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Anaesthesiology

"A comparative study of nalbuphine, fentanyl and pentazocine as intravenous analgesics for postoperative pain relief in minor general surgical procedures"

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ABSTRACT

Background and aims: 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. Our study aims at comparing the analgesic efficacy of nalbuphine, fentany and pentazocine as opioid analgesics for post operative pain relief in minor general surgical procedures **Methods:** In this prospective, double blind, randomized controlled clinical trial, 90 patients aged 18 to 60 years, ASA grade 1 or 2, posted for minor general surgery procedures, lasting less than 1 hour under general anaesthesia. **Study design:** Patients were randomly allocated into 3 groups, **Group I (Nalbuphine)** received 0.2 mg/kg of Nalbuphine hydrochloride, **Group II (Fentanyl)** received 2 mcg/kg Fentanyl and **Group III (Pentazocine)** received 0.6 mg/kg Pentazocine, intravenously prior to induction of anaesthesia. Hemodynamic parameters, postoperative analgesia, time of rescue analgesia, respiratory depression, sedation scores and side effects were studied. **Results:** Pain assessed as VAS scores were not significantly different to start with (60 mins) immediate postop in all 3 groups (p= 0.84).They were lower in Group I (nalbuphine) at 120,180 and 240 mins. At 360 mins, there was no significant difference between the mean VAS across all the groups. This suggests that all three opioids, nalbuphine, fentanyl and pentazocine provide good postoperative analgesia till 240 mins (4hrs) however nalbuphine has added effect and advantage as seen from the lesser VAS and provides longer duration of analgesia. No significant differences were seen in recovery from anaesthesia. No significant side effects of nausea, vomiting, excessive sedation and respiratory depression were noted in all the 3 groups **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 : postoperative analgesia, day care surgeries, nalbuphine, fentanyl, pentazocine

INTRODUCTION

Moderate to severe acute pain, regardless of site, can affect nearly every organ function and may adversely influence postoperative morbidity and mortality hence effective management of postoperative pain is not only humane but is a very important aspect of postoperative care **[1]** Opioid analgesics are the cornerstone of pharmacological perioperative management, especially for surgical procedures that cause moderate to severe pain. The 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.

Fentanyl is a, highly lipid soluble, synthetic opioid agonist, increasingly used in treating acute pain because of faster onset of action (3-4 mins), short duration (45mins -1hr) and is seventy five to one twenty five times more potent than morphine **[2]** Fentanyl is highly lipid soluble, highly protein bound synthetic opioid with analgesic potency 100 times that of Morphine. It is rapid in onset (3-4mins) and is having short duration (45mins -1hr) However, the use of fentanyl is associated with an increased risk of hypoxemia and apnea**[3]** which is undesirable for patients undergoing short surgical procedures.

Nalbuphine is a synthetic partial kappa agonist/mu antagonist opioid, rapid in onset (3-4mins) and duration of action is around 3-6hrs, causes less respiratory depression than other opioids and has a safety profile with minimal effect on cardiovascular function**[1,2]**It is equipotent to morphine, and is about one fourth as potent as naloxone as an antagonist **[2]** The pharmacological profile of nalbuphine and its freedom from control by the *Misuse of Drugs Act* would appear to be useful properties in an analgesic for short surgical procedures **[4]**

Pentazocine, a synthetically prepared prototypical mixed agonist-antagonist opioid, half life of 2-3 hrs is widely used in perioperative period as it is free from narcotic laws **[5]**

Many newer and effective opioid analgesics like sufentanyl, alfentanyl, remifentanyl are available today, each having its own advantages and disadvantages. Our study, is designed to compare nalbuphine, fentanyl and pentazocine as intravenous analgesics for postoperative pain relief in minor surgical procedures

