

Research Article**Nalbuphine as an Alternate Analgesic to Morphine in Total Abdominal Hysterectomy: A Prospective, Randomized, Comparative, Double-Blind Study**Ananda Bangera¹, Krishna Prasad P², Prithvi M³¹Professor & Head, Department of Anaesthesiology & Critical Care, K S Hegde Medical College, Mangalore, 575018, Karnataka, India²Associate Professor, Department of Anaesthesiology & Critical Care, K S Hegde Medical College, Mangalore, 575018, Karnataka, India³Junior Consultant, Department of Anaesthesia, SPARSH Hospital for Advanced Surgeries, Infantry Road, Bangalore, 560001, Karnataka, India***Corresponding author**

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Abstract: Pain is one of the most distressing post-operative consequences of surgeries. Opioids have been the mainstay in providing pain relief. Morphine is the considered to be the “gold standard” amongst opioids as an analgesic. Nalbuphine, a synthetic opioid agonist/antagonist has analgesic potency almost equivalent to that of morphine on a milligram basis and fewer complications like respiratory depression, sedation PONV, pruritus etc. This study was conducted to compare the efficacy of i.v. nalbuphine with i.v. morphine in terms of duration of analgesia along with the intra-operative hemodynamic profile & and post-operative side effects. Fifty patients belonging to ASA physical status I & II, scheduled to undergo elective total abdominal hysterectomy under GA were included in this prospective, randomized, double blinded trial to receive either intravenous morphine 0.1 mg/kg (Group M) or nalbuphine 0.2 mg/kg (Group N) before induction of general anaesthesia. The intra-operative hemodynamics, duration of post-operative analgesia & incidence of side-effects were studied. Blood pressures (SBP and DBP) post-intubation till 180 minutes post-extubation were low in nalbuphine group. Duration of analgesia was significantly more in nalbuphine group than in morphine group (437±63.87 min v/s 255.0±43.75 min). Intravenous nalbuphine provided better haemodynamic stability and longer duration of analgesia compared with morphine, although sedation was found to be more with nalbuphine.

Keywords: Pain, Opioid, Morphine, Nalbuphine, Analgesia, Abdominal hysterectomy

INTRODUCTION:

Ensuring optimum analgesia in the recovery room is a key stage to ensuring the best long-term outcome for the patient [1].

Unrelieved acute pain results in potentially life-threatening adverse physiological effects and psychological disturbances. In modern postoperative care, this means effective relief from pain, suffering, anxiety and sleeplessness. Thus, the postoperative recovery outcomes may be greatly influenced by effective pain management. Anaesthesiologists' main role is to enable the patient to undergo surgical procedures without pain or anxiety. In spite of the spectacular advances in the pain relief during surgery, relief of pain in the postoperative period still remains a challenge [2, 3].

Gynaecological surgeries like total abdominal hysterectomy, staging laparotomies, surgeries on ovaries are common surgeries worldwide. Though,

laparoscopic surgeries are the norm of the day, open procedures continue to be popular, especially in the developing countries. Pain is reported more often in patients undergoing open procedures than laparoscopic procedures [4, 5]. Postoperative pain is an acute pain, sharp in character which starts with the surgical trauma and ends with tissue healing [6]. Postoperative pain relief reduces the incidence of chest infections, deep vein thrombosis, stress responses and sympathetic activity, hospital stay and enables early ambulation.

The experience of gratitude from patients free from pain contributes to feeling of self esteem and job satisfaction for anaesthesiologists. In addition, the contact with the patients, nurses, physicians and administrators in the postoperative period help to define anaesthesiologists as valued perioperative physician.

Anaesthesiologists have many drugs available to treat pain: opioids, NSAIDs, local anaesthetics and adjuvant drugs like tricyclic antidepressants. Opioids

have been the mainstay of post-operative pain relief for many years, and remain so even today. But opioids have many side effects like PONV, respiratory depression, pruritus, constipation, urinary retention, bradycardia, hypotension and dependence on prolonged usage. Therefore, there is a need for the development of compounds with fewer side effects.

Morphine, considered, the “gold standard” amongst opioids for providing pain relief, has serious side-effects. Nalbuphine is one of the mixed opioid agonist-antagonist available for clinical usage. Nalbuphine is a mu antagonist and kappa agonist and therefore, has a ceiling effect for respiratory depression [7, 8]. Many studies have reported that incidence of adverse effects like pruritus and PONV is lower with nalbuphine in comparison with morphine [9-11]. Hence, it is considered to be safer than morphine.

