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Original Research Article

Efficacy of nalbuphine for suppression of hemodynamic responses to pneumoperitoneum- A prospective randomised controlled study

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ABSTRACT

Background and Aim: Pneumoperitoneum created during laparoscopic surgeries induces significant hemodynamic changes. This study was aimed to explore the efficacy of nalbuphine to suppress hemodynamic responses to pneumoperitoneum.

Materials and Methods: This was a prospective randomised controlled study conducted on 80 ASA I/II patients between 18-60 yr after institutional ethics committee approval and written informed consent. Presence of pregnancy, multiple drug therapy, cardiovascular, renal or hepatic diseases were taken as exclusion criteria. Based on a computer generated random number table patients were allocated to one of the two groups; Group N: Nalbuphine 0.3 mg/kg and Group S: Normal saline. Hemodynamic parameters, time to request of rescue analgesic, sedation and side effects were recorded. Data was analysed using student t-test and Chi square/Fisher's exact test, repeated measure ANOVA. A p-value<0.05 was taken as significant.

Results: Group N patients had lower heart rate after test drug and for the first 30 min and on deflation of pneumoperitoneum. The mean and systolic blood pressure decreased at the time of creation of pneumoperitoneum (p<0.001). VAS score was significantly lower in the first 30 min postoperatively in group N (p=0.004). Number of patients who requested for rescue analgesic within 2 h postoperatively, incidence of PONV and shivering were comparable. Sedation was higher in immediate postoperative period in group N (p=0.002).

Conclusion: Nalbuphine provides stable hemodynamics for first 30 min after creation of pneumoperitoneum for laparoscopic procedures. It also provides postoperative analgesia for a short duration of 30 min.

1. Introduction

Laparoscopic procedures have largely replaced open surgical procedures where ever possible. However, the creation of pneumoperitoneum for these procedures results in significant cardiovascular and respiratory changes, disturbance in acid base balance and activation of stress response.[1,2] The cardiovascular responses, characterized by a decrease in cardiac output and increase in systemic vascular resistance (SVR), can adversely affect patients with hypertension and coronary artery diseases.[3,4] It is thus, important to mitigate these haemodynamic responses.

Various researches focussing on the ideal technique of anaesthesia or an ideal drug to suppress these haemodynamic responses have been conducted. But they are associated with some limitations.

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Nalbuphine, a semisynthetic opioid agonist-antagonist, has analgesic potency equal to morphine. It does not increase systemic blood pressure, pulmonary artery pressure, heart rate or atrial filling pressures.[5–8] It effectively suppresses hemodynamic responses to laryngoscopy and intubation in doses of 0.2 - 0.75 mg/kg.[9–17]

A thorough search of literature, revealed two studies using 0.2 mg/kg nalbuphine to attenuate haemodynamic responses during laparoscopic surgery. However, the results were found to be contradictory.[18,19] This study was planned to find out the haemodynamic effects of 0.3 mg/kg nalbuphine administered before creation of pneumoperitoneum in patients undergoing laparoscopic surgeries.

2. Materials and Methods

This double blinded randomized controlled pilot study was undertaken after taking approval from the Institutional Ethical Committee-Human Research (Letter no- IEC-HR/2017/32/14). The trial was registered at ctri.nic.in before enrolling the patients (CTRI No-CTRI/2017/12/010818).

A total of 80 patients (40 in each group) of either sex, belonging to ASA physical status I/II between 18 and 60 years scheduled to undergo elective laparoscopic surgery were included. Patients having history of allergy to opioids, uncontrolled hypertension, ischemic heart disease, conduction defects, compromised renal/hepatic/neuronal functions, pregnant and lactating women, endocrine disease e.g. hyper and hypothyroidism, on medications like calcium channel blockers, beta blockers, magnesium sulphate were excluded from the study. Patients in whom the laparoscopic procedure was converted to open procedure and in whom the duration of pneumoperitoneum exceeded 90 min were also excluded from the final analysis.

