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INTRATHECAL NALBUPHINE AS A BEST ADJUVANT TO COMBAT THE SIDE EFFECTS OF INTRATHECAL MORPHINE AND BUPIVACAINE COMBINATION

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ABSTRACT Use of intrathecal morphine for acute and chronic pain control and perioperative analgesia is a popular option among the anesthesiologists and pain specialists. But intrathecal morphine has its own side effects like nausea, vomiting, pruritus, urinary retention and in the severe form delayed respiratory depression. Nalbuphine, a semisynthetic opioid is an option for preventing side effects of intrathecal opioids.

METHODS: We conducted one randomized control study by taking 100 patients from 18 years to 60 years with ASA Grade-I &II of either sex posted for hip and lower limb orthopedics surgery. All the patients were divided into two groups i.e. Group-I and group-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 + Nalbuphine 0.5 ml (1 mg) for spinal anesthesia. Incidence of side effects like nausea, vomiting, pruritus, hypotension, respiratory depression and onset and duration of sensory motor block and analgesia were compared.

RESULTS: Time to achieve T10 Sensory level was comparable two groups (P>0.05). There was delay in achieving Bromage grade-3 motor block in group-II as compared to Group-I (p=0.0253).

There was higher incidence of nausea &vomiting, hypotension, urinary retention, bradycardia in group –I (Bupivacaine morphine) as compared to group II (Bupivacaine+morphine+nalbuphine) (p<0.005).

CONCLUSION: Nalbuphine could be used as an effective adjuvant to prevent the adverse effect of intrathecal morphine without affecting its analgesic effect.

KEYWORDS : Bupivacaine , Intrathecal opioid ,Morphine ,Nalbuphine.

INTRODUCTION:

Intrathecal opioid is a popular option for analgesia when used as a sole agent or used with the combination of a local anesthetic agent as an adjuvant. After the detection of opiate receptor in substantia gelatinosa by Pert and Synder in 1973 and Yakesh and Rudy in 1976, opioid became a topic of research among anesthesiologists for its intrathecal use[1,2]. The first publication of official use of intrathecal morphine was released in 1979[3]. As many studies and researches were done in subsequent years regarding the advantages and disadvantages of intrathecal morphine in clinical practice. The adverse effects of intrathecal morphine are nausea vomiting[4], urinary retention, pruritus [5] and deadliest being delayed respiratory depression [6-8]. As per the large meta-analysis conducted by the cumulative analysis of multiple trials on intrathecal morphine, there is high-risk of respiratory depression with odd of 7.86 with intrathecal morphine[9].

Nalbuphine is a semi synthetic opioid with mixed mu antagonist and Kappa agonist properties [10]. Intrathecal administration of nalbuphine produces a significant analgesia accompanied by minimal pruritus and respiratory depression. However, study results have shown that nalbuphine administered either intravenous or intrathecally reduced the intrathecal morphine induced side effects without altering analgesic property of morphine. Therefore, we decided to the conducted one study to evaluate the effect of nalbuphine on side effect profile and sensorimotor block by intrathecal morphine.

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.

Inclusion Criteria:

- Either sex with age ranging from 18 to 60 years
- ASA grade I &II,
- Scheduled for hip and lower limb surgeries

Exclusion Criteria:

- Refusal of Consent
- Patients with a history of allergy to any of the study drug or any contraindication to spinal anesthesia
- History of opioid abuse, on tranquilizers, hypnotics, sedatives and other CNS depressant drugs,
- Impaired cardiac, renal, hepatic and biliary function,
- Pregnant women, posted for day care Surgical procedures,
- Preoperative urinary bladder catheterization,
- History of obstructive sleep apnea

Groups

All total 100 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 + Nalbuphine (0.5ml) 1mg

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

Pre-anesthetic Preparation:

Every patient received given oral ranitidine 150 mg night before surgery. After shifting to the operation theatre, standard monitors like ECG, Noninvasive Blood Pressure(NIBP), Pulse oximeter(SPO2) was attached. Peripheral venous access was established with 18 G cannula and patients were preloaded with 10ml/kg infusion of Ringer Lactate solution 30 minutes before starting the procedure.

Anesthetic Technique:

Under all aseptic conditions after infiltration of the skin and subcutaneous tissue with local anesthetic at the site of puncture, lumbar puncture was performed in L3 –L4 or L4 – L5 interspace with 25 G Quincke's spinal needle and the study drug injected with the patient in sitting position. Thereafter the patient was placed in supine position for surgery.

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 T10 level which was taken as level to start surgery.