METHODS AND MATERIALS

With institutional ethics committee approval, a randomized, double blind, prospective study was done on 90 patients of ASA status (1 or 2) aged between 18- 60 years for minor general surgery procedures lasting less than 1 hour (fibroadenoma, lipoma, swelling excision, incision and drainage, lymph node biopsies) under general anaesthesia. Patients were randomly allocated into 3 groups, **Group I** (Nalbuphine) received 0.2 mg/kg of Nalbuphine hydrochloride, **Group II** (Fentanyl) received 2 mcg/kg Fentanyl and **Group III** (Pentazocine) received 0.6 mg/kg Pentazocine, intravenously prior to induction of anaesthesia. Patients with history of allergy to opioids or egg or soyabean, uncontrolled systemic or metabolic disorders and ASA III and IV were excluded from the study. Detailed preanaesthetic checkup along with necessary investigations was done, procedure explained, written, valid, informed consent was obtained. Patients were also explained about the visual analogue scale (VAS) so as to grade the post-operative pain. In the operation theatre, adequate starvation status was confirmed. Monitors attached and baseline heart rate (HR), blood pressure (B.P), electrocardiogram and peripheral arterial oxygen saturation (SpO_2) were obtained. Intravenous line was secured and an infusion of ringer's lactate was started. Premedication done with iv injection Ondensetron(4 mg), inj.Ranitidine(50mg) and inj. Glycopyrrolate (0.2mg). Sedation with Midazolam (0.05mg/kg) and analgesia in the form of inj Nalbuphine (0.2mg/kg) Inj.Pentazocine (0.6mg/kg) or Inj.Fentanyl (2mcg/kg.) was given intravenously for subjects in group I, II, III respectively. General anaesthesia was given with Inj. Propofol (2mg/Kg) and 2mg/kg. of succinylcholine. and Laryngeal mask airway and maintained with inhalational agents and titrated doses of propofol with spontaneous respiration. Vitals parameters were recorded

intraoperatively (5 mins) and for every 60 mins. postoperatively in postanaesthesia care unit (PACU) . Patients were observed for sedation, pain and side effects like nausea and vomiting. Pain was assessed with visual analog score using 10 cm horizontal scale as{No pain (0), Mild pain (1-3), Moderate pain (4-6) and Severe pain (7-10)} Duration of analgesia was noted and rescue analgesia was given with injection diclofenac 75 mg.

STATISTICAL ANALYSIS

At the end of the study decoding of patients data was done and comparison between the three groups was done with all values expressed as mean ± standard deviation (SD) The means of the continuous variables (age, and duration of surgery) were compared using analysis of variance ANOVA, while the demographic data for the categorical variables (sex, ASA class, distribution of surgeries across groups) were compared using Pearson chi-square test, a p value of <0.05 was considered statistically significant.

OBSERVATION AND RESULTS

All 90 patients operated for minor general surgery procedures under general anaesthesia completed the study protocol and were included in the analysis. The demographic data (age, sex, weight, ASA status and distribution of surgeries) were comparable in both the groups and there was no statistically significant difference between them (p > 0.05)

Intraoperative and postoperative haemodynamic parameters like heart rate, blood pressure, respiratory rate, VAS, duration of postoperative analgesia and side effects were compared between the three groups as follows

Table 1: Mean heart rate

Time	Group			p value	Significance
	Group I	Group II	Group III		
0 min	77.63 ± 7.93	77.29 ± 8.28	79.79 ± 8.83	0.56	Not Significant
60 mins	72.37 ± 5.31	66.52 ± 5.91	74.81 ± 6.25	< 0.001	Significant
120 mins	73.37 ± 5.08	68.62 ± 7.79	76 ± 6.05	< 0.001	Significant
180 mins	76.07 ± 5.08	73.24 ± 8.34	79.85 ± 6.81	0	Significant
240 mins	79.97 ± 5.37	77.34 ± 7.38	80.7 ± 6.60	0.01	Significant
300 mins	82.87 ± 5.81	78.34 ± 5.79	82.22 ± 6.45	0.01	Significant
360 mins	86.47 ± 6.42	79.07 ± 5.61	83.52 ± 5.56	< 0.001	Significant