This study was undertaken to compare nalbuphine and morphine as analgesics in the post-operative period along with the intra-operative hemodynamic profile and post-operative side-effects in open total abdominal hysterectomies. The primary outcome measured was analgesia duration in the postoperative period. The secondary outcomes derived were the intraoperative hemodynamics and incidence of postoperative side effects.

MATERIALS AND METHODS

The prospective, randomized, double-blinded study was conducted to evaluate the efficacy of nalbuphine in comparison with morphine given as intravenous bolus dose pre-operatively for post operative analgesia.

Fifty patients scheduled to undergo elective, open, total abdominal hysterectomy under general anaesthesia in K S Hegde Hospital, Mangalore were selected. Institutional ethics committee approval was obtained. An informed, written consent was obtained from all the patients selected for the study.

Adults aged 30-60 years scheduled to undergo elective total abdominal hysterectomy under general anaesthesia belonging to American Society of Anaesthesiologists (ASA) physical status I & II were included. Patients with known history of sensitivity and contraindications to drugs used; with history of significant cardiac, respiratory, renal, hepatic, psychiatric or central nervous system diseases; with anticipated difficult intubation; with history of chronic opioid use; surgeries lasting for more than 3 hours and with vertical abdominal incision and patient refusal were the exclusion criteria.

Preoperative evaluation (PAE) constituted detailed history taking, physical examination and routine preoperative investigations wherever indicated (Hemoglobin, random blood sugar, blood urea, serum creatinine, serum electrolytes, Electrocardiogram, Chest

X-ray). After the PAE, on the day before the surgery, the patients were informed about the nature of the study and the anaesthetic technique employed. Written informed consent was obtained. The patients were educated about the use of visual analogue scale for the assessment of severity of pain.

Patients were kept nil by mouth for 8 hours and premedicated with diazepam 5mg (for patients weighing <50kg) or 10mg (for patients weighing >50kg) and ranitidine 150mg orally on the night before surgery and the morning of the day of surgery.

Patients were allocated randomly by closed envelope method to one of the two groups (M and N) comprising twenty five patients each. Before shifting the patients to the operating room (OR), identity of the patient, consent, NBM status, and premedications were checked and confirmed. Standard ASA monitors (ECG, non-invasive blood pressure, pulse oximeter) were connected. Intravenous access was secured on the non-dominant hand and crystalloid infusion (Lactated Ringer's solution) started. All the patients underwent standard general anaesthesia technique. Preoxygenation was accomplished with 100% oxygen for 3 minutes.

Group N received i.v. nalbuphine 0.2mg/kg and group M received i.v. morphine 0.1mg/kg after preoxygenation.

Induction of anaesthesia was accomplished with i.v. propofol 2mg/kg and neuromuscular blockade achieved with vecuronium bromide 0.1mg/kg for tracheal intubation after checking for adequate mask ventilation. Patients were intubated with appropriate sized endotracheal tubes (7 mm or 7.5mm ID cuffed endotracheal tube) after 3 minutes of ventilation. Placement of the tube was confirmed by the ETCO₂ tracing. Anaesthesia was maintained with nitrous oxide and oxygen (FiO₂ 0.33) and isoflurane 1MAC. Boluses of vecuronium were administered depending on the TOF ratio.

Haemodynamic parameters were monitored every 5 minutes and recorded by an independent observer/anaesthesiologist. At the end of surgery, after the discontinuing isoflurane and reversing the residual neuromuscular blockade with neostigmine 50mcg/kg and glycopyrrolate 10mcg/kg, patients were extubated after complete recovery from general anaesthesia and fulfilling extubation criteria.

After shifting the patients to the post operative ward, the intensity of the pain was assessed using the visual analogue scale. Hemodynamic monitoring was continued till the patients expressed a VAS>6. This duration was taken as duration of analgesia. Further pain was managed with i.v. diclofenac sodium 75mg as infusion. The VAS, SpO₂, respiratory rate, pulse rate and blood pressures were monitored at the interval of

every 15 minutes in the post operative period. Side effects/complications (nausea & vomiting, hypotension, bradycardia, dizziness, pruritus, O₂ desaturation) were noted and managed.

RESULTS

There were 25 patients in each group. Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results of categorical measurements are presented in number (%). Significance is assessed at 5 % level of significance.