A detailed pre-anaesthetic check-up was done. All patients were advised to remain nil per orally 8 hours prior to the scheduled surgery. Tablet Alprazolam 0.25 mg was administered on the night before surgery. On arrival to the operating room, monitoring of all patients for electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP) (Systolic, diastolic and mean blood pressure) and arterial oxygen saturation (SpO_2) was started and their baseline pre-operative values were recorded. After securing an intravenous access, ringer's lactate was started. Anaesthesia was induced with morphine 0.1mg/kg IV and propofol 2-2.5 mg/kg IV. Vecuronium 0.1 mg/kg IV was given to facilitate intubation. After adequate muscle relaxation, trachea was intubated using an appropriately sized cuffed endotracheal tube. Anaesthesia was maintained with a mixture of O_2 33% with N_2O 66% and isoflurane between 1-1.2 MAC. Ventilation was adjusted to maintain an end tidal carbon dioxide (EtCO2) between 35-40 mmHg. Intermittent top up doses of vecuronium were given as per the requirement.

Patients were allocated to one of the two groups using a computer generated random number table.

Group N (n=40): Patients received nalbuphine 0.3 mg/kg diluted to 10 ml with normal saline slowly 5 min after intubation

Group S (n=40): Patients received normal saline 10 ml slowly 5 min after intubation

Test drug was prepared by an anaesthesiologist not involved in the study. The patient as well as the anaesthesiologist observing the haemodynamic parameters were blinded to the group allocation. After 5 min of test drug administration the surgeons were allowed to proceed for the creation of pneumoperitoneum.

Haemodynamic parameters including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded at the time of giving the test drug (Td), creation of pneumoperitoneum (Tpp), at 5, 10, 15, 30, 45, 60, 75, 90 min after pneumoperitoneum, at the time of deflation of pneumoperitoneum (Tdef) and after extubation (Tex).

Rest of the course of general anaesthesia was as per standard protocol. At the end of surgery pneumoperitoneum was deflated and residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg IV and trachea was extubated. Incision time, time of creation and deflation of pneumoperitoneum, extubation time were noted.

Intra operative hypertension, defined as increase in systolic BP (SBP) by more than 20% of the preoperative value, was treated by increasing the concentration of isoflurane up to a maximum 2% w/v. Intra operative hypotension, defined as decrease in SBP by more than 20% of the preoperative value or SBP <90 mmHg, was initially managed by giving fast IV fluids and/or mephentermine 6 mg IV. In the event of bradycardia (HR <50/min), atropine 0.6 mg I.V was given. All these events were recorded.

Postoperatively, the HR, MAP, SBP, DBP, arterial oxygen saturation (SpO2), Visual Analogue Score (VAS) for pain were assessed and recorded every 30 min till 2 hours. Rescue analgesia in the form of paracetamol 1 gm IV was given when VAS ≥3. Sedation was measured using Ramsay sedation scale (1-Patient is anxious and agitated or restless or both, 2- Patient is co-operative, oriented and tranquil, 3-Patient respond to commands only, 4-Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5-Patient exhibit a sluggish response to light glabellar tap or loud auditory stimulus, 6- Patient exhibit no response). Side effects like hypotension, bradycardia, nausea, vomiting, shivering or any other effect reported by the patient were recorded and treated appropriately.

At the time of planning this study, there was no other research which had studied the effect of nalbuphine on

haemodynamic response to pneumoperitoneum. Sample size was calculated based on a previous study on hemodynamic parameters during pneumoperitoneum, a mean arterial pressure of 108.65±10.97 mmHg and 100.85±12.375 mmHg was observed with or without dexmedetomidine.[20] To estimate the same difference in mean arterial pressure after creation of pneumoperitoneum at 80% power and a error at 5% a sample size of 35 patients in each group was required. To account for 10% dropouts 40 patients were studied in each group.

Statistical analysis was parameters using SPSS v. 20.0. One-time measured parameters like demographic profile, important time points, maximum intraabdominal pressure were analysed using Student's t-test. Repeated measure ANOVA was applied to compare within-group and between-group haemodynamic parameters. Chi square/Fisher's exact test was applied to compare the side effects. Visual analogue scale and Ramsay Sedation Score was analysed using Mann-Whitney Test for between-group analysis and using Friedman Test for within-group comparison. A p-value less than 0.05 was taken as significant.

3. Observations and Results

A total of 89 patients were assessed for eligibility. Five out of these did not meet the inclusion criteria and four patients did not give consent to participate. So, a total of 80 patients were randomly allocated to two groups (n=40 in each group). One patient in group S was excluded as the procedure was converted to open surgery. In group N, the duration of pneumoperitoneum exceeded 90 min in two patients and in one patient the procedure was converted to open surgery. So a total of 76 patients (39 in group S and 37 in group N) were analysed (Diagram 1).

