was higher group-I i.e. 157.2± 7.91 minutes and 142.6 ± 7.76 minutes respectively. It is statistically significant (P<0.05) (TABLE-2).

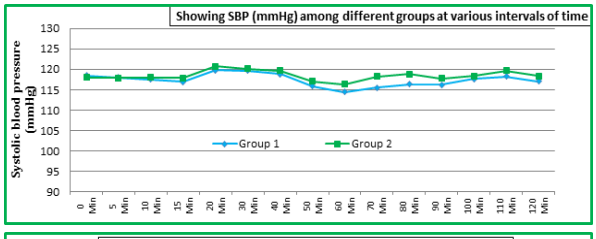
Table-2: Comparison of analgesia, duration of sensorimotor block and incidence of side effects between group-I and group-II

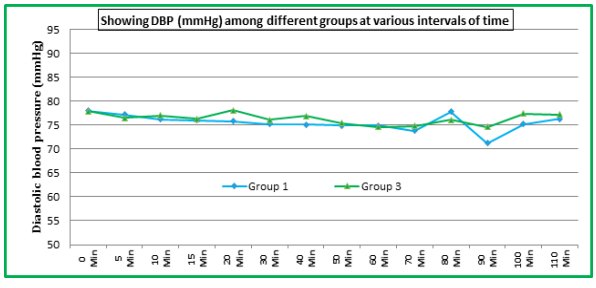
VARIABLE		GROUP -1	GROUP-II	SIGNIFICANCE P VALUE
Time to reach Bromage-0 motor block		125.1±6.22	142.6±7.76	<0.001*
Time to reach sensory regression to s1 segment (minutes)		139.1±6.39	157.2±7.91	P < 0.0001
Duration to rescue analgesia (minutes)		1148.0±114.32	866.3±111.15	P < 0.0001
Pruritus	0	28(56%)	39(78%)	0.047*
	1	14(28%)	8(16%)	
	2	5(10%)	3(6%)	
	3	3(6%)	0(0%)	
Nausea And vomiting Score	0	29(58%)	40(80%)	0.039*
	1	11(22%)	8(16%)	
	2	8(16%)	2(4%)1	
	3	2(4%)	0(0%)	
Urinary retention		12(24%)	5(10%)	P = 0.064*
Hypotension		7(14%)	2(4%)	P = 0.082*
Bradycardia		8(16%)	4(8%)	P = 0.220*

*Statistically Significant Difference (P-value<0.05)









Group-2

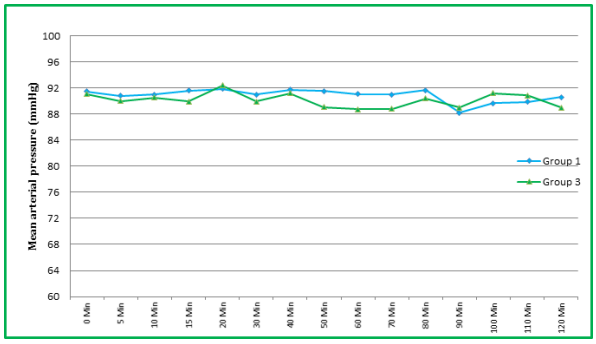


Figure [1- 5] :Hemodynamic parameters comparison of all three groups (P > 0.05)

The mean duration of Analgesia was found to be 19.13 hrs. ± 114.32 minutes in Group-I (BUPIVACAIN +MORPHINE) which was significantly longer than other group with P < 0.0001.(Table-2).

ADVERSE EFFECTS COMPARISION:

Pruritus was observed in 22 patients (44%) in group 1and 11 patients (22%) in group II. The different was statistically significant. P<0.05(Table 2). Nausea and Vomiting was observed in 10 patients (20%) in group 1and 2 patients (4%) in group II.

Urinary retention was observed in 12 patients (24%) in group 1and 5 patients (10%) in group II (TABLE-2). Hypotension was reported in 7 patients (14%) in group 1 and 2 patients (4%) in group II. On intergroup comparison between group 1 and 2 the results were found to be statistically significant among the groups. Bradycardia was seen in 8 patients (16%) in group 1and 4 patients (8%) in group 3. (TABLE-2)

There is statistical significant lower incidence of side effects profile in group-II (patient received Bupivacaine+Morphine+Butarophanol) as compared to Group-I (Bupivacaine+ Morphine) (p<0.005).

DISCUSSION

The main obstacles for optimal use of intrathecal Morphine are its side effects which include pruritus, nausea / vomiting, urinary retention, constipation, respiratory depression, undesirable sedation and the development of tolerance/dependence [2]. These side effects are attributed to the hydrophilic nature and longer stay of morphine in CSF [8]. Butorphanol could be an effective prophylactic treatment for morphine induced pruritusdue to its action on mu and kappa receptors. Our study has compared intrathecal Butorphanol with placebo for prevention of morphine related adverse effects in patients undergoing lower limb surgeries under spinal anesthesia with Bupivacaine and morphine. All demographic profile and hemodynamic parameters were comparable in two groups.