Student’s t-Test (two tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (inter group analysis) on metric parameters. Levene’s test was employed to assess the homogeneity of variance. Mann-Whitney U test was used to find the significance between two groups for parameters on non-interval scale. Statistical analysis was accomplished using SPSS 15.0 for the analysis of the data. P value <0.05 was considered as significant.

The two groups were comparable with respect to age and weight (Tables 1 & 2, Fig.1 & 2).

Table 1: Age Distribution

Age (Years)	Group M		Group N	
	n	%	n	%
30-40	3	12.0	16	64.0
41-50	19	76.0	9	36.0
51-60	3	12.0	0	0.0
Total	25	100.0	25	100.0
Mean ± SD	45.92±4.65		40.60±4.79	

Table 2: Weight distribution

Weight (Kg)	Group M		Group N	
	n	%	n	%
40-50	17	68.0	14	56.0
51-60	7	53.8	9	36.0
>60	1	4.0	2	8.0
Total	25	100.0	25	100.0
Mean ± SD	50.60±6.71		52.32±8.46	

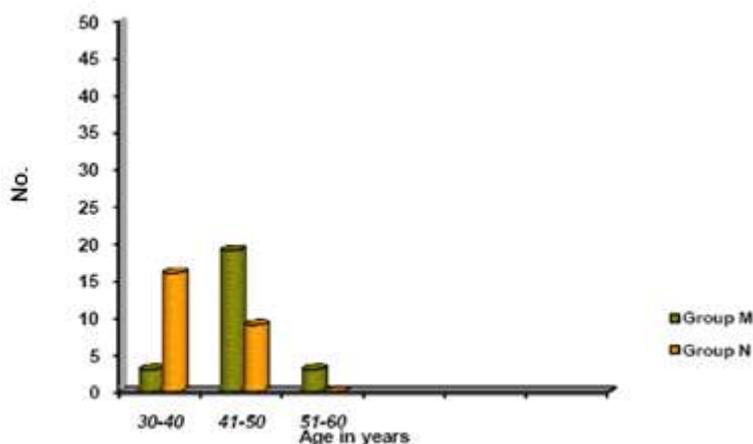


Fig. 1: Age distribution

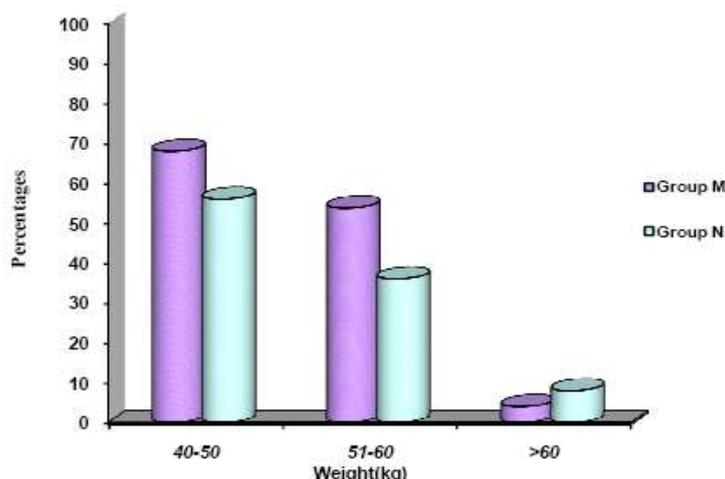


Fig. 2: Weight Distribution

The primary outcomes studied were the duration of analgesia and the need for rescue analgesics. At the time of extubation, the VAS was comparable in both the groups. After 30 minutes following extubation, VAS was 3.29±0.46 in morphine group whereas 3.00±0.00 in nalbuphine group (p=0.004) which was statistically significant. But after 30 min of extubation,

the VAS slowly increased in the morphine group and it was statistically significant after 45 min of extubation till 180 minutes. 60 minutes after the extubation, the VAS was 4.00±1.08 in morphine group whereas 3.00±0.00 in nalbuphine group (p <0.001) which was significant statistically (Table 3, Fig. 3)

