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COMPARISON OF ANALGESIC EFFECTS OF INTRAVENOUS NALBUPHINE AND PENTAZOCINE IN PATIENTS POSTED SURGICAL PROCEDURE: A PROSPECTIVE RANDOMIZED DOUBLE BLIND STUDY

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ABSTRACT

Background and objectives: Postoperative pain is acute pain and can affect nearly every organ function and may adversely influence postoperative morbidity and mortality. Pharmacological management with intravenous opioids is a common, effective and a well known method used to treat this pain. Primary objective was to compare effects of intravenous nalbuphine and intravenous pentazocine in terms of duration of analgesia and secondary objective was to study side effect profile. **Methods**: 60 American Society of Anaesthesiologists (ASA) physical status I and II patients undergoing short duration surgery under general anaesthesia were randomly allocated in two groups of 30 each to receive either nalbuphine(group A) or pentazocine (group B) intravenously. Patients were monitored for any side effects, postoperative duration of analgesia and need for rescue analgesia. Two sample t-tests was used to investigate and model the impact of various parameters like duration of analgesia and side effect profile. **Results**: Duration of analgesia in group A (7.43±1.63hours) was significantly prolonged as compared to group B (4.73±1.62hours). The difference was statistically significant (p <0.05). Sedation was not significant in group A as compared to group B. **Conclusion**: Nalbuphine, a synthetic opioid agonist- antagonist provides good postoperative analgesia in minor general surgical patients as compared to fentanyl and pentazocine, hence useful in day care surgeries.

KEYWORDS: Nalbuphine, pentazocine, postoperative analgesia.

INTRODUCTION

Postoperative pain can lead to a multitude of potentially threatening adverse physiological and psychological disturbances. Pain and tissue injury associated with surgery initiate a systemic stress response which has neuroendocrine, immunological, and haematological responses.[1]

Opioid analgesics are the cornerstone of pharmacological perioperative management, especially for surgical procedures that cause moderate to severe pain. 3e intravenous route, for post-operative analgesia offers added advantage as intravenous access already used during operation and single shot intravenous analgesics offers benefits for short surgical procedures. Pentazocine, a synthetically prepared prototypical mixed agonistantagonist opioid, half life of 2-3 hrs is widely used in perioperative period as it is free from narcotic laws.[2]

Nalbuphine is a semi-synthetic agonist-antagonist opioid analgesic of the phenanthrene series. It is structurally similar to the narcotic antagonist naloxone, differing in having a cyclobutylmethyl group on the nitrogen-containing ring instead of the allyl group of naloxone. It is an effective agonist as well havirig antagonist properties. Nalbuphine has been used in postoperative pain, during anaesthesia[3], and in chronic pain management. Side effects include those expected from an opioid analgesic, ie sedation, drowsiness, and, less frequently, nausea and vomiting. Respiratory depression is comparable to morphine at doses of 10mg[4,5], but, unlike morphine, there is a ceiling to respiratory depression at doses above 30 mg. Cardiovascular effects of nalbuphine differ from those of pentazocine, to which nalbuphine is otherwise similar. Pentazocine causes an increase in pulmonary artery pressures, and an increase in right ventricular work[6], whereas nalbuphine is free from these undesirable effects.[7] It has recently been licensed for use in myocardial infarction.

Not many studies comparing the two drugs were seen in literature. We thus decided to compare the two drugs and evaluate their effectiveness as analgesics postoperatively.

Primary objective of this study was to compare effects of intravenous nalbuphine and intravenous pentazocine in terms of duration of analgesia,the need for rescue analgesia and secondary objective was to study side effect profile.

METHODS

The study was conducted at Late Shri Lakhiram Agrawal Government Medical College, Raigarh. Sixty patients of ASA grade I or II in the age group of 18-60years posted for various elective surgeries requiring general anaesthesia like thyroidectomy,modified radical mastectomy,laparoscopic appendicectomy and cholecystectomy were included in this study and divided into 2 groups of 30 subjects each by using computer generated randomization charts. Each patient was given all information and details about the procedure and drugs used. Written informed consent was taken from all patients. Drugs were loaded by one person and syringes were covered and drugs were given by another person for blinding. Patients under the study had undergone thorough preoperative assessment including detailed case history, clinical examination & all necessary investigations. On arrival in the operation theatre an intravenous line was secured. Basal values of pulse, blood pressure and oxygen saturation (SpO_2) were noted.

