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COMPARATIVE EVALUATION OF MORPHINE VERSUS NALBUPHINE AS INTRATHECAL ADJUVANTS TO 0.5% HYPERBARIC BUPIVACAINE FOR SUBARACHNOID BLOCK IN LOWER ABDOMINAL SURGERIES: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY.

Anaesthesiology

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ABSTRACT

Introduction: Spinal anesthesia is the most frequently used procedure for lower abdominal surgeries as this technique is safe as well as easy to administer and very economical. A postoperative period free from pain and stress definitely helps in early mobilization and recovery, thereby reducing morbidity and mortality. Intrathecal (IT) administration of adjuvants to local anesthetics improves quality and duration of the spinal blockade, prolongs post-operative analgesia and also reduce the dose and amount of local anesthetic drugs during the subarachnoid block (SAB). Various adjuvants are used for the prolongation of anesthesia during the subarachnoid block.

The present study is aimed to comparatively evaluate the clinical efficacy of morphine with nalbuphine when co-administered intrathecally with 0.5% hyperbaric bupivacaine for lower abdominal procedures.

Material And Methods: This study was conducted on 60 patients scheduled for elective lower abdominal surgeries under subarachnoid block. Group M: Morphine + 0.5% hyperbaric bupivacaine. Group N (30 patients) : Nalbuphine + 0.5% hyperbaric bupivacaine.

Results: Postoperative analgesia lasted significantly longer in the morphine group, compared with the nalbuphine groups ($P < 0.05$). Time to first dose of rescue analgesia was significantly more with morphine (386 min) as compared to nalbuphine (192 min) ($P= 0.0002$). Onset of motor block in Group M was 6.43 ± 1.70 and in Group N was 5.76 ± 1.63 ($p=0.12$), which was statistically insignificant in between groups. Duration of motor blockade and onset of sensory blockade in Group M and Group N was statistically significant among groups ($P < 0.05$).

Conclusion: In summary, the postoperative analgesic efficacy of intrathecal morphine was better than nalbuphine when used in lower abdominal surgeries, resulting in longer duration postoperative pain relief and lesser requirement of rescue analgesic.

KEYWORDS

Spinal Anaesthesia, Morphine, Nalbuphine, VAS

INTRODUCTION

Spinal anesthesia is the most frequently used procedure for lower abdominal surgeries as this technique is both easy to administer and very economical. It has the benefit of being cost-effective, easy technique of administration, rapid onset of action, and relatively fewer adverse effects, and most importantly patient remaining aroused throughout the procedure. A postoperative period free from pain and stress definitely helps in early mobilization and recovery, thereby reducing morbidity and mortality. However, due to the short duration of action and early arising post-operative pain the role of various adjuvants has been proposed and evaluated. Post-operative pain and tissue injury associated with surgery initiate a systemic stress response that has neuroendocrine, immunological, and hematological responses. Intrathecal (IT) administration of adjuvants to local anesthetics improves quality and duration of the spinal blockade, prolongs post-operative analgesia and also reduce the dose and amount of local anesthetic drugs during the subarachnoid block (SAB). The most commonly utilized adjuvants which are used to improve the quality and duration of neuraxial anesthesia include intrathecal opioids (morphine, nalbuphine, fentanyl and sufentanil), alpha 2 adrenergic agonists (clonidine and dexmedetomidine). The technique of intrathecal administration of opioids along with local anesthetics has been extensively studied and found to provide superior quality of analgesia in a number of surgical procedures.[1][2] The rationale for the combination of opioids and local anesthetics is that these drugs eliminate pain by acting at two different sites. Local anesthetics act at the nerve axon and the opioid at the receptor site in the spinal cord.[3]

Intrathecal opioids act by binding with a family of G-protein linked pre- and postsynaptic opioid receptors (Mu, Delta and Kappa) in laminae I and II of the dorsal horn→leading to opening of potassium channels and closure of calcium channels with subsequent reduction in intracellular calcium levels. These changes reduce the release of excitatory transmitters (glutamate and substance P) from presynaptic C fibers, but not A fiber terminals with consequent reduction in nociceptive transmission.[4,5] Other suggested mechanisms of action include: Adenosine mediated hyperpolarization of nerve fibre and reduced release of GABA from the dorsal horn.[5]