Table 3: Visual Analogue Scores

VAS	Group M	Group N	p value
Extubation	2.96±0.20	3.00±0.00	0.332
15 Minutes	3.00±0.29	3.00±0.00	1.000
30 Minutes	3.28±0.46	3.00±0.00	0.004
45 Minutes	3.52±0.77	3.00±0.00	0.002
60 Minutes	4.00±1.08	3.00±0.00	<0.001
90 Minutes	4.45±0.86	3.04±0.20	<0.001
120 Minutes	5.25±0.45	4.00±0.88	<0.001
150 Minutes	6.00±0.00	4.52±0.95	<0.001
180 Minutes	2.96±0.20	3.00±0.00	<0.001

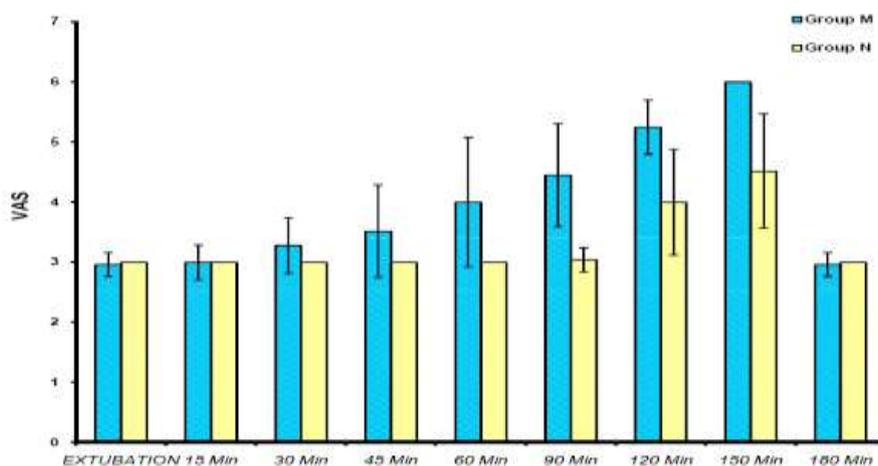


Fig. 3: Comparison of VAS

Duration of analgesia was taken from the time of injection of the drug till the patient achieved a VAS of >6 in the post operative period. There was significant difference in the duration of analgesia and use of rescue analgesic (RA) between the two groups. The duration of analgesia was 255.0±43.75 min in morphine group

compared to 437±63.87 in nalbuphine group. It was noted that there was early usage of rescue analgesic (diclofenac sodium 75 mg i.v.) in Group M (255 minutes) compared to Group N (437 minutes), which was statistically significant (p=0.001) (Table 4, Fig. 4).

Table 4: Duration of analgesia

Time of RA	Group M	Group N
Min-Max (minutes)	180.0-325.0	300.0-600.0
Mean ± SD (minutes)	255.0±43.75	437±63.87
Inference	Significantly early RA in Group M (255 minutes) compared to Group N (437 minutes) with p<0.001	

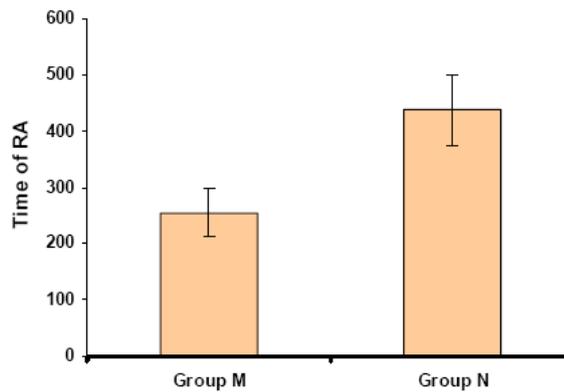


Fig. 4: Duration of analgesia

The hemodynamic profile intra-operatively and the incidence of adverse effects were the secondary outcomes of the study. The cardiovascular parameters monitored were heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP). Post-induction and post-intubation heart rates were low in

morphine group compared to nalbuphine group, which was statistically significant (p=0.005). We noticed that even after 25 to 60 minutes following intubation, heart rate continued to remain low compared to baseline in morphine group than nalbuphine group (p=0.001) (Fig. 5).

