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Original Research Paper

Anesthesiology

NALBUPHINE VS PENTAZOCINE-DOSE DEPENDENT COMPARISON FOR POST-OPERATIVE ANALGESIA.

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ABSTRACT

Aim: to assess the safety and efficacy of Nalbuphine hydrochloride over Pentazocine Lactate for postoperative analgesia and to note the side effects of Nalbuphine, if any.

Materials and methods: A prospective randomized study with 60 adult patients (18–60 years of age), having ASA physical status I and II undergoing elective laparoscopic cholecystectomy, under general anesthesia were included in this study. Group N (Nalbuphine) received 0.2mg/kg IV, whereas group P (Pentazocine) received 0.6mg/kg IV before induction and after surgery. No other additional analgesic was given. Visual Analogue Scale(VAS) was used to assess the severity of pain. Rescue analgesia was provided post-operatively with the same opioid analgesic in the same doses which was used prior to induction of anaesthesia whenever VAS scores ≥ 4. Statistical analysis: The data obtained was expressed as mean standard deviation. Data was analyzed using chi-x^2 test, paired t-test within the group and unpaired t-test for group of comparisons. $P < 0.05$ was taken as significant.

Results: Tachycardia and raised blood pressure after extubation returned to baseline with Inj Nalbuphine post-operatively. Group P was clinically and statistically more sedated. Group P required post-operative analgesia earlier than group N (within 30mins of extubation). Mean duration of analgesic effect of first dose of the drug was (36.50 ± 19.571 minutes) with Pentazocine as compared to Nalbuphine (62.00 ± 20.026 minutes).

Conclusion: Intravenous nalbuphine provides better and enhanced post-operative analgesia as compared to intravenous pentazocine, while both can be safely used as none causes respiratory depression which may need intervention.

KEYWORDS : Nalbuphine, pentazocine, post-operative, analgesia

INTRODUCTION

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage [(1)]." Anaesthesia for surgery is not just making the patient free from postoperative pain but also taking care of intraoperative events. Moderate to severe postoperative pain may have some physiological effects on body which increases stress response leading to cascades of endocrinal & metabolic inflammatory events that contribute to the organ dysfunction, morbidity, increased hospital stay and mortality. To avoid all these consequences, good analgesia should be supplemented.

Of all analgesics, opioids have the widest range of efficacy, providing the most reliable and effective method for rapid pain relief [(2)]. Opioids produce analgesia by binding to opioid receptors both within and outside the central nervous system. Most clinically useful opioids achieve their analgesic effect through binding and activation of mu and kappa-opioid receptors.

Mixed agonist-antagonist drugs maintain effective analgesia while reducing adverse effects like nausea, vomiting, pruritus and most importantly respiratory depression. [(3)] Safety advantages of these drugs along with potent analgesic property make them an alternative to pure opioid agonist.

Pentazocine is a synthetic partial opiate agonist-antagonist, which is benzomorphone derivative. The analgesic effects of pentazocine are due to agonistic actions at kappa opioid receptors. Ceiling effects for analgesia and respiratory depression are observed, when used in the dose above 50 to 100 mg [(3)].

Nalbuphine [(3,4)] is a mixed opioid agonist-antagonist, structurally closely related to naloxone (opioid antagonist) and to oxymorphone (a strong agonist). It is a kappa receptor agonist and mu receptor antagonist and provides analgesia and sedation without profound euphoria or nausea and vomiting. Nalbuphine has a ceiling effect on respiratory depression as well as on analgesia when used in doses above 20 mg[(5)]. This property increases safety of Nalbuphine for perioperative analgesia. It can antagonize mu-agonist opioid induced respiratory depression.

Both these drugs have comparable pharmacological and clinical profile. While Pentazocine is well established for use in perioperative period, nalbuphine is relatively newer drug available to us.

Keeping above mentioned points in mind, the present study was conducted to compare the safety, efficacy and potency of these two drugs in controlling postoperative pain.

AIMS AND OBJECTIVES

Primary objective of the study is to assess the safety and efficacy of nalbuphine hydrochloride over Pentazocine for postoperative analgesia.

Secondary Objective is to note the side effects of nalbuphine hydrochloride, if any.

