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Anesthesiology

A COMPARATIVE STUDY OF NALBUPHINE (0.3 mg/kg) + 0.5% BUPIVACAINE WITH 0.5% BUPIVACAINE ALONE IN EPIDURAL ANESTHESIA INVOLVING INFRA UMBILICAL SURGERIES

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KEYWORDS :

Introduction

Anesthesiology is an amalgam of specialized techniques, drugs and knowledge. Analgesia today is being achieved by use of drugs administered through different routes and techniques. The deposition of drug around the spinal cord, either in epidural space or subarachnoid space, for intra as well as post operative pain management has paved a new era in pain relief. Management of postoperative pain is one of the most challenging and gratifying domains of anesthesia. Any method of postoperative analgesia must meet three basic criteria: it must be effective, safe and feasible. Despite advances in knowledge of pathophysiology of pain, pharmacology of analgesics and develop ment of effective techniques for postoperative pain control, many patients continue to experience considerable discomfort.The majority of patients after surgery managed with parenteral drugs are left with unrelieved pain.Neuraxial anesthesia is the term for central blocks involving the spinal,epidural, and caudal spaces. While it is now an invaluable adjunct and even occasionally an alternative to general anesthesia, its use is not a new phenomenon. Physicians such as Corning published studies documenting success with neuraxial blocks as early as 1885. Even more ambitious physician-scientists such as Bier became knowledgeable about spinal anesthesia, in particular, through self-investigation. It unfortunately was also through this type of dedication that he became all too familiar with postduralpuncture headaches. Despite its early use, though, much of the gains we have with neuraxial blocks did not occur until the early 1900's. Prior to 1904,the only drug available for neuraxial use was cocaine, and development of epidural technology was still a ways off. With a larger drug base and equipment advancements came an expansion of the role of neuraxial anaesthesia in anaesthesia practice. Excluding the obvious fact that surgical conditions primarily dictate the type of anesthesia performed, most operations below the neck can be performed under neuraxial anaesthesia. Various studies have shown a decrease in postoperative morbidity and even mortality when used either with general anesthesia or alone. Neuraxial blocks have even been shown to reduce the incidence of venous thrombosis and pulmonary embolism while also minimizing transfusion requirements and respiratory compromise following thoracic and upper abdominal surgery. A decreased stress response has also been noted which may have positive cardiac benefits such as reduced perioperative and postoperative ischemia. Epidural anesthesia is a versatile technique widely used in anesthetic practice. Its potential to decrease postoperative morbidity and mortality has been demonstrated by numerous studies.Epidural anaesthesia gives excellent alternative due to its various advantages:

1. Lesser cardio-pulmonary risk.
2. Provide prolong and continuous postoperative analgesia via intermittent injections or continuous infusion using a catheter.
3. Duration and depth of anaesthesia can be regulated according to the extent of surgery.

Local anesthetics are the mainstay of therapy for obtaining analgesia or anesthesia with an epidural. Understanding the pharmacology of loca lanesthetics is therefore paramount. Specifically, factors such as surgical location and duration, desire to have a sensory and/or motor block, or the expected potency and duration of a specific local anesthetic agent should beconsidered prior to placing an epidural block. The choice of which local anesthetic agent to use can be categorized based on desired length ofaction.

Bupivacaine is a long-acting, effective local anesthetic that is commonly administered by the epidural route for the relief of postoperative pain. The concentration of bupivacaine exceeding 0.125% may be associated with excessive motor blockade when used in epidural infusions in the lumbar region.Bupivacaine is more cardiotoxic than other commonly used local anesthetics, with a narrow gap between convulsant and lethal doses in experimental studies.8 The cardiotoxic effects may be due to direct effect on the myocardium or mediated through the central nervous system.Opioids remain the analgesic adjuvant of choice for augmenting the effects of local anesthetics in the epidural. Various opioids have been used along with bupivacaine to prolong its effect, to improve the quality of analgesia and minimize the requirement of postoperative analgesics. Epidural analgesia with local anesthetic is a powerful method of relieving postoperativepain.After abdominal surgery, the combination of epidural local anesthesia and opioid has been shown to produce superior pain relief compared with the same dose of epidural local anesthesia alone. However improved pain relief may be at the expense of impaired gastrointestinal function. Epidural bupivacaine alone affect gastric emptying or bowel function, whereas addition of epidural opioid delayed gastric emptying and prolongs orocaecal transit time.Nalbuphine is a mixed agonist–antagonist opioid. Nalbuphine derives its analgesic and sleep-producing effects through agonism at the kappa-opioid receptor, and it also has the potential to attenuate the mu-opioid receptor-related adverse events. Although morphine is the most common opioid used, it may induce many adverse events including pruritus, nausea,vomiting, constipation, urinary retention, respiratory depression, and drowsiness. Nalbuphine is a strong analgesic with very low abusive potential,offers a potent alternative to morphine. At higher dose (>30 mg) it produces lesser respiratory depression than morphine. It can also be used to produce satisfactory anaesthesia when used as a component of balanced anaesthesia technique.Culebras et al. in 2002 used intrathecal nalbuphine in doses 0.2, 0.8and 1.6 mg with 10 mg of 0.5% hyperbaric bupivacaine in patients undergoing caesarean section under subarachnoid block (SAB) and found 0.8 mg of nalbuphine as an effective dose.So the study compares the effect of inj.Nalbuphine (0.3mg/kg) + 0.5%inj.Bupivacaine with 0.5% inj.Bupivacaine alone through epidural route in various patients undergoing infraumbilical surgery.