- mins: minutes

At induction(0 min)the mean heart rate in Group I(nalbuphine) was 77.63 ± 7.93 which was not significantly different from Group II(fentanyl) and Group III(pentacozine) Postoperative at 60 mins HR was less in grp II (66.52 ±5.91) compared to grp I and III which was significant(p< 0.001) and remained less thereafter till 180 mins and returned to baseline values in 240 mins

Table 2: Mean systolic blood pressure

Time	Group			p value	Significane
	Group I	Group II	Group III		
0 min	125.13 ± 6.89	129.48 ± 10.47	125.78 ± 10.22	0.23	NS
60 mins	110.5 ± 8.05	118.28 ± 9.35	120.78 ± 7.58	<0.001	S
120 mins	111.2 ± 7.73	122.97 ± 9.35	120.74 ± 7.58	<0.001	S
180 mins	113.9 ± 7.98	123.9 ± 6.56	124.3 ± 5.40	<0.001	S
240 mins	118.07 ± 8.02	125.93 ± 7.59	125.26 ± 5.93	<0.001	S
300 mins	120.9 ± 7.14	127.45 ± 4.98	126.96 ± 4.94	<0.001	S
360 mins	123.33 ± 8.19	127.52 ± 4.10	126.59 ± 4.18	<0.001	S

NS = Not Significant S = Significant mins: minutes

The baseline mean systolic blood pressure in the three groups were not significantly different to start with (0 mins) at induction (p=0.23). At 60 mins MSBP in grp I(nalbuphine) was less(110.5 ± 8.05) compared to grp IIfentanyl) and grp III(pentazocine) which was significant(p<0.001) Postoperatively it remained less in nalbuphine grp as compared to fentanyl and pentazocine grps till 300 mins(4-5 hrs) suggesting better hemodynamic stability

Table 3: Mean diastolic blood pressure

Time	Group			p value	Significance
	Group I	Group II	Group III		
0 min	78.37 ± 7.7	83.31 ± 9.96	78.63 ± 8.03	0.095	NS
60 mins	74.57 ± 7.02	80.62 ± 9.80	76.11 ± 6.17	0.016	S
120 mins	75.07 ± 6.73	81.86 ± 8.37	77.15 ± 5.76	0.002	S
180 mins	75.57 ± 6.38	83.45 ± 7.46	77.81 ± 4.94	<0.001	S
240 mins	77.73 ± 5.79	83.93 ± 7.27	78.85 ± 4.39	<0.001	S
300 mins	78.83 ± 5.63	84.62 ± 6.86	79.74 ± 3.58	0.001	S
360 mins	80.4 ± 5.33	84.76 ± 6.58	80.15 ± 3.02	0.003	S

NS = Not Significant S = Significant mins: minutes

The mean diastolic blood pressure at 0 mins(induction) was lower in grp I (Nalbuphine) 78.37 ± 7.7 and grp III(Pentazocine) 78.63 ± 8.03. At 60 mins there was a fall in MDBP in all the three grps(p=0.016) and remained less in grp I (75.57 ± 6.38) and III (77.81 ± 4.94) till 180 mins (3 hrs) (P<0.001) which is significant

Table 4: Mean Visual Analogue Score (VAS)

Time	Group			p value	Significance
	Group I	Group II	Group III		
60 mins	1.52 ± 1.33	1.06 ± 1.32	1.78 ± 1.29	0.84	NS
120 mins	3.07 ± 1.31	4.07 ± 1.10	4.11 ± 0.97	0	S
180 mins	4.13 ± 1.22	4.62 ± 0.82	4.67 ± 0.92	0.08	S
240 mins	5.03 ± 0.85	5.17 ± 0.71	5.11 ± 0.80	0.88	NS
300 mins	5.3 ± 0.70	5.24 ± 0.64	5.3 ± 0.61	0.97	NS
360 mins	5.47 ± 0.63	5.31 ± 0.71	5.26 ± 0.59	0.48	NS