MATERIALS AND METHODS

In this prospective randomized study, 60 adult patients (18–60 years of age) with the American Society of Anesthesiologists physical status class I and II undergoing elective laproscopic cholecystectomy surgeries performed under general anesthesia were included in the study. Based on the pilot study conducted and earlier study articles, power of the study was calculated to be 80% with α value of 0.5 and the sample size was calculated as 25 in each group. To consider the dropouts the total no. of patients included were taken as 60 and thereafter obtaining institutional ethical committee approval the enrolled patients were randomly assigned to either intravenous nalbuphine group (N) or intravenous pentazocine (P) group. Randomization was carried out as per the randomization chart.

Patients with physical dependence to opioids; hepatic and renal disease; who were pregnant and lactating, elderly, with

diabetes, hypertension, asthma, epilepsy, bleeding disorder, and any symptom of cardiovascular disease; receiving central nervous system depressants, monoamine oxidase, tricyclic antidepressants, selective serotonin reuptake inhibitors, and warfarin; established respiratory depression; a history of hypersensitivity to study drugs; or not willing to participate in the study were excluded. After general and systemic examination, routine laboratory investigations required for the fitness of general anesthesia were performed. Informed and written consent was obtained

Group N: Patients receiving Nalbuphine Hydrochloride 0.2 mg/kg intravenously before induction and after surgery
Group P: Patient receiving Pentazocine Lactate 0.6 mg/kg intravenously before induction and after surgery

All patients were intravenously premedicated with injection Glycopyrrolate 0.004 mg/kg, injection Ranitidine 1 mg/kg, and injection Ondensetron 0.008 mg/kg. After one minute of premedication, according to randomization patients were given either study drug injection Nalbuphine Hydrochloride 0.2 mg/kg intravenously or control drug injection Pentazocine 0.6 mg/kg intravenously slowly over 30 seconds. Ramsay Sedation Score [6]

1. Anxious, agitated or restless.
2. Cooperative, oriented and tranquil.
3. Responds to commands.
4. Asleep but has a brisk response to glabellar tap or loud auditory stimulus.
5. Asleep, has sluggish response to glabellar tap or loud auditory stimulus.
6. Asleep, no response.

Induction was done with injection Propofol (1%) 2 mg/kg. Neuromuscular blockade was achieved with injection Vecuronium 0.1 mg/kg and then tracheal intubation was done. All patients were maintained on O_2: Air (40:60) and sevoflurane 2% with controlled ventilation.

No other additional analgesia was given throughout period of surgery and also at the end of surgery. Reversal of neuromuscular blockade was done with injection neostigmine (0.05 mg/kg) and glycopyrrolate(8 μg/kg). Severity of pain, which was scored according to visual analogue score (VAS) scale, is a 10 cm. horizontal line as shown below.

0 1 2 3 4 5 6 7 8 9 10

No pain Worst pain.

Rescue analgesia was provided post-operatively with the same opioid analgesic in the same doses which was used prior to induction of anaesthesia whenever VAS scores ≥ 4. Then duration of post-operative analgesia was noted till the patient demanded analgesia for second time which was provided with injection Pentazocine 1 mg/kg and the study was terminated.

Total duration of surgery and anaesthesia, time from extubation to postoperative need of study or control drug, interval from first preoperative dose of study or control drug to requirement of tramadol and from postoperative dose of study or control drug to requirement of tramadol were noted for statistical comparison.

Side effects, if any, occurring during intraoperative or post-operative period were noted and treated with appropriate standard measures.

STASTICAL ANALYSIS:

The data thus obtained was expressed as mean standard deviation. Difference in demographic data between the two groups was sought with chi-x^2 test. The haemodynamic variables were analyzed using paired t-test within the group and unpaired t-test for group of comparisons. Visual analogue score was compared using unpaired t-test. Incidence of side effects was analyzed with chi-square test. For all stastical comparisons, $P < 0.05$ was taken as significant.