Motor Blockade:
Degree of motor blockade attained was assessed every minute according to Modified Bromage Scale after spinal block. (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 deemed fit to undertake 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. Postoperatively, sensory level, Bromage score and sedation score were recorded every 30 minutes in the recovery room. The time from spinal injection of drug to two dermatomal regressions, indicating start of regression of sensory block were noted. Sensory regression to S1 dermatome and motor regression to Modified Bromage 0 were recorded indicating the total duration of the sensory and motor block respectively.

Nausea and Vomiting was assessed using a three point scale.

(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).

Pruritus was assessed using a three-point scale. (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
The method used to diagnose POUR (Postoperative urinary retention) was by history, physical examination and the need for bladder catheterization.

Duration Of Analgesia
Pain intensity was assessed every 30 minutes with the help of Linear Visual Analogue Scale (VAS) using a 10 cm line, 0 denoting no pain while 10 denoting worst possible pain. Duration of analgesia was taken as time period till VAS of 4 was recorded. After this, postoperative pain was managed by rescue analgesia of 1gm paracetamol infusion.

Cardiorespiratory parameters of heart rate, blood pressure, SPO2 was recorded every 5 minutes for first half an hour and thereafter every 10 minutes till the end of surgery. Postoperatively these parameters were recorded every 30 minutes for 1st 3 hours and thereafter every two hours up to 24 hours. Data so collected was analyzed, compared and subjected to statistical analysis.

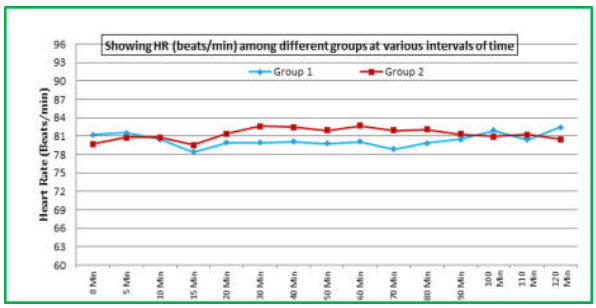
Statistical Analysis
The recorded data was analyzed by the help of SPSS Version 20.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables were represented as Mean ±SD whereas categorical variables were represented as frequencies and percentages. Quantitative data were analyzed with student's t test. Bar and line diagrams were used to represent data graphically. Chi-square test or Fisher's exact test were used to analyzed categorical data Statistically significance of the data was considered when p value was less than or equal to 0.05.

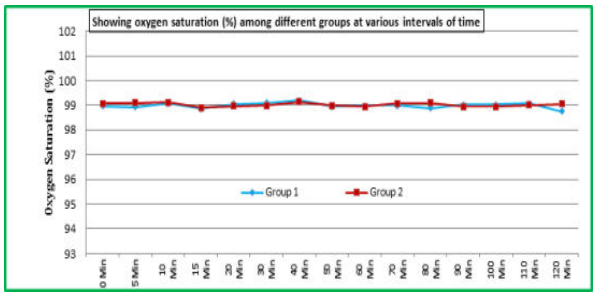
RESULTS
1. All the demographic variables like age, weight, height, gender distribution was comparable in all two groups (P>0.05.) (Table-1).
2. Vital signs like Systolic Blood pressure (SBP), Diastolic blood Pressure(DBP), Mean blood Pressure, Oxygen saturation (SpO2) at all the observation time were comparable in two groups (P>0.05) Fig 1-5.
3. Time to achieve T10 Sensory level was comparable two groups (P>0.05). There was delay in achieving Bromage grade-3 motor block in group-II as compared to Group-I (p=0.0253) Table-1.
4. Results of our study showed that the time taken to segmental regression to S1 dermatome & time to reach Bromage 0 Motor Block were 149.0±6.66 min and 134.3± 6.76min respectively which is significantly longer as compared to Group-I(p<0.001) (Table-2).
5. The mean duration of Analgesia was found to be 1148.0 ± 114.32 minutes in Group 1 (BUPIVACAIN +MORPHINE) which was longer than other group(p<0.001) (table-2).
6. Pruritus was observed in 22 patients (44%) in group -I, 6 patients (12%) in group II. The different was statistically significant. P<0.05(Table 2).
7. Nausea and Vomiting was observed in 10 patients (20%) in group 1, 1 patient (2%) in group II.(TABLE-2). Urinary retention was observed in 12 patients (24%) in group I, 3 patients (6%) in group II. Hypotension was reported in 7 patients (14%) in group I and 1 patient (2%) 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 1, 1 patient (2%) in group 2. (TABLE-2)