Materials and Method

This study was done on patient admitted for elective surgery in our Medical College. Local ethical committee approval was obtained and only then the prospective study over 60 patients undergoing various infra umbilical surgery was undertaken.

Complete history with preanesthetic examination was done. Latest lab investigation was checked and an informed valid written consent was obtained after explaining the procedure to the patient. The patients were explained about the 10 point visual analogue of pain scale. The patients were randomly chosen into two groups.

Group A: patients received inj. Nalbuphine (0.3 mg/kg) + 15 ml of 0.5%inj.Bupivacaine

Group B: patient received 15 ml of 0.5% inj. Bupivacaine alone

TECHNIQUE

The patients were asked to remain nil by mouth for minimum 6 hours

before the surgery. I.v. line was secured with 18 G cannula and preloaded with Ringer Lactate solution. Baseline pulse rate, blood pressure, respiratoryrate and oxygen saturation noted down. Patient was catheterized before shifting to OT and urine output was noted. Epidural anesthesia was performed with the patient in the lateral position using 18-gauge Tuohy needle at the L2-3 or L3-4 interspaces. The epidural space was identified by loss of resistance technique. Epidural catheter was inserted and fixed. Aspiration was done to rule out subarachnoid or intravascular placement of the catheter. 3 ml of 2 %lignocaine with 1:200,000 adrenaline was injected as a test dose through the epidural catheter. 15 ml of 0.5% bupivacaine with injection nalbuphine was injected through the catheter. The patient was gently turned and placed supine.After epidural block HR, RR, SpO2 and NIBP were measured every 5minutes for first 20 minutes and thereafter every 10 minute till the end of surgery. A fall in systolic blood pressure by 20% from the base line value was considered as hypotension and managed with IV fluids, oxygen and by trendelenberg position. Patient not responding to these measures were given inj. Ephedrine in incremental doses. Bradycardia was defined 20% decrease of HR from baseline and was treated with inj. Atropine 0.6mg i.v. The following variables were recorded, time of onset of sensory block at T10, time of onset of motor blockade, intraoperative hemodynamic changes,intraoperative degree of sedation, duration of analgesia and any adverse effect of the drug.The level of sensory anesthesia defined as loss of pain sensation to pinprick and was measured every 1 min till it reached T10 dermatome level. The time taken to reach T10 dermatome level was taken as the time of onset forsensory blockade.

Time to motor block was assessed after every 1 min until maximum **Bromage scale77** was achieved

0= no motor loss
1= unable to flex the hip with free movement of feet
2= unable to flex knees with fee movement of feet
3= unable to flex the ankle
Time taken to achieve grade 3 bromage scale was taken as the time of onset for motor blockade.

Duration of analgesia
The duration of analgesia was taken as the period from the time of giving epidural analgesia till the patient's first requirement of systemic analgesic medication. For pain assessment VAPS78 was used. Patient was given a scale marked from 0 to 10 and were asked to mark on a scale the degree of pain he or she experienced ranging from no pain at 0 to maximum pain at 10 point. At the time of rescue analgesia, quality of analgesia was assessed by asking the patient to give a global assessment of overall effectiveness of the analgesic treatment. When VAS > 4, rescue analgesia with inj. diclofenac sodium given and study ended. The reading was taken every 30 min till first 180 min and then every 1 hourly till the time of rescue analgesia.

VAPS Quality of analgesia
0-1 Excellent
2-4 good
5-7 fair
8-10 slight or no relief

The level of consciousness was assessed every 5 min till first 20 min and then every 30 min till the end of surgery and graded according to sedationscore.

