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INTRATHECAL NALBUPHINE: AN EFFECTIVE ADJUVANT FOR POST OPERATIVE ANALGESIA

Shehla Shakooh, Pooja Bhosle

Bharati Vidyapeeth deemed university medical college, Pune, Maharashtra, India.

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Corresponding Author:
Shehla Shakooh
Bharati Vidyapeeth deemed university medical college, Pune, Maharashtra
shehlashakooh@gmail.com

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ABSTRACT

Various adjuvants have been used along with local anaesthetics for prolongation of analgesia post operatively in neuraxial blockade. The frequently used adjuvants are opioids, midazolam, neostigmine, ketamine etc. Neuraxial opioids bind to intrathecal opioid receptors and produce effective pain relief post operatively with minimal untoward effects. However, certain adverse effects like pruritis, post operative nausea and vomiting, urinary retention and respiratory depression have been observed with the use of majority of opioids. Nalbuphine is an opioid drug with mixed μ antagonist and κ agonist properties. Thus we conducted a prospective, randomized study to observe the effect of intrathecal nalbuphine on pain relief after lower limb and lower abdominal surgeries. Sixty patients of ASA grades I and II of either sex in the age group of 18-65 years were randomly allocated to one of the two groups. Group B (n = 30) received 0.5% hyperbaric bupivacaine intrathecally; group N (n = 30) received 0.5% hyperbaric bupivacaine + 0.8 mg nalbuphine (preservative free) intrathecally. The onset of sensory and motor blockade, highest level of sensory blockade, duration of motor blockade and analgesia, VAS score, hemodynamic and respiratory changes, side effects were recorded, tabulated, and analyzed. Onset of sensory and motor blockade was faster in group N. The VAS scores showed that post operative analgesia lasted significantly in patients in group N than in group B. No significant side effects were observed in either of the two groups. Thus we conclude that intrathecal nalbuphine improved the quality of intraoperative and postoperative analgesia, with minimal side effects.

INTRODUCTION

Analgesia is one of the main demands of all patients post operatively. There has been a radical improvement in the quality of pain relief ever since W.T.G. Morton demonstrated ether anaesthesia. There is still scope to make analgesia not only more effective but also less hazardous.

Various types of medications can be used to overcome pain but opioids provide the most effective pain relief and are a standard of care.[1] The main obstacles for optimal use of opioids are their side effects which include pruritis, nausea/ emesis, constipation, urinary retention, respiratory depression, undesirable sedation and the development of tolerance/ dependence. Though some side effects may be benign but others like respiratory depression can prove to be life threatening. In the developing countries like India it is not possible to monitor all patients post operatively for prolonged periods. The use of nalbuphine, a mixed opioid agonist antagonist can prove to be a boon because when used singly or in combination with other agents it has the potential to maintain or even enhance opioid based analgesia while simultaneously mitigating the common mu-opioid side effects. Nalbuphine binds readily to both mu- and kappa-receptors. The binding of nalbuphine to mu receptors only serves to competitively displace other mu-agonists from the receptor, without itself displaying any agonist activity. When nalbuphine binds to kappa-receptors, however, it has an agonist effect. Kappa-opioid receptors are distributed throughout brain and spinal cord involved in nociception. Nalbuphine binds avidly to kappa-receptors in these areas to produce analgesia. This pattern of binding and effects defines nalbuphine as a mixed agonist—antagonist.[1]

There are very few studies of IT nalbuphine for postoperative analgesia. Hence, we have tried to study the effect of IT nalbuphine along with its pharmacodynamics, side effects, neurotoxicity and postoperative analgesia. In this study we compare the duration and quality of post operative analgesia and any side effects by the addition of IT nalbuphine with bupivacaine compared with bupivacaine alone.