All the patients were done under general anaesthesia. The patients were premedicated with glycopyrrolate 5 µ/kg intramuscularly (I/M), ondansetron 0.08 mg/kg and midazolam 0.03 mg/kg intravenously(I/V).Group A recieved nalbuphine 0.3 mg/kg and group B was given pentazocine 0.3mg/kg intravenously. Patients were monitored for changes in heart rate, blood pressure, electrocardiogram (ECG), SpO_2 and respiratory rate after giving drug. All the patients were induced with injection thiopentone sodium 5mg/kg and injection succinylcholine was given for intubation in the dose of 2mg/kg. Patients were maintained on oxygen, nitrous oxide and inhalational isoflurane and inj atracurium for muscle relaxation. Intraoperatively patients were monitored for heart rate, blood pressure, ECG, SpO_2. No analgesic was given till the end of surgery. After completion of surgery inj glycopyrrolate (10mcg/kg) and inj neostigmine(0.05mg/kg) were given for reversal of relaxant. After completion of surgery patients were asked for any complaints. If patient complained of pain the visual analogue score (VAS) was assessed and if the score was more than four rescue analgesic was given like in the form of diclofenac 1.5mg/kg intramuscularly. If patient had no pain on table then patient was followed up for 24 hours postoperatively every 1 hourly and VAS score was assessed.VAS score of 4 was considered as end point of duration of analgesia. If VAS score was more than 4 rescue analgesic was given. Besides side effects like nausea, vomiting, sedation and respiratory depression were noted.

Statistical analysis

With power of study 80% and Type 1 error of 5% (level of significance[α] = 0.05), the sample size required was calculated as 25 in each group and to compensate for any possible dropouts and for better validation of results a sample size of 30 subjects per group was chosen. Group A and Group B were compared for postoperative duration of analgesia and any side effects like nausea, vomiting, sedation, respiratory depression and need for supplemental analgesia. Data was expressed as mean +/- SD (standard deviation). Two sample t -test was used to investigate and model impact of various parameters like duration of surgery and duration of analgesia. A '*p*' value <0.05 was considered statistically significant. All statistical analysis was done using Minitab 16.

RESULTS

Both groups were comparable in terms of age, weight, sex, ASA grade and duration of surgery. Average age of the patient was 37.07±11.86 years in A group and 37.03±12.02 years in B group (*p*=0.99). Average weight of the patient was 54.5±5.26 kilograms (kg) in A group and 54.37±7.07 kg in B group (*p*=0.93). Average duration of surgery was 109.67±22.79minutes in group A and 109.3±22.53minutes in group B (*p*=0.95). Types of surgeries in both the groups are comparable. [Table1].

All the patients in both the groups were monitored for pulse rate, systolic and diastolic blood pressure, SpO_2 and ECG intraoperatively at five minutes after giving drug and then at fifteen minutes thereafter till the end of surgery. No ECG changes were noted in any patient intraoperatively.

Mean duration of analgesia was 7.53±1.53 hours in group A while that in group B was 4.83±1.52hours. [Figure1].The difference was statistically significant (*p*=0.0001: p<0.05).

Nausea, vomiting, respiratory depression was not seen in both the groups. Sedation was assessed by Ramsay sedation score and found to be 2 in all the patients of group A while score of more than 2 was obtained in 17 patients of group B.[Table2]. In no patient was a sedation score of 4 or more noted.

Table1: Types of surgery.

Type of Surgery	No. of Patients	
	Group A	Group B
Thyroidectomy	8	8
Modified radical mastectomy	9	8
Laparoscopic appendicectomy	7	9
Laparoscopic cholecystectomy	6	5

Table 2:Sedation Score.

Group	Ramsay sedation score=2	Ramsay sedation score>2
A(n=30)	30 (100%)	0
B(n=30)	13 (43.33%)	17(56.67%)

DISCUSSION

Analgesia is important in preoperative, intraoperative as well as postoperative period. Prevention of pain before surgical incision is helpful as it prevents central sensitization and thereby amplification of postoperative pain. Surgery produces histamine release as result of tissue injury and inflammatory mediators such as peptides and neurotransmitters. It leads to activation of peripheral nociceptors and ultimately stimuli reach central nervous system causing further release of mediators leading to vasodilation and extravasation of plasma. Also pain causes neuroendocrine stress response leading to sympathetic stimulation. Catabolic hormones increase leading to sodium and water retention, hyperglycemia, increased metabolism and oxygen consumption. Also stress response leads to hypercoagulability, immunosupression, poor wound healing in postoperative period.[1]