The demographic data of the patients of both groups is presented inTable 1. Important time points and maximum intra-abdominal pressures are given in Table 2. Both the groups were comparable.

The haemodynamic variables were comparable between the two groups at all the time points during the intra-operative period and at the time of extubation (Figures 1, 2 and 3). The postoperative HR, SBP, DBP, MAP and oxygen saturation were also comparable between the two groups.

The RSS and VAS score are shown in Table 3. Twenty two patients in group S and 13 patients in group N required rescue analgesia (p=0.063). In group S, 19 patient were given first rescue analgesia in immediate (0min) postoperative period whereas in three patients it was given after 30min in postoperative period. In group N, nine patient were given first rescue analgesia in immediate (0min) postoperative period whereas in three patients it was given after 30min and in one patient after 60min in postoperative period. The requirement of rescue analgesic was comparable in both the groups in initial 2 hr postoperatively.

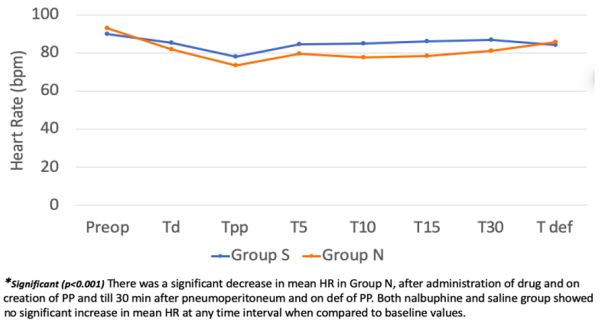

Fig. 1: Intraoperative heart rate (bpm) at various time points

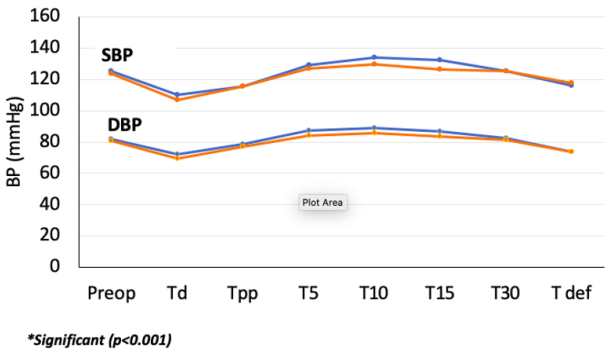

Fig. 2: Intraoperative SBP and DBP at various time points

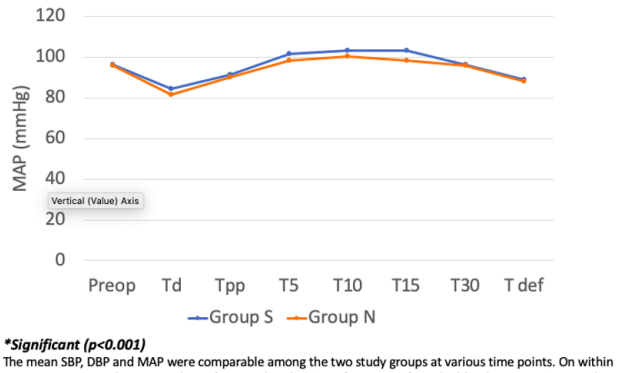

Fig. 3: Intraoperative MAP at various time points

The incidence of intraoperative and postoperative complications was comparable in the two groups. One patient in group N developed bronchospasm and one patient in group S developed arrhythmia at the time of creation of pneumoperitoneum. Bronchospasm was managed by increasing the depth of anaesthesia. Arrhythmia was managed by reducing the rate of insufflation of carbon dioxide.