MATERIALS AND METHODS

After approval by the hospital ethics committee, a bilingual written informed consent was obtained from all the participating patients. Sixty patients, ASA physical status I and II aged 20 to 65 years, scheduled for elective lower limb or lower abdominal surgery of duration less than 3 hrs were selected. Thirty patients each were randomly allocated to one of the two groups B and N. Group B received 0.5% bupivacaine heavy (3cc) while Group N received 0.5% bupivacaine heavy (3cc) with 0.8mg nalbuphine (preservative free) for spinal anaesthesia.

Patients with history of hypersensitivity to any of the drugs, on long term analgesic therapy, those having peripheral neuropathy, local skin infections and spinal deformities or coagulation abnormalities were excluded from the study.

Intraoperatively, intravenous line was secured with 18/20 Gauge canula. Monitors were attached before giving spinal anaesthesia. All the patients preloaded with 10 ml/kg Ringer's lactate solution. Inj ondensetron 4mg given I/V was given to all patients. Intrathecal block under strict aseptic conditions performed in sitting position at L3-4 or L4-5 interspinous space with 25G Quinkes spinal needle. Patients were placed in the supine position with 10-20 degree tilt.

Observations were made for time of drug administration, time of onset and complete sensory and motor block and recovery from the block, intraoperative sedation, time of occurrence of pain (VAS >3 cm)and any adverse effects.

The level of sensory block was assessed by pin prick. The degree of motor block was assessed with the modified Bromage scale.[2] Intraoperative sedation scores were defined by Ramsay sedation score.[3] Post operatively, pain, sensory level, and motor block was evaluated every 30 min during the first 2 hours, every 60 min for the next 6 hours, and at 12 and 24 hours after arrival in the recovery room. Pain intensity was evaluated by using a visual analog scale (VAS).[4] Side effects (pruritus, PONV, sedation, urinary retention, euphoria or dysphoria, and respiratory depression) were recorded for 24 h. The durations of complete analgesia (time from the intrathecal injection to the first pain report, VAS score > 1) and effective analgesia (time from the Intrathecal injection to the first analgesic requirement, VAS score > 3) was noted.

All the data was analysed statistically and the significance was measured as probability of occurrence by the t test and Mann Whitney U test.

RESULTS

Both the groups were comparable in various demographic data like age, gender, weight and also regarding ASA class distribution (table 1). There was no significant difference found in various hemodynamic or vital parameters intra operatively between the two groups.

Table 1: Demographic data (mean±SD)

VARIABLE	GROUP N	GROUP B	P-VALUE
Age(years)	40.13 ±14.09	46.90 ±15.88	0.086
Weight(kg)	58.23 ±9.68	59.27 ±6.98	0.637
Gender(M:F)	21:9	23:7	0.873
ASA Grade(I:II)	23:7	17:13	0.170

However, there was significant difference (p-value < 0.001) between mean onset and complete sensory block in group N and group B. The mean onset and complete motor block in group N and group B also showed statistical significance (p-value<0.05). Group N showing a faster onset compared to group B in both the cases (table 2). The distribution of sensory level in both the groups was similar. The mean regression in sensory (taken as regression up to L1 level) and motor block in group N and group B showed statistical significance (p-value < 0.001). Similarly, mean duration of requirement of first rescue analgesia in group N and group B showed significant difference (p-value <0.001), thus highlighting the fact that group N had prolonged post operative analgesia (table 2). Group N showed a significantly higher median Ramsay sedation score than group B (p-value<0.001).

Table 2: Duration of sensory and motor block and first rescue analgesia (mean±SD)

Parameter	Group N	Group B	p-Value
Onset Of Sensory Block(min)	1.43±0.57	3.03±1.03	<0.001
Onset Of Motor Block(min)	3.47±1.01	4.47±1.46	0.003
Regression Of Sensory Block(min)	218.50±34.72	124.50±20.14	<0.001
Regression Of Motor Block(min)	243.3±56.46	141.17±22.58	<0.001
First Rescue Analgesia(min)	298.0±51.02	161±16.68	<0.001
Median Ramsay Sedation Score	3	2	<0.001

Side effects observed in group N were nausea, vomiting and urinary retention each in one patient. Two patients in group B had nausea while two had urinary retention (table 3).