Poor control of acute postoperative pain can lead to chronic postsurgical pain (CPSP). Opioids are an important modality of postoperative pain management. They blunt the neuroendocrine stress response to pain. [3] Morphine is the most common opioid used for postoperative analgesia. However it is associated with several adverse effects like respiratory depression, nausea, vomiting, pruritus, constipation, urinary retention, bradycardia, and hypotension. Nalbuphine, on the other hand, being mu antagonist and kappa agonist, has a ceiling effect in its respiratory depression.[3] Hence it is considered to be safer than morphine. Many studies have reported that incidence of adverse effects like pruritus and PONV is lower with nalbuphine in comparison with morphine.[4-9] Reviews on nalbuphine's pre-clinical pharmacology sugest that the nalbuphine moiety is approximately ten times more pharmacologically potent than the mixed opioid agonist-antagonist butorphanol on an "antagonist index" scale which quantitates the drug's ability to act both as an analgesic (via opioid κ-receptor agonism) as well as an μ-receptor antagonist.[10] The opioid antagonist activity of Nalbuphine is one-fourth as potent as nalorphine and 10 times that of pentazocine. Nalbuphine binds with high affinity to the μ-opioid receptor (K_i = 0.89 nM) and κ-opioid receptor (K_i = 2.2 nM) and has relatively low affinity for the δ-opioid receptor (K_i = 240 nM). It behaves as a moderate-efficacy partial agonist (or mixed agonist-antagonist) of the μ-opioid receptor (IA = 47%; EC_{50} = 14 nM) and as a high-efficacy partial agonist of the κ-opioid receptor.[11] In one clinical trial, on a milligram basis, nalbuphine seemed to be about three times as potent as pentazocine in terms of analgesia.[12] The most common side effect of both the drugs is sedation. As compared to pentazocine nalbuphine causes less dysphoria. Pentazocine produces increase in the plasma concentrations of catecholamines, which may account for increases in heart rate, systemic blood pressure, pulmonary artery pressure and left ventricular end-diastolic pressure.Thus, nalbuphine provides a safe and effective alternative to pentazocine in patients with heart disease. The advantage of nalbuphine and pentazocine in control of pain is that there is no analgesic ceiling but ceiling to respiratory depression is present.In the study of **c**omparison of the analgesic effects of intravenous nalbuphine and pentazocine in patients with postoperative pain after upper abdominal operations were studied.[12] Authors found that on a milligram basis, nalbuphine was about three times as potent as pentazocine.

The duration of action seemed to be slightly longer after nalbuphine, but 2 1/2 hrs after the injection the pain had returned to preinjection level in 2/3 of the patients, even after the higher doses of both drugs. Except for sleepiness, there were few side effects and they were similar after both drugs.

In our study the mean duration of analgesia was mean duration of analgesia was 7.43±1.63 hours in the nalbuphine group while that in the pentazocine group was 4.73±1.62hours. Major upper abdominal surgeries were not a part of our group. The sedation score was higher in the pentazocine group in our cases. The type, duration and expertise in performing surgery including tissue trauma has its effect on postoperative pain.

In the study of **c**omparison of nalbuphine and pentazocine in the treatment of postoperative pain by self-administration after upper abdominal surgery authors found that the only parameters significantly different between the two groups were systolic BP and rate pressure product, being higher in the pentazocine group. There were no significant differences in the side-effects.[13]

In Double-blind comparison between nalbuphine and pentazocine in the control of postoperative pain after orthopedic surgery[14]authors found onset, duration and quality of pain relief were significantly superior for nalbuphine with 50% of the patients having no or only moderate pain at the end of the observation period. Cardiovascular and side effect were minor in both groups. Since the haemodynamic profile was not clinically significantly altered in our groups, we did not consider it as a part of our study. All our patient showed a stable haemodynamic profile.The nalbuphine group definitely showed a longer duration of pain relief in our study.

In another study, nalbuphine and pentazocine in an opioid-benzoiazepine sedative technique, it was found that nalbuphine is a safe and effective alternative to pentazocine when used in combination with diazepam for sedation in invasive radiology.[15]

Nalbuphine also produces provides longer duration of postoperative analgesia with less respiratory depression and risk of chest wall rigidity and apnea.[16]

In our study, duration of analgesia was significantly prolonged in nalbuphine group (7.43±1.63 hours) as compared to pentazocine group (4.73±1.62hours). Thus the need for rescue analgesia was more in pentazocine group as compared to nalbuphine group.

Side effect profile was similar in both the groups except for sedation which was less in patients receiving nalbuphine.

The limitation of our study was that we did not consider major open upper abdominal surgeries.

The surgeries though major there was no uniformity with regards to site of surgery. Besides the haemadynamic profile though not clinically significant was not statistically considered.

CONCLUSION

In conclusion, it can be said that nalbuphine is superior to pentazocine in terms of duration of analgesia and less sedation. It can be safely used as an analgesic intraoperative and postoperative.

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