NS = Not Significant; S = significant. Mins: minutes

VAS scores were not significantly different to start with (60 mins) immediate postop in all 3 groups (p= 0.84).They were lower in Group I at 120,180 and 240 mins. At 360 mins, there was no significant difference between the mean VAS across the groups. This suggests that all three opioids, nalbuphine, fentanyl and pentazocine provide good postoperative analgesia till 240 mins(4hrs) however nalbuphine has added effect and advantage as seen from the lesser VAS and provides longer duration of analgesia

Table 9: Mean time to first dose of Diclofenac

Group	Mean time to first dose of Diclofenac in minutes	Total Diclofenac requirement (in mg)
Group I	295.47	145
Group II	144.5	182.5
Group III	165	185

The mean time to first dose of rescue analgesia with inj. diclofenac in Group I (295.47mins) is significantly higher than Group II (144.5mins) and III (165mins)

Table 10: Side effects (Nausea/ Vomiting)

Nausea/ Vomiting	Group I	Group II	Group III	Total
Yes	1	0	0	1
No	29	30	30	89
Total	30	30	30	90

Only one patient in Group I (nalbuphine) had nausea but no vomiting. No nausea or vomiting was observed in the other 2 groups (fentanyl and pentazocine)

DISCUSSION

Minor general surgical procedures like fibroadenoma, lipoma excision, excision of swellings, incision and drainage are increasingly done as day care surgery cases. This asks for good intraoperative hemodynamics, good analgesia, decreased requirement of other

anesthetics, reduced total requirement of analgesics and minimal or no nausea/vomiting in the postoperative period, a smooth and rapid recovery and stable postoperative period. Over the years, new drugs are compared with the old and the search for an ideal analgesic continues. Opioids have been used since centuries to treat pain, of which morphine, gave excellent analgesia as concluded by the study by Claxton AR, McGuire G, Chung F, Cruise C who evaluated morphine versus fentanyl for postoperative analgesia after ambulatory surgical procedures. They found fentanyl group had higher pain scores and required more oral analgesia. Morphine produced a better quality of analgesia but was associated with an increased incidence of nausea and vomiting, the majority of which occurred after discharge [6]

Our study, compared the efficacy of the three opioids, nalbuphine, fentanyl and pentazocine as intravenous analgesics for postoperative pain relief, in minor surgical procedures. The effects on haemodynamic parameters like heart rate, blood pressure, respiratory rate, recovery and pain scores were assessed.

HEART RATE

At induction (0 min) the mean heart rate in Group I (nalbuphine) was (77.63 ± 7.93) which was not significantly different from Group II(fentanyl) (77.29 ± 8.28) and Group III(pentacozine) (79.79 ± 8.83) i.e no statistically significant difference in the heart rate in all three groups. In the postoperative period, rise in heart rate in Group II is significantly less as compared to Group I and Group III suggesting better hemodynamic stability with fentanyl. Postoperative at 60 mins HR was less in grp II (66.52 ±5.91) compared to grp I and III which was significant ($p< 0.001$) and remained less thereafter till 180 mins and returned to baseline values in 240 mins(4 hrs)

Van Den Berg et al used nalbuphine 0.1-0.15 mg/kg or fentanyl 1.5-2.0mcg/kg at induction for routine ENT surgery and found that intraoperatively, their effects on heart rate and blood pressure, were similar in ENT surgery patients**[7]** Ahsan-ul-Haq *et al[8]* reported an increase in HR (+15.5%) and MAP (+10.5%) with nalbuphine immediately after intubation. Similarly, Lefevre et al studied nalbuphine and fentanyl in 24 medically compromised patients undergoing oral surgery with local anaesthesia. Patients received 0.2mg/kg nalbuphine or 2mcg/kg fentanyl. Analgesia and sedation appeared sufficient and comparable in the two groups, and there were no significant differences in blood pressure or heart rate. Respiratory rate and SpO_2 were lower in patients treated with fentanyl, and eight patients of this group experienced episodes of oxygen desaturation (SpO_2 < 90%) compared with only two patients who received nalbuphine. Nalbuphine produced less respiratory depression and was considered a suitable alternative to fentanyl for use in medically compromised patients **[9]**