Effective action of morphine or other opiates can be achieved by their specific action at the dorsal horn[6]. Morphine is the basic reference opioid to which all analgesics of its kind are compared. It is a phenanthrene derivative, the prototypical agonist opiate at mu and kappa opioid receptors. Its poor lipid solubility favours its behaviour when injected into the intrathecal space-producing slow analgesic onset with long duration and rostral migration that facilitates some of its side effects such as pruritus, emesis, hypothermia, and respiratory depression.[7,8]

Nalbuphine is highly lipid soluble synthetic opioid analgesic with agonist-antagonist activity. It acts as antagonist at μ-receptors and agonist at κ-receptors. Its affinity to k-opioid receptors results in analgesia, sedation, and cardiovascular stability with minimal respiratory depression. Nalbuphine is widely studied as an adjuvant to local anesthetics in central neuraxial techniques to improve the quality of perioperative analgesia as it provides reasonably potent analgesia for visceral nociception.[9,10]

Lesser data is available that compare the intrathecal administration of morphine with intrathecal nalbuphine during lower abdominal surgeries.

Hence, the aim of the present study was to evaluate and compare the clinical efficacy of morphine with nalbuphine when co-administered intrathecally with 0.5% hyperbaric bupivacaine for lower abdominal procedures.

MATERIAL AND METHODS

After getting approval from institutional ethical committee, a prospective randomized double blind study was conducted on 60 patients scheduled for elective lower abdominal surgeries under subarachnoid block. All patients were subjected to thorough pre anaesthetic evaluation before the study. The procedure was explained and a written informed consent was obtained.

All subjects of age group 18-60 years of American Society of Anaesthesiologists (ASA) grade I and II patients giving valid written consent undergoing elective lower abdominal surgery were included in the study. Patients who refused to participate in the study or who had history of allergy to study drug, with morbid obesity, failure of spinal blockade, bleeding disorders, infection at the site, anatomic abnormalities and inability to comprehend or participate in pain scoring system were excluded from the study.

Patients were divided randomly in a double-blind manner into two equal groups (total 30 patients in each):
Group M (30 patients): Morphine + 0.5% hyperbaric bupivacaine
Group N (30 patients): Nalbuphine + 0.5% hyperbaric bupivacaine

Randomisation was done according to computer generate random number table, where each number was referred to one of the two groups. Block randomisation was used to ensure equality of the groups. Each number was enclosed in an opaque envelope. Each patient was then be asked to pick one of the sealed opaque envelop and give it to an anaesthesiologist, who compared it with the computer-generated list and thereby assign the patient to one of the two groups.

Patient of Group M were given 3 ml 0.5% hyperbaric bupivacaine plus 100 mcg morphine intrathecally [10mg morphine diluted in 10 ml saline→ 1 ml of this diluted morphine (1 mg) further diluted into 2 ml saline →0.5 mg morphine taken in 1ml syringe (each division contain 0.05 mg morphine)→ 2 divisions of 1 ml syringe (0.1 mg) 100 mcg morphine]. Total volume of 3.2 ml.[11]

Patient in Group N were given 3 ml of 0.5% hyperbaric bupivacaine plus 400 mcg nalbuphine intrathecally [10 mg of nalbuphine dilutes in 5 ml saline→2 mg of this nalbuphine taken in 1 ml of syringe (each division contain 0.2 mg nalbuphine)→2 divisions of 1 ml syringe (0.4 mg) 400 mcg nalbuphine] Total volume of 3.2 ml.

To ensure the study's double blindness, another anaesthesiologist prepared the intrathecal drugs while the investigator handled the subarachnoid block. Resident unaware of group allocation recorded perioperative data.