RESULTS

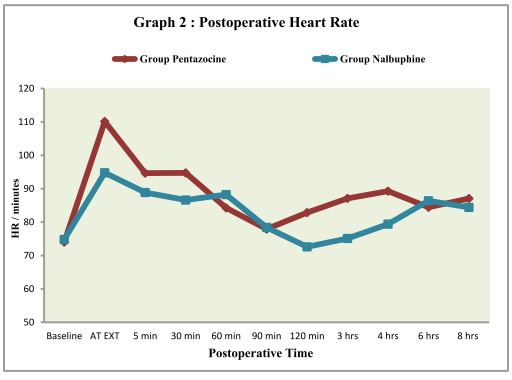
Table I: Demographic Data

Parameters	Group P (n = 30) (mean ± SD)	Group N (n = 30) (mean ± SD)	'P' value
Age (Years)	33.00 ± 4.418	33.27 ± 7.134	0.526
Weight (Kg)	53.40 ± 3.756	52.80 ± 3.517	0.862
Gender (M:F)	17:13	15:15	0.605
ASA I:II	25:05	24:06	0.739

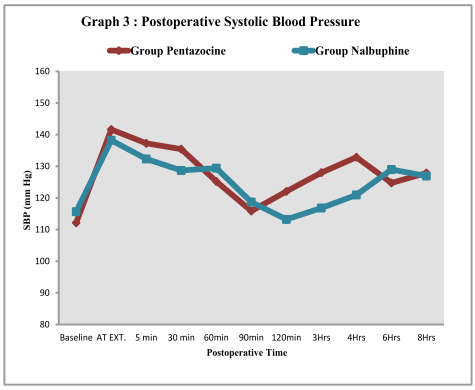
P' > 0.05 Nonsignificant

Demographic Data was comparable among the two groups.

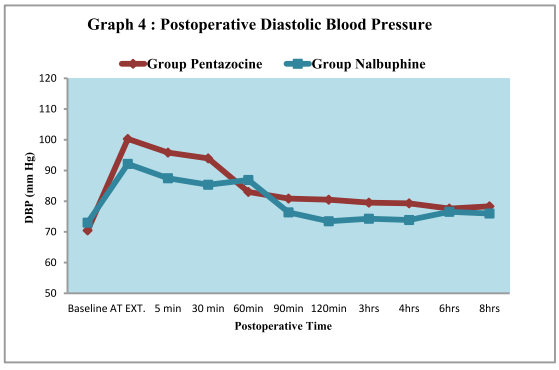
Graph 2 shows variations of heart rate at and after extubation in both groups. Both the groups had significant increase in heart rate at the time of extubation and in the first postoperative hour. In nalbuphine group when postoperative analgesia was given, heart rate returned close to baseline for 1.5 to 3 hours while it was not so in pentazocine group. The difference in heart rate was significant between the two groups, initially in first half an hour and then between 2 to 4 hours.



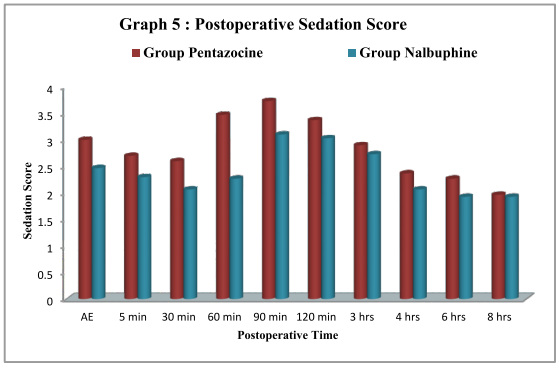
Graph 3 shows variations in systolic blood pressure after extubation. There were significant rises in systolic blood pressure after extubation till first 30 minutes postoperatively in both the groups. Rise of systolic blood pressure was significantly higher with pentazocine till 30 minutes after extubation. When nalbuphine was given for postoperative analgesia, mean systolic blood pressure returned back to the baseline and was maintained until 3 hours, but in pentazocine group even after giving the analgesic, systolic blood pressure remained above the baseline throughout the postoperative period.



Graph 4, shows results of diastolic blood pressure after extubation, which was significantly raised until 30 minutes after extubation in both groups. In pentazocine group, the rise remained significant even after giving the postoperative analgesic for one hour and after that it became non-significant and returned near the baseline. After administration of nalbuphine diastolic blood pressure immediately returned back to the baseline and was maintained. Between the groups, the difference in diastolic blood pressure was statistically significant for initial 2 to 3 hours after giving these drugs for pain relief.



Graph 5. As in the graph, patients of pentazocine group were clinically and statistically more sedated, while patients of nalbuphine group seemed to be relatively alert and more oriented in immediate postoperative period. At 6 hours of observation period it appears that the mean sedation score was low with nalbuphine as compared pentazocine, though 'p' value was statistically nonsignificant.