BLOOD PRESSURE

The mean systolic blood pressure in the three groups was not significantly different at 0 min (induction time). Postoperatively it remained less in nalbuphine grp as compared to fentanyl and pentazocine till 300 mins(5-6 hrs) suggesting better hemodynamic stability. Also, the mean diastolic blood pressure in the three groups was not significantly different at 0 min but decreased significantly over the period in Group I (nalbuphine). At 60 mins there was a fall in MDBP in all the three grps ($p=0.016$) and remained less in grp I (75.57 ± 6.38) and III (77.81 ± 4.94) till 180 mins(3 hrs) ($p<0.001$) which is significant. This showed that both nalbuphine and pentazocine maintained diastolic BP on a lower side compared to fentanyl. Studies by Nonaka A, Suzuki S, Abe F, Masui k C suggest that pentazocine would provide a stable hemodynamic state, rapid recovery and an effective postoperative pain relief to the same degree as with fentanyl in TIVA with propofol[10] Also, studies by Miller RR**[11]** showed that nalbuphine has few effects on cardiovascular hemodynamics in patients without cardiac disease or with stable ischemic disease. In patients with acute myocardial infarction, nalbuphine has an advantage over morphine, pentazocine, and butorphanol of not producing hypotension. Khalid Maudood Siddiqui et al compared intravenous tramadol 1.5mg/kg and nalbuphine 0.1mg/kg in dilatation and evacuation patients.They found nalbuphine had a better haemodynamic stability and an early postoperative recovery with better pain control in comparison with tramadol, Nalbuphine was a better choice when using TIVA technique in the day care surgery for D and E**[12]** B.LefÃ¨vre, M. Freysz, J. LÃ¨pine, J. M. Royer, D. Perrin, and G. Malka compared the efficacy and side effects of equianalgesic doses of nalbuphine and fentanyl as intravenous (IV) analgesics for medically compromised patients undergoing oral surgery with local anesthesia. Analgesia and sedation appeared sufficient and comparable in the two groups, and there were no significant differences in blood pressure or heart rate. Their study showed that nalbuphine produced less respiratory depression and should be considered a suitable alternative to fentanyl for use in medically compromised patients undergoing oral surgery**[9]** Studies by Minai FN, Khan concluded that nalbuphine provides better haemodynamic stability and better analgesia, recovery profile and postoperative pain relief compared to morphine in patients undergoing total abdominal hysterectomy**[13]**

VAS

VAS scores were not significantly different to start with (0 min) immediate postop in all 3 groups ($p= 0.93$).Nalbuphine group had lesser pain scores till 4-6 hrs postoperatively. At 360 minutes, there was no significant difference between the mean VAS across the groups. This suggests that all three opioids, nalbuphine, fentanyl and pentazocine provide good postoperative analgesia till 240 mins (4hrs) however, nalbuphine has added effect and advantage as seen from the lesser VAS and provides longer duration of analgesia. Also nalbuphine group required rescue analgesia with inj.diclofenac after longer duration compared to fentanyl and pentazocine and total dose required of diclofenac was also less in the postoperative period. However, Nonaka A, Suzuki S, Abe F, Masui K C, studied eighty-nine patients scheduled for mastectomy retrospectively and their results suggested that pentazocine would provide a stable hemodynamic state, rapid recovery and an effective postoperative pain relief to the same degree as with Fentanyl in TIVA with Propofol**[10]**Similar studies by Zhang Xiu-yan, LI Ming-rui, Zhan Hong, Huang Li-fang, concluded that pentazocine and fentanyl produced equivalent analgesia for patient-controlled intravenous analgesia in patients undergoing gynecological laparoscopic surgery, and pentazocine produced less side effects **[14]** Also,Khalid Maudood Siddiqui et al compared tramadol with nalbuphine for dilatation and evacuation . Nalbuphine had a better haemodynamic stability and an early postoperative recovery with better pain control in comparison with tramadol, nalbuphine was a better choice when using TIVA technique in the day care surgery for dilatation and evacuation**[12]** Similar studies by Tammisto T, Tigerstedt compared one hundred patients, who were in pain during the immediate postoperative period after upper abdominal operations and received nalbuphine and pentazocine, concluded that nalbuphine seemed to be about three times as potent as pentazocine **[15]**