Sedation score level
0 wide awake
1 sleeping but responding to verbal commands
2 deep sleep but arousable
3 not arousable

Adverse effects
Side effects of the drug like pruritus, respiratory depression, nausea,vomiting, and dizziness were noted. Respiratory depression was defined as oxygen saturation less than 90% on pulse oximetry or respiratory rate fall below 10 breaths per minute. The patient will be supplemented with 100%oxygen till saturation improves. Patients not responding to supportive measures will be given naloxone for reversal of respiratory depression.Nausea and vomiting would be treated with inj.ondansetron 4mg.Comparison between group A and B were done using students 't' test and the level of significance were taken below 0.05.

Discussion
Pain is an incredibly common complaint on inpatient medical wards and pain intensity tends to be underestimated by care providers. Epidural analgesia with local anaesthetic is a powerful method of relieving postoperative pain. After abdominal surgery, the combination of epidural local anaesthesia and opioids has been shown to produce superior pain relief compared to the same dose of epidural local anaesthetic alone. However the drug that has been used most widely i.e. morphine, produced distressing side effects and sometimes potentially lethal complications like respiratory depression. Several other narcotics have been tried in order to identify a drug which could be equipotent to morphine but with less adverse effects on the body. The agonist/antagonist drug can be expected to offer some scope in this respect as the drug has the property of ceiling effect to respiratory depression with higher receptor occupancy at higher dose. The agonist/antagonist class of drug have the advantage of less histamine release and thus cause less hypotension. They have less abusive potential. Nalbuphine hydrochloride is a lipophilic agonist/antagonist opioid reported to be approximately equipotent with morphine at doses up to 0.15mg/kg im/iv. The greater lipophilicity of nalbuphine compared to morphine result in more of the epidurally administered drug penetrating to the opioid receptors in the spinal cord, and less persisting in the CSF.

This study was designed to compare the hemodynamic and analgesic effects of nalbuphine and bupivacaine over bupivacaine alone in epidural anaesthesia. Rawal and co-workers studied several spinal opioids in sheep, including nalbuphine; although spinal nalbuphine was not the less neurotoxic; the authors found that this opioid was associated with relative minor behavioural and EEG changes, sedation, spinal cord mild inflammatory and neuronal changes. Following intrathecal nalbuphine, the above-mentioned changes were similar to those seen in control animals. One animal developed motor impairment during 60 minutes. The analgesic effect of spinal nalbuphine can be reverted by naloxone.

Mean age in group A was 42.1 ± 9.05 and group B was 45.07 ± 10.45. There was no statistical difference between two groups. (p> 0.05). In group A 18 patients were male and 12 patients were female while in group B 17 were male and 13 were female. There was statistically no significant (p> 0.05) difference in gender between the group. Maximum patients in both the groups were between 50 to 60kgs.There was no statistical significance between two groups in terms of weight distribution (p > 0.05). Mean duration of surgery in group A was 90.67 ± 8.23 and in group B was 90.33 ± 10.98. There was no statistical difference between the two groups. All the demographic variables like age, weight, sex ratio, duration of surgery and baseline parameters at the starting of procedure were comparable in all the four groups, P>0.05. Similar findings are seen in the study conducted by Clubras et al,Tiwari et al,Mostafa et al.The onset time of sensory block was found to be clinically and statistically significant among the two groups. There was no case of failure or inadequate blockade. In our study the mean time of sensory onset was rapid in group A than in group B. In Group A the minimum time for onset of sensory block was 5 min and maximum time 9 min. The mean time for onset of sensory blockade was 6.8 ±1.13. In Group B the minimum time for onset of sensory block was 8 min and maximum time was 13 min. The mean time for onset of sensory blockade was

11.03 ± 1.33
This was clinically and statistically significant with p value 0.00. R. Fournier et al. Oct 1998 studied and reported the administration of intrathecal nalbuphine resulting in a significantly faster onset related with the time to the lowest pain score (18 + 11 VS 66 + 75 minutes, P < 0.001). In the study also rapid onset in group A patients is due to synergistic effect of nalbuphine and bupivacaine.

All patients in both the groups developed grade 3 motor block. The time period to develop grade 3 motor block was taken as the time of onset of motor blockade. In Group A the minimum time taken to achieve grade 3 motor block was 8 min and maximum time was 12 min. The mean time for onset of motor blockade was 9.87 ± 1.22. In Group B the minimum time taken to achieve grade 3 motor block was 14 min and maximum time was 17 min. The mean time for onset of motor blockade was 15.3 ± 0.88.