Postoperative visual analogue scale (VAS) shown in Graph 6: Nalbuphine group had lower VAS score in first hour of postoperative period as well as 4 to 6 hrs after rescue analgesic. The lowest VAS score in pentazocine group was 0.93+0.691 at 90 minutes postoperatively whereas in nalbuphine group it was 0.27 ± 0.640 at two hours. No patient had inadequate pain relief following either of the drugs and no patient demanded additional analgesia within two hours of administration of either pentazocine or nalbuphine.

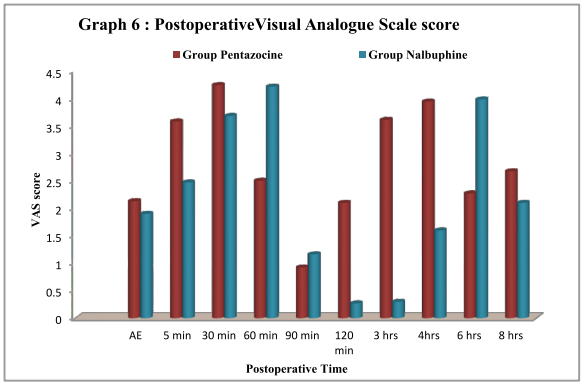


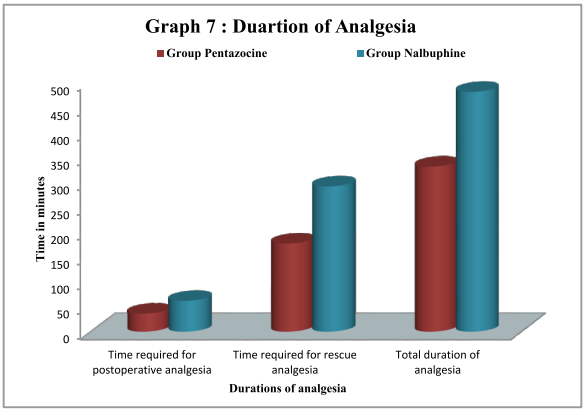
Table 2: Time Wise Distribution Of First Dose Of Postoperative Analgesia

Postoperative time	Group P (n=30) No. of patients (%)	Group N (n=30) No. of patients (%)
< 30 min.	18 (60%)	5 (16.66%)
< 60 min.	30 (100%)	21 (70%)
< 90 min.	-	30 (100%)

'P' < 0.05 Significant

Table 2 shows time wise distribution of total number of patients requiring analgesic drugs in early postoperative observation period. As seen in the table, 60% patients of pentazocine group and only 16.66% patients of nalbuphine group required first dose of postoperative analgesia within 30 minutes of extubation. Further in next 30 minutes that is within first hour of postoperative period all patients (100%) of pentazocine group had received first dose of analgesia for pain relief but in the same period only 70% of patients of nalbuphine group had required analgesia postoperatively. As seen in table all patients had required postoperative analgesia within one and half hours. Thus, patients receiving pentazocine required postoperative analgesia earlier as compared to those receiving nalbuphine.

The results of duration of analgesia is depicted in Graph 7. It is seen that mean duration of analgesic effect of first dose of the drug was shorter in the patients receiving pentazocine (36.50 ±19.571 minutes) as compared to nalbuphine (62.00 ± 20.026 minutes).



As seen in the table in the second row, nalbuphine provided significantly longer duration of analgesia (291.33± 29.767 minutes) as compared with pentazocine (177.00 ± 24.090 minutes) and p value was highly significant (p=0.000). Total duration of analgesia was highly significant statistically and clinically as well.

None of the patients had any incidence of hypoxia in the post operative period. One patient in the pentazocine group showed hypertension. One incidence of hypotension was noted in a patient receiving nalbuphine. There were no any incidence of Bradycardia in both groups but incidence of tachycardia was occurred in two cases of pentazocine group. Only one patient of Nalbuphine group had nausea in postoperative period within 10 to 15 minutes of extubation. One patient of pentazocine group and two patients of nalbuphine group had shivering in postoperative period which was treated by providing warming blankets and in one case with injection Dexamethasone 0.2 mg/kg. There was one incidence of probable psychotomimetic effect (patient was talking irrelevantly) in pentazocine group.