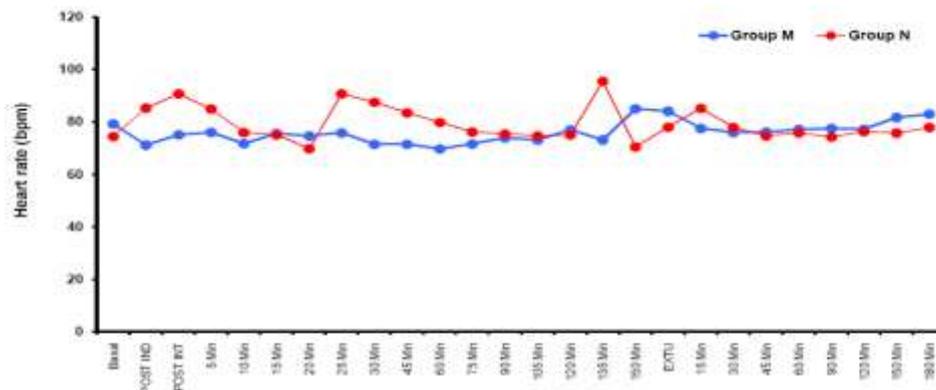


Fig. 5: Change in HR

Post-intubation blood pressures (SBP & DBP) were low in nalbuphine group compared to morphine group (p=0.043). Two hours following intubation it was noted that SBP was low in nalbuphine group which was

statistically significant (p=0.004). 30 minutes following extubation till 180 minutes, statistically significant low systolic blood pressures were noted in nalbuphine group (p=0.001) (Fig. 6).

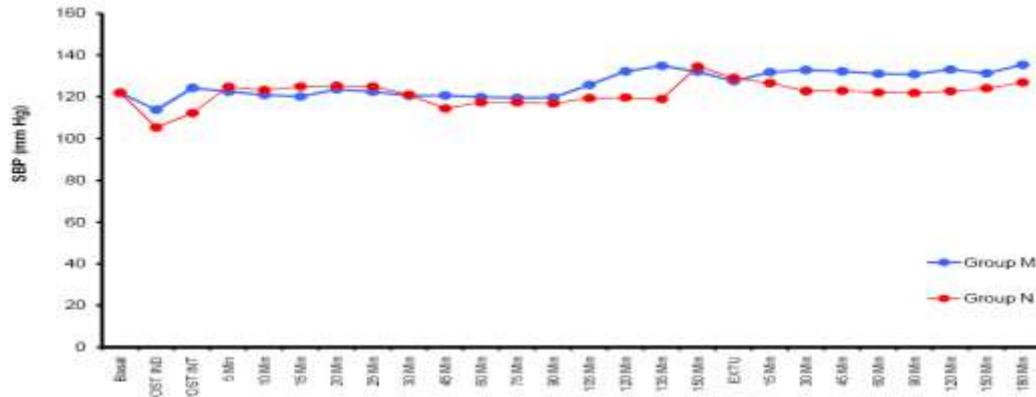


Fig. 6: Change in SBP

Similar values were noted in DBP in nalbuphine group post intubation. 90 minutes to 120 minutes following intubation low DBP were noted in

the nalbuphine group. But these low blood pressures and heart rates were within clinically accepted limits and did not warrant any interventions (Fig. 7).

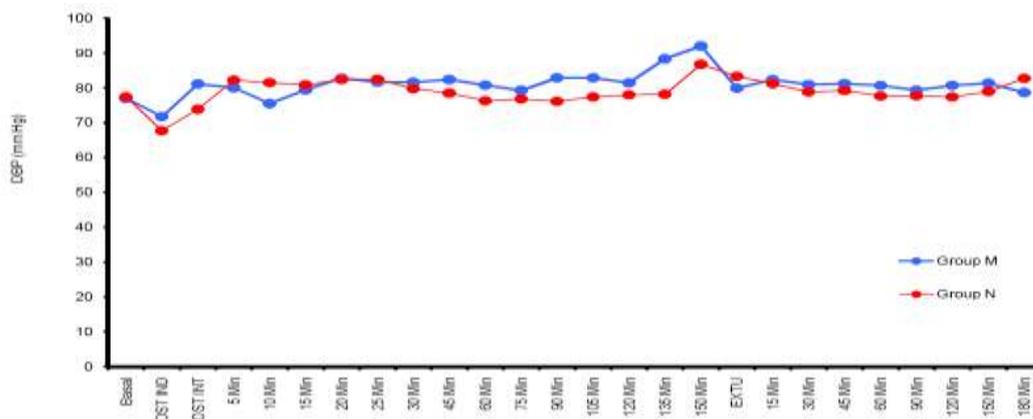


Fig. 7: Change in DBP

Data suggested variable significance of P values with respect to the O₂ saturation (SpO₂), but the

values were always maintained above 96%. Hence, it was not significant clinically (Fig. 8).