Table 3: Side effects

Side effects	Group N	Group B
Nausea	1	2
Vomiting	1	0
Urinary Retention	1	2

DISCUSSION

Intrathecal opioids have certain specific advantages like rapid onset of action, sympathetic and motor nerve sparing activities, technical ease of administration and simplicity of postoperative management. The major short comings of opioids are their side effects, some of which, like respiratory depression, could prove to be dangerous. To overcome the side effects, opioids with partial agonist antagonist action have been studied extensively. Nalbuphine is an opioid having agonist activity at kappa receptors and antagonistic activity at mu receptors. It provides potent analgesia in certain models of visceral nociception. Nalbuphine given systemically has reduced incidence of respiratory depression and has been used to antagonize the side effects of spinal opiates.[5]

It has been reasoned that spinal nalbuphine should demonstrate an improved therapeutic ratio, consistent with that seen after systemic administration. There have been a few studies, of varying quality, that have supported the utility of neuraxially administered nalbuphine in managing postoperative pain. The general trend of these reports is that epidural or intrathecal delivery of nalbuphine produces a significant analgesia accompanied by minimal pruritis and respiratory depression.[6]

In our study we used nalbuphine (preservative free) 0.8mg as an adjuvant to intrathecal bupivacaine (0.5%) heavy for various lower abdominal and lower limb surgeries and compared its postoperative analgesic effect under spinal anaesthesia using bupivacaine (0.5%) heavy alone.

Our results showed that the onset of sensory and motor block was faster and time taken to attain complete sensory and motor block to occur was shorter in the nalbuphine group as compared to bupivacaine group. The mean onset of sensory block in group N was 1.43±0.57 min and complete sensory block was attained in 4.73±1.31 min compared to 3.03±1.03 min and 8.60±2.36 min in group B respectively. . Similar results were documented by Xavier et al in their study on 100 females posted for elective caesarean section who were given three different doses of nalbuphine (0.2mg, 0.8mg or 1.6mg) or morphine (0.2mg) intrathecally. They found that IT nalbuphine provided significantly faster onset of pain relief compared to IT morphine, probably because of its lipophillic nature.[7]

Fournier et al have also demonstrated that after total hip replacement, administration of nalbuphine through an indwelling IT catheter resulted in a significantly faster onset of pain relief as compared to IT morphine. They conducted their study on 40 patients posted for total hip replacement.[8]

In contrast to these studies, Tiwari et al in their study have shown that onset of sensory and motor blockade was not affected by adding nalbuphine intrathecally. Seventy five patients posted for lower limb and lower abdominal surgeries received either 0.2mg or 0.4 mg nalbuphine or plain bupivacaine intrathecally. This disparity in the onset of blockade could be related to lower dose of nalbuphine used in this study.[9]

We observed that the postoperative regression of both sensory and motor block was significantly slower in group N than in group B and the first rescue analgesic requirement in group N (298±51 min) was significantly late than in group B (161±16 min). These results are in accordance to the study done by Mukherjee et al who demonstrated longest duration of postoperative analgesia in the group in which 0.8 mg nalbuphine was used as an adjuvant as compared to lower doses of nalbuphine i.e. 0.2 and 0.4mg.[10] Similar results were also demonstrated by Tiwari et al who showed significant increase in postoperative analgesia in patients given 0.2 or 0.4mg nalbuphine intrathecally.[9]

During spinal anaesthesia, as the patient is conscious about the surroundings, most of the time it becomes imperative to sedate the patient which not only allays his anxiety but also minimizes awareness about routine operating room proceedings. Intrathecal nalbuphine has an added advantage of providing intraoperative sedation thus reducing or even abolishing the need for any other sedative drug.