DISCUSSION

Acute postoperative pain is a concern among most of the patients undergoing surgical procedures. Similarly, inadequate pain relief is also a common problem in these

patients, which may adversely affect their quality of life and functions[7] In earlier studies authors have mentioned that the single dose of drugs do not provide sufficient insights to the the safety and efficacy of study drugs , hence in the present study, we compared double dose (at induction and as 1st rescue analgesic) intravenous pentazocine and nalbuphine for postoperative analgesia. Both the drugs relieved pain immediately, but significantly better relief from pain was seen with nalbuphine as noted with lower individual VAS scores.

Pentazocine is an early opioid and its analgesic profile has been widely studied since ancient times. Nalbuphine has lately been studied via various routes and hence we decided to study the analgesic profile of both drugs with double dose.

Various earlier studies have been conducted to compare pentazocine with Nalbuphine and they have concluded that nalbuphine has a better analgesic effect than pentazocine or few studies also mentioned in their results as both drugs had comparable analgesic effect.[8,9,10]

Studies conducted between nalbuphine and pentazocine by Graham J[8] et al, Dandoni R[9] et al, Rita L[11] et al found very few side effects in both groups and no any significant difference in side effects of both groups. Pendel G[12] et al, and Hook PC[10] et al also observed that there were no any adverse effects with use of these drugs. Tammisto T[13] et al. noticed that patients with pentazocine had mild psychotomimetic side effects whereas nalbuphine group patients did not show such effects *Praveen P. V. V.S. B., Vijaya Chandra Reddy Konda, Lohit K.*[14] compared the efficacy and safety of intramuscularly administered nalbuphine, butorphanol and pentazocine for post-operative pain relief after abdominal hysterectomy and found that Intramuscular nalbuphine and butorphanol provided effective analgesia with rapid onset and longer duration of action, with lower incidence of nausea and vomiting when compared to pentazocine. In particular, nalbuphine can be a suitable agent to provide post-operative pain relief in gynecologic lower abdominal surgery.

R N Solanki, N D Gosai, G M Joshi, B M Patel, H V Modi, & R Jain[15] compared the post-operative analgesic efficacy & side effects of Nalbuphine and Tramadol in orthopaedic surgeries and concluded that Nalbuphine produces better pain relief and hemodynamic stability in postoperative period in patients undergoing orthopaedic surgeries when compared to tramadol which is associated with more nausea,vomiting and rescue analgesic requirement.

Yang Zhang, ki jiang and Tao li[16] investigated the analgesic effects of nalbuphine on patients undergoing thoracoscopic lobectomy during the perioperative period, as well as its effects on inflammatory cytokines and stated that the application of nalbuphine can reduce the incidence of adverse reactions, reduce postoperative inflammatory responses, and promote rapid patient recovery, thus demonstrating the clinical value of nalbuphine.

Sai Durga Krishna Kiran K, Varsha Vyas1, Surekha Patil [7] compared the efficacy and safety of single-dose intravenous nalbuphine versus intravenous tramadol for postoperative analgesia and found that both tramadol and nalbuphine were equally effective but tramadol caused more of nausea and vomiting.

Shiv Akshat, **Rashmi Ramachandran**, Vimi Rewari, Chandralekha, Anjan Trikha, and Renu Sinha[17] compared the intraoperative and postoperative analgesic efficacy and side effect profile of the two drugs. They found that Nalbuphine provides less effective intraoperative analgesia than morphine in patients undergoing open gynaecological surgery under general anaesthesia. Both drugs, however, provided similar postoperative analgesia and had similar haemodynamic and side effect profile. This study was similar to ours but unlike us they used single dose of study drugs while we used double dose to improve the study profile.

Siddiqui MK, and Chohan U[18] compared nalbuphine and tramadol in dilatation and evacuation cases and observed that tramadol had more sedating effect than Nalbuphine and patients receiving Nalbuphine woke up earlier and well oriented compared to tramadol. In our study we had observed better sedation profile of nalbuphin eas compared to pentazocine.

CONCLUSION

To conclude nalbuphine hydrochloride is able to provide good quality and long lasting analgesia, with stable haemodynamics, in contrast to pentazocine lactate which gives comparatively lesser duration of analgesia with stimulation of sympathetic system. Another outcome of our study was that, inspite of both drugs causing sedation, each of them can be used safely as both of them do not cause respiratory depression (which may require oxygen supplementation).

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