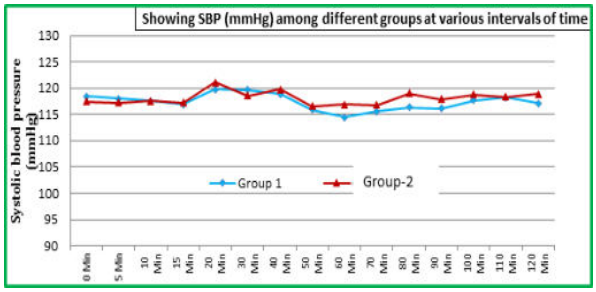
The result was found to be statistically significant (P< 0.05) among groups 1 and 2. Higher incidence of nausea &vomiting, hypotension, urinary retention, bradycardia was more in group –I as compared to group II.

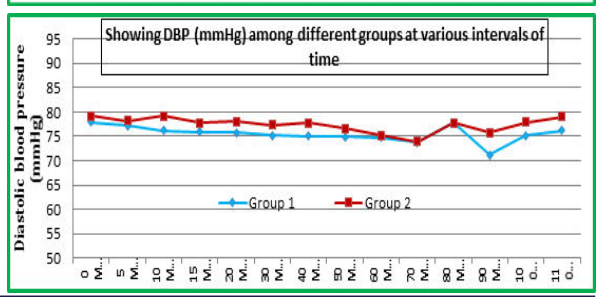
Table-1: Comparison Of Demographic Profile And Time To Achieve Motor And Sensory Level In Two Groups.

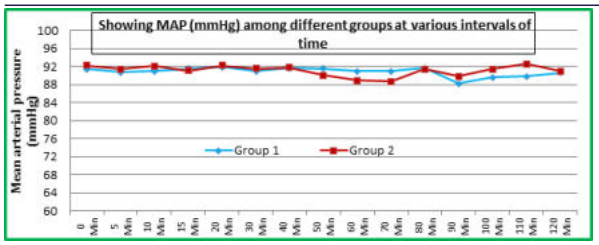
VARIABLES	GROUP I (n=50)	GROUP II (n=50)	P VALUE
AGE(in yrs.)	37.3±12.67	38±12.61	P= 0.7824
WEIGHT(in kg.)	65.06 ±6.849	66.84±7.590	P = 0.2212
HEIGHT(in cm.)	158.54 ±7.404	157.68±7.839	P = 0.5741
MALE %	60	54	—
FEMALE%	40	46	
Time to reach the T10 level (in min.)	7.1±1.8	7.4±1.01	P = 0.3066
Time to reach Bromage 3 motor blockade(in min.)	6.5±1.13	7.0±1.07	0.0253











Figure[1- 5] Hemodynamic Parameters Comparison Of All Three Groups (P > 0.05)

Table-2 : Comparison Of Duration Of Sensorimotor Block, Duration Of Analgesia And Incidence Of Side Effects Between Group-I And Group-II.

VARIABLE		GROUP -I	GROUP-II	P VALUE
Time to reach sensory regression to S1 Segment (in min.)		139.1±6.39	149.0±6.66	<0.001*
Time to reach Bromage 0 Motor Block(in min.)		125.1±6.22	134.3± 6.76	<0.001*
duration to rescue analgesia (in min.)		1148.0 ±114.32	1033.9 ±129.02	<0.001*
PRURITUS (NUMBER &%)	0	28(56%)	44(88%)	0.004*
	1	14(28%)	5(10%)	
	2	5(10%)	1(2%)	
	3	3(6%)	0(0%)	
Nausea And vomiting score (Number &%)	0	29(58%)	45(90%)	0.003*
	1	11(22%)	4(8%)	
	2	8(16%)	1(2%)	
	3	2(4%)	0(0%)	
Urinary Retention (Number&%)		12(24%)	3(6%)	0.012*
HYPOTENSION (Number&%)		7(14%)	1(2%)	0.027*
BRADYCARDIA (Number&%)		8(16%)	1(2%)	0.014*

*Statistically
Significant Difference (P-value<0.05)

DISCUSSION

In perioperative period, analgesia is one of the main demand of all patients. There are different options for perioperative analgesia but opioids provide the most effective pain relief and are a standard of care. 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[3]. Morphine, which is -more hydrophilic than other opioids, stays for longer time in the CSF and therefore may reach rostral sites over a longer period than other opioids.