In our study 20 out of 30 patients in group N had an intraoperative Ramsay sedation score of 3 or 4 as compared to only 3 patients in group B. Xavier et al found comparable sedation scores in all four groups in their study which could be because of the fact that they were comparing sedation scores of nalbuphine with morphine which in itself has some sedative effects.[7]

None of our patients in either group in our study had any significant side effect like respiratory depression or pruritis. The side effects noted in group N were nausea, vomiting and urinary retention in one patient each. In group B two patients had nausea and urinary retention.

Xavier et al, in 2000, performed a comparative study to evaluate post operative analgesia and adverse effects after using three doses i.e. 0.2mg, 0.8mg, 1.6mg of intrathecal nalbuphine or morphine 0.2mg given for caesarean section along with bupivacaine. The longest durations of complete and effective analgesia among the nalbuphine-treated groups were provided by 0.8 mg added to bupivacaine. Neither pruritis nor PONV were observed with nalbuphine 0.2 and 0.8 mg. Intrathecal nalbuphine 0.8–1.6 mg improved the quality of intraoperative analgesia and provided a significantly faster onset of pain relief, compared with intrathecal morphine, probably because of its lipophilic properties. They concluded that 0.8mg of intrathecal nalbuphine improves intraoperative analgesia and prolongs early postoperative analgesia without increasing risk of side effects.[7]

In 2011, **Mukherjee** et al formulated a study to determine whether nalbuphine prolongs analgesia by comparing with control and to find out the optimum dose of intrathecal nalbuphine by comparing the 0.2, 0.4 and 0.8mg doses which prolonged post operative analgesia without increased side effects. It was observed that effective analgesia increased with increase in concentration and the ultimate observation of prolongation of analgesia was with 0.4mg of nalbuphine with 0.5% hyperbaric bupivacaine without any side effects.[10]

Mostafa et al, in 2011 compared the analgesic effects and duration of analgesia as well as the side effects of 50 mg tramadol or 2 mg nalbuphine administered via the IT route for postoperative pain relief after transurethral resection tumour of the bladder. They demonstrated that in both the groups there was similar motor block, nearly equal analgesia, delayed first analgesic request and less analgesic supplement over the first 24 hours after operation. No major postoperative complication like, itching, respiratory depression, neurological sequelae or complaints were observed among the two groups. The incidence of hemodynamic side effects like decreased blood pressure, bradycardia, respiratory depression and other side effects like somnolence and dryness of mouth were minimum and well tolerated by the patients studied. In conclusion, intrathecal administration of 50 mg tramadol and intrathecal 2 mg nalbuphine when used with 0.5% bupivacaine had a similar postoperative analgesia in the patients without producing significant related side effects like nausea, vomiting, pruritis and respiratory depression.[11]

Thus from our study it was observed that 0.8mg nalbuphine as an adjunct to spinal bupivacaine prolongs the postoperative analgesia with minimal side effects and with desirable sedation intraoperatively which helps in taking care of psychological impact of operation theatre environment.

The practice of IT nalbuphine for over ten years did not have any reports of neurotoxicity. The previous studies have been conducted on pregnant patients also but did not reveal any untoward effects. **Rawal** et al in 1991 studied the behavioral and histopathological effects following intrathecal administration of butorphanol, sufentanil and nalbuphine in sheep. They found that nalbuphine was the least irritating to neural tissue even when used in large doses and was associated with minor behavioral and EEG changes.[12] Hence, we formulated to conduct the study. Further evaluation is needed with still more research studies with intrathecal nalbuphine.

CONCLUSION

From the present study, we conclude that nalbuphine as an adjuvant to spinal anaesthesia shortens the onset of sensory and motor block, prolongs the

duration of sensory and motor blockade, provides effective postoperative analgesia and prolongs the duration for first rescue analgesia, provides desirable sedation intraoperatively and does not result in any major adverse effects.

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