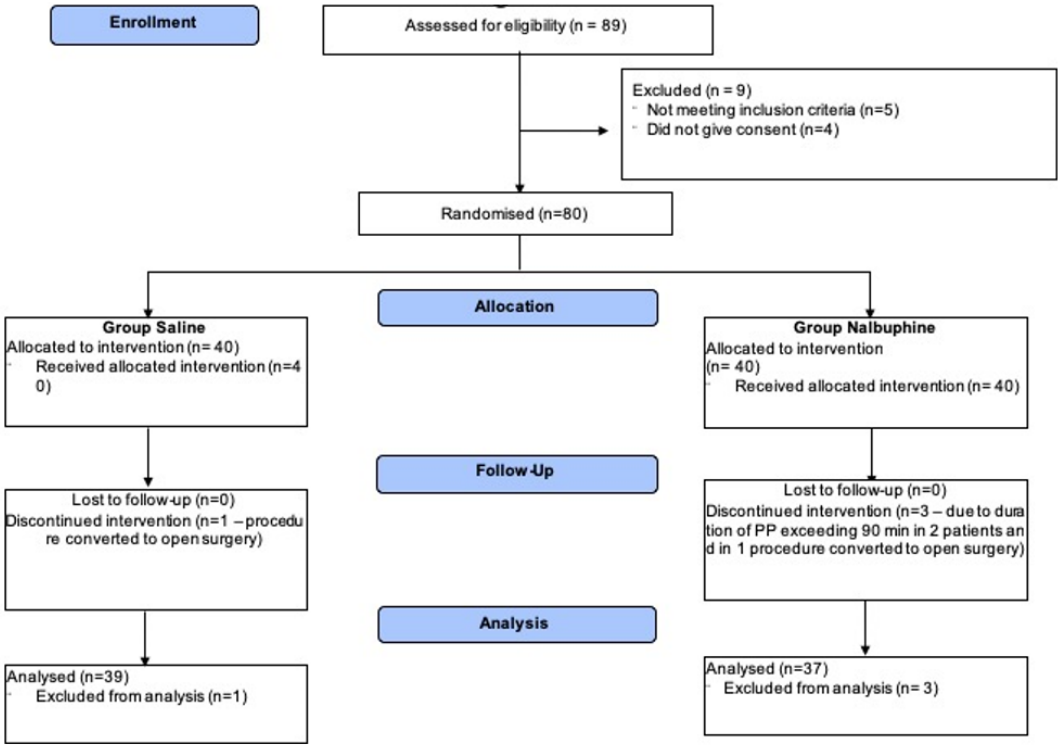

Diagram 1:

Table 1: Demographic profile

Parameters	Group S (n=39)	Group N (n=37)	P-value
Age (yrs)*	34.9 ± 9.8	38.1 ± 11.1	0.189
Body Wt. (Kg)*	57.0 ± 11.6	57.3 ± 11.0	0.901
F:M#	38:1	37:0	1.000
ASA Grade (I:II)#	36:3	33:4	

*values are expressed as mean±SD, #expressed as a ratio; p<0.05 - Significant

Table 2: Important time points and maximum intra-abdominal pressure

Parameters	Group S (n=39)	Group N (n=37)	P-value
Incision time (min)	10.8 ± 4.3	9.8 ± 2.3	0.198
Creation of pneumoperitoneum (min)	17.8 ± 5.9	16.1 ± 4.6	0.175
Deflation time (min)	73.5 ± 19.6	72.4 ± 16.4	0.795
Duration of pneumoperitoneum (min)	57.3 ± 17.7	56.3 ± 15.5	0.792
Extubation time (min)	89.8 ± 22.7	88.3 ± 17.6	0.754
Maximum intra-abdominal pressure (mm Hg)	13.9 ± 0.6	14.0 ± 0.7	0.386

Values are expressed as mean±SD, *p<0.05 - Significant

Table 3: Post-operative sedation and pain score

	Ramsay Sedation Score			Visual Analog Score		
Time	Group S	Group N	p-value	Group S	Group N	P-value
0 min	2 [1-3]	3 [2-4]	0.002*	3 [0-5]	0 [0-2.5]	0.002*
30 min	2 [2-2]	2 [2-2]	0.382	2 [2-3]	1 [0-2]	0.004*
60 min	2 [2-2]	2 [2-2]	0.282	2 [0-2]	0 [0-2]	0.262
90 min	2 [1-2]	2 [1-2]	0.806	1 [0-2]	1 [0-2]	0.662
120 min	2 [1-2]	1 [1-2]	0.384	1 [0-2]	1 [0-2]	0.920

Values are expressed as score, *p<0.05 - Significant

Table 4: Incidence of side effects in the intraoperative and post-operative period