Subarachnoid Block was performed under strict aseptic conditions in the sitting position at the level of L3- L4 / L4-L5 intervertebral space using 25G Quincke's spinal needle. After ensuring free flow of CSF, 3.2 ml of study drug solution was administered according to group allocation. Patients were placed in the supine position. According to the type of surgery adequate level of sensory block was achieved. The time of end of intrathecal injection was taken as zero time of induction of anesthesia.

After performing the spinal injections, the parameters were recorded at onset of sensory blockade at T10 dermatome using pin prick method. Highest level of sensory block, duration of sensory block (two segment regression time from highest level of sensory block), bilateral evaluation of lower extremities for motor block using modified bromage scale, onset of complete motor blockade (time taken from the end of injection to the development of grade 3 motor block, modified Bromage criteria), duration of motor blockade (time required for motor blockade return to Bromage grade 0 from the time of onset of motor blockade), hemodynamic parameters of non-invasive blood pressure, heart rate, pulse oximetry and electrocardiogram (ECG) was monitored at every 5 minute intervals for initial 30 min after spinal anesthesia, followed by every 15 min until the end of surgery.

Injection atropine 0.01 mg/kg iv was administered if PR<60/min., injection mephentermine was administered for hypotension (defined as >20% fall of BP from baseline). Intraoperative complications such as hypotension, bradycardia, shivering, respiratory depression (respiratory rate <10 breaths/min), nausea, vomiting, urinary retention and pruritus were recorded and appropriately managed. Intraoperative level of consciousness was monitored continuously according to Ramsay Sedation Score 1-6. Nausea and vomiting were treated with IV ondansetron 0.1 mg/kg. Postoperatively, sensory and motor block levels were assessed every 15 minutes until the return of normal sensations.

The presence and severity of pain, nausea, vomiting, and rescue analgesia requirement was assessed postoperatively at 0, 1, 2, 6,12 and 24 h by an investigator blinded to group allocation. Postoperatively, all these patients were assessed for pain using 10 cm visual analogue scale (VAS) until the first 24 postoperative hours. If VAS >4 rescue analgesia was administered in the post-operative period with injection paracetamol 15mg/kg. Time for first request of rescue analgesia and also total dose of analgesia requirement in first 24 hours was noted. Post-operative hemodynamics monitoring was done continuously. Level of consciousness (according to Ramsay Sedation Score 1-6), respiratory depression, and pulse oximetry was continuously monitored up to initial 24 h postoperative period.

RESULTS

Table 1: Demographic Data

Variables	Group M (n=30)	Group N (n=30)	P value
Age (yrs)	43.44 ± 12.13	42.91 ± 11.84	0.865
Weight (Kg)	68.43 ± 6.70	70.71 ± 7.65	0.224
Height (cm)	166.02 ± 8.11	165.51 ± 8.89	0.817
Duration of Surgery (mins)	64.75 ± 18.11	70.13 ± 20.17	0.282

The two groups were comparable with respect to age, weight, height and duration of surgery (Table 1).

Table 2: Block Characteristics

Variables	Group M (n=30)	Group N (n=30)	P value
Onset of sensory block (min)	1.44 ± 0.43	2.12 ± 1.40	0.014
Onset of motor block (min)	6.43 ± 1.70	5.76 ± 1.63	0.125
Duration of sensory block (min)	163.34 ± 27.64	158.48 ± 28.34	0.504
Duration of motor block (min)	248.02 ± 28.11	221.45 ± 38.38	0.003

The onset time of sensory block in Group M was 1.44 ± 0.43 min while in Group N was 2.12 ± 1.40 min ($P < 0.014$), which was statistically significant. Onset of motor block in Group M was 6.43 ± 1.70 and in Group N was 5.76 ± 1.63 (p=0.12), which was statistically insignificant in between groups (Table 2). The duration of sensory block in Group M and Group N was statistical nonsignificant. Duration of motor blockade (Group M; 248.02 ± 28.11 min and Group N; 221.45 ± 38.38 min) was statistically significant among groups ($P < 0.05$).