The mean duration of first rescue analgesia was 1148.0 minutes (19.13 hrs.) ± 114.32 minutes and 866.3 minutes (14.43 hrs.) ± 111.15 minutes in group –I & II respectively. The difference was found to be statistically significant among two group. The duration is larger in Bupivacaine morphine group as compared to other group received intrathecal morphine with Butorphanol.

Our study finding is consistent with study of Sfeir et al. [9]and also a similar study by Karaman et al.[10] who demonstrated that preoperative intrathecal morphine enhanced the quality of postoperative analgesia.

Slappendel et al. conducted a study of optimization of the dose of intrathecal morphine in total hip surgery [11]. They concluded that 100 mcg of intrathecal morphine is the optimal dose for pain relief after hip surgery with minimal side effects. Our study findings are similar to above mentioned study that a dose of 100 mcg of morphine provides a balance between optimal analgesia minimal side effects.

Pruritus was observed in 22 patients (44%) in Group -I (morphine) and 11 patients (22%) in Group II (Morphine + Butorphanol). The difference was found to be statistically significant among groups I &II. Gwirtz et al. conducted a study for the safety and efficiency of intrathecal opioid analgesia for acute postoperative pain[3]. They found the pruritus was the most common (37%) and respiratory depression the least common of (3%) of side effects. Our study findings were also consistent with the above study findings.

In a retrospective data review, Chinachoti, et al. found the incidence of nausea, vomiting and pruritus were 21.5%, 14.8% and 59.5 % respectively with intrathecal morphine 0.3 mg (more than our study) [12]. No Respiratory depression and urinary retention was recorded. This is in accordance with our study which has shown similar results.

BO-Xiang et al. conducted a systematic randomized controlled trial that compared the use of Butorphanol with morphine and morphine with placebo for preventing morphine induced pruritus [6]. They found the potential benefits of using Butorphanol to prevent morphine induced pruritus which is in accordance to our study where we found the incidence of morphine with placebo to be 44% and morphine with Butorphanol to be 22%.

Nausea and Vomiting was observed in 10 patients (20%) in Group I (Morphine), and 2 patients (4%) in Group II (morphine + Butorphanol). The result was found to be statistically significant among Group-I &II. The high incidence of nausea and vomiting which we found in the morphine group (20 %) is in concordance with the study of Chaney MA (1995) who showed a 30% incidence of nausea and vomiting following intrathecal & epidural opioids[13].

URINARY RETENTION:

In our study urinary retention was observed in 12 patients (24%) in Morphine Group (Group-I). This increased incidence of urinary retention is because of decreased detrusor muscle contractility and decreased sensation of urge. In the second group (Morphine + Butorphanol) the incidence of urinary retention was 5 patients (10%) which is statistically significant when compared with group First (Morphine Group).

According to Raffaeli et al. a prospective, randomized, double blind dose response study, no urinary retention was observed in the population receiving 60 and 250mcg morphine after 2 hours but after 4 hours, 20-40% of cases of urinary retention were seen and it decreased to 10% after 24 hours of drug injection [14]. This is in accordance with our study where we found 24% of urinary retention cases in group one (morphine + bupivacaine).

Hypotension was reported in 7 patients (14%) in group -I (morphine) and 2 patients (4%) in group-II (morphine + butorphanol). On intergroup comparison between group I and group II, the results were found to be statistically significant. Not a single patient had an excessive cephalad spread of block.

Bradycardia was seen in 8 patients (16%) in group I (morphine) and 4 patients (8%) in group II (morphine + butorphanol). Thus the incidence of Bradycardia was found to be statistically significant between group I and II, with the highest incidence in group 1.

Kumar et al. conducted a comparison study of intrathecal Bupivacaine, fentanyl and Bupivacaine – Butorphanol mixture (0.5% of 2.5ml Bupivacaine + 1ml 25mcg Butorphanol) for lower limb orthopedic procedures [15]. There was no single case reported of Bradycardia and 5% of the patients in the Bupivacaine-Butorphanol Group developed hypotension which is in concordance with the results of our study where we found 4% of hypotension incidence although we used butorphanol in combination with morphine.

RESPIRATORY DEPRESSION:

In our study none of the patients developed respiratory depression. None of the patients in our study developed sweating, constipation, headache, persistent hiccups, hypothermia throughout the observation period of the study.

CONCLUSION:

Butorphanol was found to be better adjuvant with morphine and bupivacaine as it provides best balance between analgesic effect and morphine induced side effects. It is recommended to use butorphanol as an adjuvant to prevent the side effect of morphine.

CONFLICTS OF INTERESTS:

There are no conflicts of interests

FINANCIAL SUPPORT: Nil

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