Side effects	Group S(n=39)	Group N(n=37)	P-value
Hypotension	9 (23.1%)	13 (35.1%)	0.247
Hypertension	3 (7.7%)	5 (13.5%)	0.475
Bradycardia	7 (17.9%)	4 (10.8%)	0.377
Shivering	2 (5.1%)	5(13.5%)	0.256
Nausea and vomiting	12(30.8%)	13(35.1%)	0.686

Values are expressed as number (percentage), p<0.05 - Significant

4. Discussion

The results of this randomised controlled study showed that nalbuphine 0.3 mg/kg i.v was not better than saline in controlling hemodynamic responses to pneumoperitoneum. At the time of and after the creation of pneumoperitoneum the blood pressure started rising in both the groups but the rise was more sustained in saline group. At the time of deflation and extubation the blood pressure was comparable between the two groups. The side effect profile was also similar in the two groups. Postoperative sedation was slightly more in the immediate post-operative period in nalbuphine group but the patients were arousable on commands. Post-operative pain score was significantly lower in nalbuphine group till the first 30 min with lesser number of patients demanding rescue analgesia within the first two postoperative hours.

According to previous studies, smaller dose of nalbuphine (0.1 mg/kg) may be associated with a decrease in heart rate during intubation and pneumoperitoneum.[21] However, most of the other studies which have used nalbuphine (0.2-0.3 mg/kg) have reported it to be efficacious in suppressing the heart rate.[14–16] In study by Rekhi et al. they found nalbuphine (0.2mg/kg) effective in obtunding hemodynamic response to pneumoperitoneum, whereas Vidhya et al. found the same dose less effective.[18,19] In our study, we found that heart rate did not increase at the time of creation of pneumoperitoneum or at any subsequent time points in both the groups. This may be attributed to the use of a balanced technique of anaesthesia for all the patients. The average IAP was between 13-15 mm Hg in saline group and between 12-15 mm Hg in nalbuphine group.

In the study by Mishra et al, the mean blood pressure decreased after the administration of nalbuphine and increased subsequently during surgery till 40 min after pneumoperitoneum.[21] Nalbuphine (0.3 mg/kg) is effective in suppressing the blood pressure in response to intubation response.[15,16] In our study, the arterial blood pressure was comparable among the two groups.

The sedative effect of nalbuphine has been reported in literature.[15,22] In our study also patients who received nalbuphine were more sedated but arousable. Postoperative oxygen saturation was also maintained. Madhu et al. reported a longer duration of sedation (up to 6hrs) with nalbuphine contrary to our finding of shorter duration of sedation for the first 30 min only.[22]

Post-operative pain score was significantly lower in nalbuphine group till the first 30 min with lesser number of patients demanding rescue analgesia within the first 2 hr postoperatively. The requirement of additional analgesic after inj. PCM administration was also less in nalbuphine group. This finding was similar to many other studies. (Sadafule et al, Apte et al, Sharma et al, Madhu S et al.).[16,22,23] The incidence of side-effects like shivering, nausea and vomiting was also not increased with the use of nalbuphine. Our results are similar to previous studies.[9–11]

The present study had a few limitations. The hemodynamic response to pneumoperitoneum beyond 30 min could not be analysed as most of the surgeries were completed within this time. Secondly, a balanced anesthesia technique including the use of opioid, intravenous induction and maintenance with inhalation anesthetic was used to provide anaesthesia, which may have resulted in less hemodynamic perturbations to pneumoperitoneum in nalbuphine as well as in saline group. We did not use invasive hemodynamic monitoring which is more reliable to study the hemodynamic changes. Another limitation was that we did not do a quantitative analysis of stress markers. The study involved ASA I and II patients, so the results may not be applicable to patients with ASA III and IV physical status.

Based on the above results we conclude that nalbuphine provides stable hemodynamics with better analgesia for first 30min in postoperative period in ASA I and II adults undergoing laparoscopic procedures under balanced general anaesthesia. Further, studies in patients with cardiac compromise or uncontrolled hypertension are recommended to find out the efficacy of nalbuphine for suppressing the hemodynamic response to pneumoperitoneum in this subgroup of patients. The use of invasive hemodynamic monitoring and stress hormone analysis may also be incorporated in future studies.

5. Source of Funding

None.

6. Conflict of Interest

None.

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