Table 3: VAS Scores Comparison

Time (hours)		Group M (n=30)	Group N (n=30)	P value
0	At Rest	0	0	-
	At movement	0	0	-
1	At Rest	0	0.56±0.13	-
	At movement	0.92±0.22	1.04±0.29	0.076
2	At Rest	1.33±0.5	1.12±0.41	0.081
	At movement	1.43±0.42	1.72±0.31	0.004
6	At Rest	1.81±0.35	1.99±0.29	0.034
	At movement	1.98±0.37	1.76±0.46	0.046
12	At Rest	1.3±0.5	3.8±1.8	0.01(S)
	At movement	1.8±0.8	4.2±1.9	0.001(S)
24	At Rest	0.9±0.4	2.9±1.3	0.02(S)
	At movement	1.2±0.6	3.1 ±1.2	0.003(S)

Table 4: Rescue Analgesia Requirement

	Group M (n=30)	Group N (n=30)	P value
Time to first rescue analgesia (minutes)	386±233.84	192±134.77	0.0002(S)
Total rescue analgesia (mg)	142.58±105.57	307±143.72	<0.001(S)

The primary outcome, postoperative pain as measured by VAS, was significantly different between the two groups at various time points (Table 3). While analysing statistically, it was seen that VAS at rest and movement 12 hours and 24 hours was significantly lower among Group M patients in comparison to Group N. It was found that mean time to first analgesic requirement among Group M (386 minutes) was significantly higher in comparison to Group N (192 minutes) (p- value = 0.0002). If a pain VAS score of 4 or more persisted, a rescue analgesic drug was used. While comparing between GroupM and Group N, it

was found that Total rescue analgesia consumed among Group M (142.58 mg) was significantly lower in comparison to Group N (307 mg) (p- value< 0.001). However, four patients reported nausea/vomiting in Group M, but only 1 patient complained about the same in Group N, thereby injection ondansetron (4 mg IV) given and patients were relieved. Whereas, 2 patients in Group M reported pruritis.

Table 4: Side-Effects/ Complications

Side-Effects (Complications)	Group M (n=30)	Group N (n=30)
Nausea/ Vomiting	4 (13.33%)	1(3.33%)
Urinary retention	-	-
Respiratory depression	-	-
Bradycardia	2 (6.66%)	-
Pruritus	2(6.66%)	-

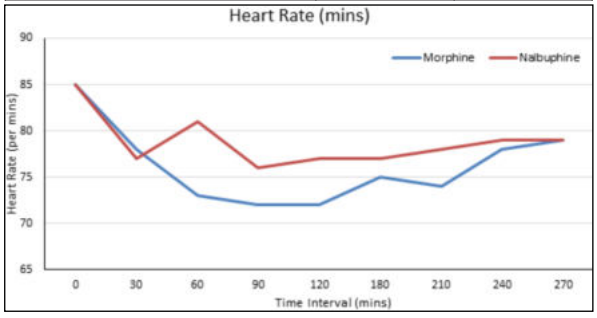

Figure 1: Heart Rate In Intraoperative Period In Both Groups

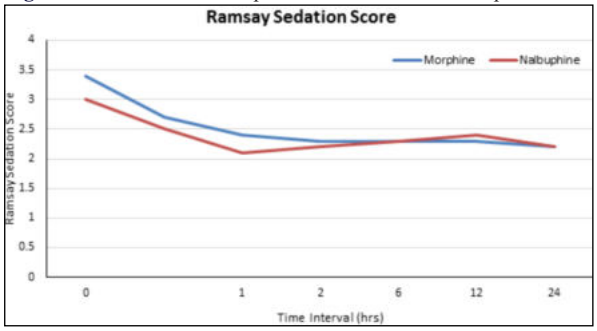

Figure 2: Ramsay Sedation Score In Postoperative Period In Both Groups

Postoperative haemodynamic parameters were not different between the two groups. Intraoperative heart rate in Morphine was on lower side compared to Nalbuphine group however there were some incidences of bradycardia in morphine group. Postoperative sedation score with Ramsay sedation score is shown in Figure 2.