This was clinically and statistically significant with p value 0.00. The mean preoperative (baseline) heart rate in both the groups A and B were 74.77 ± 5.85 and 77.03 ± 8.24 respectively with p value 0.224 which was statistically insignificant.

Intraoperative fall in heart rate was observed in both the groups at 5,15, 30 and 60 min intervals with p value of 0.005, 0.000, 0.000 and 0.002 respectively which was statistically significant. There was no episode of bradycardia in either group. So none of the patient in either groups required inj. Atropine supplement. The mean preoperative (baseline) systolic blood pressure in both the groups A and B were 126.2 ± 7.8 and 127.7 ± 8.09 respectively with p value 0.460 which was statistically insignificant. Intraoperative fall in systolic blood pressure was observed in both the groups at 5, 15, 30 and 60 min intervals. The mean systolic blood pressure at 5 min was statistically insignificant with p value 0.793 while systolic blood pressure at 15, 30 and 60 min were significant with p value 0.005, 0.000 and 0.000 respectively.

The mean preoperative (baseline) diastolic blood pressure in both the groups A and B were 75.7 ± 5.2 and 75.4 ± 6.04 respectively with p value 0.82 which was statistically insignificant.

Intraoperative fall in diastolic blood pressure was observed in both the groups at 5, 15, 30 and 60 min intervals. The mean diastolic blood pressure at 5 min was statistically insignificant with p value 0.65 while mean diastolic blood pressure at 15, 30 and 60 min were significant with p value 0.04, 0.02 and 0.01 respectively.

The mean preoperative (baseline) mean blood pressure in both the groups A and B were 92.5 ± 5.3 and 92.9 ± 6.04 respectively with p value 0.77 which was statistically insignificant.

Intraoperative fall in mean blood pressure was observed in both the groups at 5, 15, 30 and 60 min intervals. The mean blood pressure at 5 min was statistically insignificant with p value 0.64 while mean blood pressure at 15, 30 and 60 min were significant with p value 0.01, 0.00 and 0.00 respectively.

None of the patient in group A had hypotension during intraoperative period. 10 patients in group B had intraoperative hypotension which was corrected by IV fluid and head low position. None of the patient required inj. ephedrine. Nalbupnine provided better hemodynamic stability. Similar findings are seen in the study conducted by Clubras et al,Tiwari et al,Mostafa et al,where there was no gross hemodynamic changes throughout their study. In the study conducted by Schmidt WK et al, and Miller RR et al,Greenbaum RA et al., no significant hemodynamic effects were found. So we can conclude that the use of nalbuphine along with bupivacaine causes no gross hemodynamic disturbances. F. N. Minai and F. A. Khan (2003), they compared morphine and nalbuphine. They concluded that nalbuphine in a dose of 0.2 mg/kg provided better analgesia and greater hemodynamic stability, as a component of balanced anesthesia in lower abdominal surgery. Respiratory depression: no patient in either group had respiratory depression. Respiratory rate was maintained above 10 per min, oxygen saturation was above 90% throughout intraoperative period in both the groups.

Nalbuphine exhibit ceiling effect for respiratory depression. Since respiratory depression is predominantly μ receptor mediated and nalbuphineis a μ receptor antagonist, this effect is expected to be attenuated by nalbuphine. This was proved in the study done by Romagnoli and Keats et al,Thomas et al. In the study conducted by Clubras et al,Tiwari et al.,Mostafa et al, no difference were found with respect to maternal oxygen saturation, Apgar scores or neonatal umbilical blood gas values. There were no cases of newborn respiratory depression. Schmidt WK et al., found limited respiratory depression in man and animals. Nalbuphine has been found to effectively antagonize the respiratory depressant activity of narcotic analgesics while concomitantly adding to their analgesic responses. Miller RR et al, stated that respiratory depression produced by usual therapeutic dose of nalbuphine is equivalent to that of morphine, at higher dose nalbuphine produces less respiratory depression.

In group A 11 patients had sedation score of 2 which resembled deep sleep not responding to verbal commands but were arousable and remaining 19 patients had sedation score of 1 which resembled sleep but patient responded to verbal commands.

All patients in group B were wide awake throughout intraoperative period. Similar results were seen in study conducted by Clubras et al.,Tiwari et al., Mostafa et al., where there were minimum side effects with sedation. Miller RR et al., stated that sedation is the most common side effect and occur about as often as with other strong narcotics.