Opioid receptor activation inhibits the presynaptic release and post synaptic response to excitatory neurotransmitters from nociceptive neurons. Transmission of pain impulses are interrupted at the Spinal Cord level which have abundant opioid receptors on the Substantia Gelatinosa of the Spinal cord. Consequently, there is a potential of achieving adequate and long lasting analgesia with an intrathecal injection of morphine. [2]. But side effects associated with systemic and intrathecal opioids like nausea, vomiting, pruritus, urinary retention and lastly respiratory depression discourages anesthesiologist for its use. The most dangerous adverse effect of intrathecal opioids mainly for intrathecal morphine which needs special mention is delayed respiratory depression.

All demographic profile and hemodynamic parameters were comparable in two groups. The mean duration of first rescue analgesia is longer in Bupivacaine morphine group as compared to other two groups. Our study finding is consistent with study of Sfeir et al. and also a similar study by Karaman et al. who demonstrated that preoperative intrathecal morphine enhanced the quality of postoperative analgesia [11,12]. The possible explanation being Opioids and local anesthetics administered together intrathecally have a potent synergistic analgesic effect. Opioids produce analgesia by specific binding and activation of opioid receptors present in substantia gelatinosa whereas local anesthetics provide analgesia by blocking impulse transmission at nerve root and dorsal root ganglia[2].

Slappendel et al. conducted a study to determine the optimized dose of intrathecal morphine in total hip surgery with lesser possible side effects [13]. As per their findings, the optimum dose of intrathecal morphine was 100 µg after hip surgery with minimal side effects. Our study findings are similar to Slappendel et al. study that a dose of 100 mcg of morphine can be used in intrathecal route for better analgesia profile with minimal side effects.

According to the results of study conducted by Gehling et al. to determine the optimized dose of intrathecal morphine for analgesia in orthopedic patients who received spinal Bupivacain,0.1 mg and 0.2 mg of intrathecal morphine are the two optimized dose [14]. The dose between 0.1mg to 0.2 mg provided long duration of analgesia with minimal adverse effects. In our study, we also used 0.1 mg of morphine as our study drug to avoid bias.

A prospective study was conducted by Gwirtz et al. by taking details 5969 patients underwent major urologic, orthopedic, general/vascular, thoracic, and non-obstetrical, gynecologic surgery and received intrathecal morphine to determine the safety and efficacy of intrathecal morphine [15]. Their results suggested that pruritus was the most common (37%) and respiratory depression the least common (3%) of side effects which was reversible with Naloxone. There was not a single case of any death or any life threatening events. Our study results suggested similar findings that pruritus was observed in 22 patients (44%) in Group -I (morphine), 6 patients (12%) in Group-II (morphine +nalbuphine). There was a not a single case of respiratory depression among the study population.

Kumar et al. conducted a study to determine the optimal dose of intrathecal nalbuphine for prevention of adverse effects related to intrathecal morphine [5]. In the group of Bupivacaine +Morphine (100 mcg) ,53.3 % of patients developed nausea and vomiting requiring treatment as compared to 10% in patients receiving Bupivacaine +Morphine (100 mcg) + Nalbuphine (1mg). Our study findings match the above study where we also found the lower incidence of nausea and vomiting in the Nalbuphine group (2% as against 20% of Morphine +Bupivacaine group).

In a prospective, randomized, double blind dose response study, Raffaeli et al. included opioid naïve patients suffering from chronic back pain [16]. They divided the population in to five subgroups. One of these group was taken as control where as other four groups received intrathecal morphine at a dose of 0.015mg,0.03mg,0.06mg and 0.25 mg respectively. In their control group, no urinary retention was observed while after 2 hrs. of intrathecal injection of morphine, urinary retention was observed in 20-40%of cases and it decreased to less than 10%, after 24hr of intrathecal morphine injection. This is in accordance with our study where we found 24% of urinary retention cases in group one (morphine + bupivacaine). Repeated reassurance was given to them void and none required bladder catheterization.

Similarly, in another comparative study conducted by Jyothi et al. regarding the analgesic effect of different doses (0.8mg,1.6mg, 2.5mg) of intrathecal Nalbuphine with Bupivacaine and Bupivacaine alone for lower abdominal and orthopedic surgeries [17]. They observed that none of the patients in the Nalbuphine –Bupivacaine group developed hypotension and bradycardia whereas in our study it was found out to be 2% although in combination with morphine.

CONCLUSION:

Nalbuphine 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 Nalbuphine as an adjuvant to prevent the side effect of morphine.

CONFLICTS OF INTEREST: There are no conflicts of interest.
FINANCIAL SUPPORT: Nil

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