DISCUSSION

The results of the present study showed that the supplementation of spinal morphine with 0.5% of hyperbaric bupivacaine produced a prolonged analgesic effect and motor blockade as compared to nalbuphine. VAS score was significantly lower in Group M till 24 hrs. Patients were hemodynamically stable in both the groups, and none of the patients had respiratory depression.

Spinal anesthesia was successful in all patients, and all patients completed the study. All groups were comparable with respect to age, ASA status, height, weight, type of surgery, and duration of the surgery. In the current study, there was no statistically significant difference between Group N and Group M in relation to the duration of sensory block, onset of motor block, time to reach maximum level of sensory block. The results of the present study are in accordance with the studies done by Akshat S et al.[12] Similar results were observed by Kurhekar, et al. (2016).[13]

Whereas, onset time of sensory block and total duration pf motor block was statistically significant between both the groups. (Table 2)

The primary outcome, postoperative pain as measured by VAS, was significantly different between the two groups at various time points (Table 3). While analysing statistically, it was seen that VAS at rest and movement 12 hours and 24 hours was significantly lower among Group M patients in comparison to the Group N.

Yoon et al. studied sixty obstetric patients scheduled for cesarean section under spinal anesthesia. Patients received morphine 0.1 mg or nalbuphine 1 mg or morphine 0.1 mg with nalbuphine 1 mg in addition to 0.5% bupivacaine (10 mg) and concluded that effective analgesia was prolonged in the morphine group and morphine with nalbuphine group, but the incidence of pruritis, was significantly lower in the nalbuphine group.[14]

There was no significant difference between the mean HR and MAP in both the groups throughout the observation period. The respiratory rate was always lesser, in Group M compared to Group N, at different time intervals, but none of the patients had respiratory depression. Sedation score was measured in both the groups which was statistically non significant.

Time to first request for analgesia was significantly prolonged in Group M than Group N, with significantly reduced need for rescue analgesics. Intrathecal morphine acts by the inhibition of nociceptive neurons by stimulation of α-ARs at the substantial gelatinosa of the dorsal horn in the spinal cord. Prolongation of the duration of analgesia in the morphine group may be due to an additive or synergistic effect secondary to the different mechanisms of action of local anesthetic and α2-AR agonist.[15]

Culebras et al (2000) reported in their study postoperative analgesia lasted significantly longer in the morphine group, compared with the nalbuphine groups ($P < 0.0001$). In the nalbuphine groups, postoperative analgesia lasted longest with the 0.8 mg dose. Itching and PONV incidence was superior with intrathecal morphine.[16]

The incidence of pruritus was more in morphine group (2 versus 0) although the difference did not reach statistical significance. Pruritis is a common side effect of use of opioids and occurs via *agonism* at mu receptors. Nalbuphine, on the other hand, is an *antagonist* at mu receptors and thus does not cause any pruritis. Absence of pruritus with nalbuphine has also been reported by other authors (Yeh et al[17]; Minai and Khan[18]).

In our study four patients reported nausea/vomiting in Group M, and only one patient complained about the same in Group N, thereby injection ondansetron (4 mg IV) given and patients were relieved. Similar results were seen by Culebras et al.[16]

Ahluwalia, et al. (2015) suggested intrathecal nalbuphine improved the quality of intraoperative and post-operative analgesia, with minimal side effects.[19] Tomar et al (2013) nalbuphine hydrochloride significantly prolongs the duration of sensory blockade and postoperative analgesia without any side effect or complication when introduced intrathecally along with hyperbaric bupivacaine.[20]

0.5% hyperbaric bupivacaine used with morphine resulted in prolonged anesthesia and analgesia with reduced need of rescue analgesics.

CONCLUSION

In summary intrathecal morphine provided postoperative analgesia better than nalbuphine in patients undergoing lower abdominal surgery. But, intrathecal nalbuphine additive provided less side effects than morphine. No patient in nalbuphine group had pruritus whereas two patients in morphine group had pruritus. Also, the incidence of postoperative nausea and vomiting was more in morphine group compared to nalbuphine group.

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