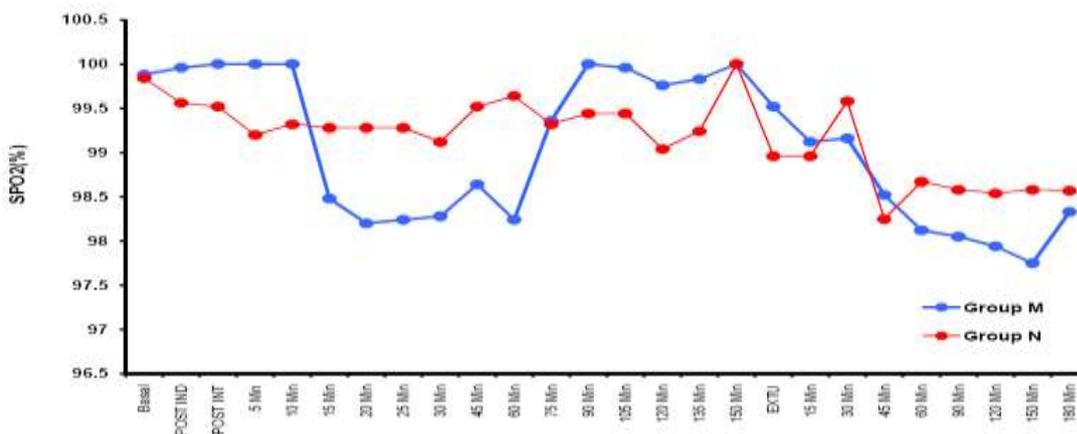


Fig. 8: Change in SpO₂

DISCUSSION

Thousands of patients undergo surgery each year and benefit from the knowledge, skills and sophisticated technology that characterize most aspects of modern surgery and anaesthesia. Despite advances in

pharmacology of analgesics and the development of more effective techniques for postoperative pain control, many patients continue to experience and suffer considerable discomfort.

Our study was conducted to evaluate the available analgesics for alleviating post operative pain, which is considered as one of the severe types of acute pain. Varieties of drugs are used during intra-operative period as analgesics. Opioids form the mainstay as they are the most potent. But they are also associated with many side effects.

This study was undertaken to compare the analgesic efficacy of nalbuphine (kappa agonist) with morphine (predominantly mu agonist) during intra-operative period as a part of balanced anaesthesia and the overall duration of analgesia in the post-operative period. Study by Gear *et al* found the property of sexual dimorphism in opioids to be more prominent for kappa agonists, i.e. nalbuphine and butorphanol [12].

Opioids are potent analgesics, but also cause respiratory depression, haemodynamic changes (hypotension, bradycardia), pruritus, urinary retention and excessive sedation. This has been proved in the studies done by Vickers MD *et al.* and Houmes RJ *et al.* [13, 14]. Morphine is the prototype opioid used in our study. Keeping in mind the various side effects associated with opioids against the excellent pain relief, we sought out to compare an opioid agonist-antagonist nalbuphine with morphine.

Morphine is a pure agonist whereas nalbuphine is an opioid agonist-antagonist. Morphine has an agonist action on all opioid receptors whereas nalbuphine is kappa agonist and weak mu antagonist. Morphine has both spinal and supraspinal components in its analgesic effect whereas nalbuphine has predominantly spinal component. Respiratory depression caused by nalbuphine has a ceiling effect at higher doses.

The study was a prospective, randomized, double blind clinical study. There were no significant differences in the demographic profile of the patients. The nature of the surgical procedure was constant; all the patients selected underwent open total abdominal hysterectomy under general anaesthesia. The quality of post-operative pain varies considerably amongst patients due to several factors: age, sex, surgical procedure, and psychological makeup of the patient [15]. Due to these reasons, an attempt was made to have the pain evaluations recorded by the same trained observer. In addition, the premedications and the anaesthetic techniques were kept constant.

As analgesic, nalbuphine is 0.5 to 0.8 times as potent as morphine on a milligram basis. Thus, the doses used were 0.1 mg/kg morphine and 0.2 mg/kg nalbuphine as intravenous bolus doses at the start of anaesthesia. The dosages used were equi-analgesic determined by previous reviews [16]. Similar doses were used by Minai FN *et al.* in their study [10].