The mean duration of analgesia in group A patients was 414.6 ± 37.7 and in group B 255.67 ± 26.6 with p value 0.00 which was statistically significant. So patients who received nalbuphine with bupivacaine had longer duration of analgesia as compared to patients who received bupivacaine alone. Addition of nalbuphine significantly prolonged the duration of analgesia which correlate to the studies done by Lin, Clubras et al., Tiwari et al., Mostafa et al, where nalbuphine was found to provide good intraoperative analgesia and prolonged postoperative analgesia. However, Yoon et al found better intraoperative analgesia with reduced postoperative analgesia duration in caesarean patient. F. N. Minai and F. A. Khan (2003), they compared morphine and nalbuphine for intraoperative and postoperative analgesia. They concluded that nalbuphine in a dose of 0.2 mg/kg provided better analgesia and greater hemodynamic stability, as a component of balanced anesthesia in lower abdominal surgery, with a lower incidence of nausea and vomiting in the postoperative period compared to morphine 0.1 mg/kg. The duration of analgesia with Nalbuphine was significantly longer, reducing the need for supplements in the immediate postoperative period. In the study conducted by Pugh and Drummond GB, Thomas et al.,proved that nalbuphine exhibits a ceiling effect to analgesia that is increasing the dose of drug increases analgesia only up to a certain point. The patients who received only bupivacaine had significantly higher pain scores than patients who received nalbuphine with bupivacaine combination as assessed by VAPS. Study done by Tiwari et al,Mostafa et al7, also reported that nalbuphine prolonged the duration of analgesia with reduced VAPS.

Nausea and Vomiting: 1 patient in group A and 6 patients in group B had episode of nausea and vomiting. These patients were given inj. Ondansetron 4mg stat. The nausea and emesis which occur after administration of opioid analgesics are thought to be due to stimulation of the chemoreceptor trigger zone in the area postrema of the lower brainstem. Since these effects appear to be mu-receptor-mediated, nalbuphine should not cause nausea or emesis, and it should diminish the occurrence of nausea and emesis provoked by mu-receptor acting analgesics. F. N. Minai and F. A. Khan (2003), they compared morphine and nalbuphine for intraoperative and postoperative analgesia. They concluded that nalbuphine in a dose of 0.2 mg/kg provided better analgesia and greater hemodynamic stability, as a component of balanced anesthesia in lower abdominal surgery, with a lower incidence of nausea and vomiting in the postoperative period compared to morphine 0.1 mg/kg. Hypotension: none of the patient in group A had hypotension during intraoperative period. 10 patients in group B had intraoperative hypotension which was corrected by iv fluid and head low position. None of the patient required inj. ephedrine. There was no incidence of pruritis, respiratory depression, and urinary retention.

Xavier et al., (2000) suggested that the intrathecal nalbuphine 0.8 mg good analgesia with side effects like pruritis and post-operative nausea and vomiting. Rawalet al (1991) showed in sheep model using histopathological methods that intrathecal nalbuphine was not neurotoxic.

Miller RR found nausea and vomiting to be less common with nalbuphine. Schmidt WK et al., found nalbuphine to produce few psychomimetic effects along with less inhibition of gastrointestinal activity than any other clinically used narcotics and agonist/antagonist. The disadvantages associated with nalbuphine use are fewer, but require careful consideration. The ceiling effect of nalbuphine means that increasing the dose for increasing discomfort will not necessarily provide increasing analgesia. If more pain is encountered than nalbuphine and adjuncts (e.g. non-steroidal anti inflammatory, acetaminophen) can alleviate, the next step would often be to transition to mu-agonist based analgesia. The mu-antagonist property of nalbuphine means, though, that transition to a mu agonistbased regime with a nalbuphine load already in place would require careful planning and execution. Similarly, adding nalbuphine to a patient already on a mu-agonist regime must be done with care, since an excessive nalbuphine dose could negate some of the existing mu-analgesia or in the case of a higher nalbuphine dose, induce a frank opioid withdrawal

syndrome. A final disadvantage of nalbuphine is its relative unfamiliarity; while all practitioners have considerable experience with the classic mu-agonists, few have much exposure to the use of the mixed agonists—antagonists.

CONCLUSION

From our study, which aimed at evaluating the efficacy of epidurally administered Nalbuphine in a dose of 0.3 mg/kg along with bupivacaine, we can conclude that nalbuphine provided prolong and superior level of analgesia, stable hemodynamic parameters, rapid onset of sensory and motor block, mild level of sedation and minimum side effect.