M. E. Bone's, Dowson, G Smith compared forty patients, allocated randomly to receive nalbuphine 0.25 mg/kg or fentanyl 1.5 g/kg immediately before induction of anaesthesia. Patients who received nalbuphine had significantly lower pain scores at 1 hour and 2 hours and required significantly less postoperative analgesia. Freedom from Controlled Drug Act regulations and improved analgesia with nalbuphine, render it more satisfactory for day case surgery than the more commonly used fentanyl **[16]** Studies by Donadoni R, Rolly G, Devulder J, Verdonck R, in their double-blind comparison between nalbuphine(20mg I.M) and pentazocine(30 mg IM) in the control of postoperative pain after orthopedic surgery observed that onset, duration and quality of pain relief were significantly superior for nalbuphine with 50% of the patients still having no or only moderate pain at the end of the observation period. Cardiovascular and side effects were minor in both groups [17] Khan FA, Hameedullah in their studies fentanyl and nalbuphine in laproscopic cholycystectomy found that fentanyl provided better intraoperative haemodynamic stability in comparison to nalbuphine when used as the analgesic

component in total intravenous anaesthesia with propofol. Lesser number of patients required analgesia in the recovery in the nalbuphine group **[18]** Studies by Sharma K, Audichya P C et al showed that postoperative pain was better managed with Nalbuphine and Tramadol as compared to Fentanyl **[19]**

NAUSEA VOMITING

In our study, only one patient in Group I (nalbuphine) had nausea but no vomiting. No nausea or vomiting was observed in the other 2 groups. Garfield et al similarly found in their study that the nalbuphine group had a significantly higher incidence of nausea than did the fentanyl group, a suggestion of a dose-effect relation **[20]**

Similar studies by Bone ME, Dowson S,Smith G[16]showed no significant differences between nalbuphine and fentanyl for incidence of nausea. Van Den Berg et al in their study of ENT patients concluded that fentanyl, nalbuphine and pethidine had moderate rates of vomiting incidence as compared to morphine and buprenorphine which had maximum rates**[7]** Studies by Minai FN, Khan FA showed that postoperative nausea and vomiting was significantly less in the nalbuphine group**[13]** Crul JF, van Egmond J in their studies of gynaecological and urological surgeries concluded that nalbuphine cases has lower incidence of nausea vomiting[21] than morphine.

CONCLUSION

From our study, we concluded that all the three opioids when given intravenously provided good analgesia in the postoperative period however, nalbuphine was better as seen from the lower VAS till 4 hrs(240 mins).The time to first rescue dose of analgesic with diclofenac was increased with nalbuphine as compared to fentanyl and pentazocine and also the total dose required is reduced. Fentanyl caused fall in heart rate till 3-4 hrs(180-240mins) while Nalbuphine caused a slight fall in mean systolic blood pressure for 4 to 5 hrs(240-300 mins) while both pentazocine and nalbuphine showed less mean diastolic pressure till 4hrs(240 mins) No side effects of nausea, vomiting or respiratory depression were seen. Nalbuphine had added advantage over fentanyl and pentazocine for postoperative analgesia in minor surgical procedures

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