Comparison of analgesia

Nalbuphine is an agonist at kappa receptors and antagonist at mu receptors [7, 8]. The dosages used were equianalgesic: nalbuphine 0.2 mg/kg and morphine 0.1mg/kg. Similar analgesic profiles were seen in studies done by Minai FN *et al.* [10] and Van den Berg AA *et al.* [17].

Comparison of cardiovascular effects

Cardiovascular parameters monitored were heart rate (HR), systolic and diastolic blood pressures (SBP and DBP). Heart rates were low in morphine group compared to nalbuphine group (P=0.005). Even after 25 to 60 minutes following intubation, heart rate continued to remain low compared to baseline in morphine group than nalbuphine group (p=0.001). Intraoperatively, two patients developed bradycardia following 30 minutes of nalbuphine injection which was treated with i.v. atropine 0.6 mg.

Post intubation blood pressures (SBP and DBP) were low in nalbuphine group compared to morphine group (p=0.043). 30 minutes following extubation till 180 minutes, statistically significant low SBP were noted in nalbuphine group (p=0.001). 90 minutes to 120 minutes following intubation, low DBP were noted in the nalbuphine group. But these low blood pressures and heart rates were within clinically accepted limits and did not warrant any interventions.

In our study, we noticed that nalbuphine group had more stable intra-operative haemodynamics when compared to morphine. Even after extubation, nalbuphine group showed more stable haemodynamic parameters when compared to morphine group. These results were similar to the previous studies done by Minai FN *et al.* [10] and Zsigmond EK *et al.* [18]. Another study done by Rawal N and Wennhager M did not show much advantage between drugs when haemodynamics were compared between nalbuphine and fentanyl [19].

Morphine causes bradycardia, probably by stimulation of vagal nuclei in medulla and direct depressant action on sinoatrial node, especially when co-administered with volatile anaesthetic agents [20]. Lake *et al.* have also reported less cardiac depression with nalbuphine when compared to morphine [21].

Adverse effects

In nalbuphine group, two patients developed bradycardia which was treated with i.v. atropine 0.6 mg. There was no respiratory depression in the post-operative period in both groups. None of the patients complained of urticaria or constipation. Morphine causes pruritus, whereas nalbuphine does not share this side effect. Nalbuphine is an antagonist at mu receptors and thus does not cause any pruritis [9, 10].

Surprisingly, it was observed that patients in nalbuphine group were more sedated even after 60 min post-extubation when compared to morphine. This effect was unlike observed in studies by Fragen and Caldwell & Ho *et al.* [22, 23]. Mechanism of PONV after use of opioids is not exactly known. None of the patients had PONV which may be attributed to the i.v. ondansetron 4mg administered before the extubation. Morphine is known to cause more PONV (48%) than nalbuphine (36%) [24].

O₂ saturation

Data suggested variable significance of P value; but SpO₂ was always maintained above 96%. Hence it was not clinically significant.

Limitations of the study

- Assessment of pain: Pain has no standard definition (though IASP taxonomy definition is widely accepted). It is a subjective phenomenon associated with variable responses amongst different individuals. So, standardization becomes difficult in spite of the development of innumerable tools for the assessment of pain.
- Co-morbid conditions: This study did not consider patients belonging to ASA physical status III and above. The pain relief in this group requires more vigilance compared to ASA I and II patients.
- Sedation: Even though we noted many patients in nalbuphine group to be more sedated than morphine group, sedation was not quantified employing a scale (e.g. Ramsay Sedation Scale). Sedation being a more common side-effect of morphine needed to be quantified or assessed in the post-operative period.

CONCLUSION

Pain is the most frequent reason patients seek the care of a physician. In addition to the personal suffering, pain carries economic burdens associated with loss of productivity, cost of workers' compensation & adds to the healthcare costs as increased duration of hospital stay.

Pharmacological treatment is the most important element in the multi-modal approach to analgesia. Opioids are powerful, centrally acting analgesic agents and are the mainstay in the management of pain but associated with unwanted effects. Moreover, due to the abuse potential & risk of dependence, they are difficult to procure which makes their use limited.

Nalbuphine, on the other hand, appears to be safe and effective analgesic for relief of post-operative pain. It has very minimal circulatory effects, less respiratory depression, provides good sedation without causing the troublesome side-effects of opioids. It can

be used in intra-operative as well as post-operative period for analgesia.

In conclusion, nalbuphine proves to be an excellent tool in our armamentarium against postoperative pain & is also easily available to the hospital and patients with a doctor's prescription without many hassles.

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