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Original Article

Anaesthesia Section

Clinical Evaluation of Analgesic Efficacy and Safety of IV Nalbuphine versus IV Butorphanol in Patients Undergoing Tympanoplasty: A Randomised Clinical Study

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ABSTRACT

Introduction: Middle Ear Surgeries (MESs) are generally performed using local anaesthesia under sedation. Butorphanol and nalbuphine both are well-known synthetic opioid with agonist-antagonist characteristics. However, no reports present a direct comparison of the analgesic efficacy of these two drugs.

Aim: To evaluate analgesic efficacy of intravenous butorphanol versus intravenous nalbuphine during Monitored Anaesthesia Care (MAC) in patients undergoing tympanoplasty.

Materials and Methods: This randomised clinical trial was conducted at the Department of Anaesthesiology, School of Medicine, D.Y. Patil Deemed to be University, Mumbai, Maharashtra India, from March 2018 to March 2021. Total 112 adult patients, undergoing tympanoplasty, were randomly allocated into two groups. Group N received 0.2 mg/kg nalbuphine intravenous (i.v.) and group B received i.v. 0.02 mg/kg butorphanol. The patients were then evaluated for analgesic efficacy, sedation, blood pressure, Mean Arterial Pressure (MAP), Heart Rate (HR), Respiratory Rate (RR), blood oxygen levels (SpO_2), Visual Analogue Scale (VAS) Score, need for intraoperative rescue sedation/analgesia, duration of action and side-effects.

Results: A significant difference was observed in the patients' responses to needle prick, where only 8 (13.3%) subjects gave a vocal response in group N versus 22 (36.6%) in group B. A significant difference in the mean time of onset of pain amongst both the group was recorded (3.16±1.38 hours in group N and 2.63±1.19 hours in group B). A significant difference was also recorded in the mean VAS at 15th (p-value=0.012) and 30th min (p-value=0.017). Only 7 patients (11.6%) from group N, and 12 patients (20%) from group B required rescue agent (0.5 mcg/kg/hour dexmedetomidine injection and 75 mg diclofenac sodium injection intravenous).

Conclusion: Both 0.2 mg/kg nalbuphine and 0.2 mg/kg butorphanolprovide satisfactory results in terms of analgesic efficacy, sedation, haemodynamic and respiratory parameters, albeit, nalbuphine can be coined to be superior in terms of response to pin prick and duration of action.

Keywords: Anaesthesia, Blood pressure, Intravenous, Monitored anaesthesia care, Respiratory rate

INTRODUCTION

Monitored Anaesthesia Care (MAC) is qualified by American Society of Anaesthesiology (ASA) as a strategic procedure for undergoing local anaesthesia using analgesia alongwith sedation [1]. Various ear procedures can benefit from MAC, which provides appropriate sedation and analgesia without respiratory depression [2]. Owing to the number of advantages during the procedure, including minimal intraoperative bleeding, feasibility to test hearing, and maintaining facial nerve integrity makes local anaesthesia a popular choice for middle ear surgeries. Claustrophobia, drilling noise, and head and neck position manipulations are common causes of patient discomfort [3]. During procedures under MAC, anaesthetic drugs are administered with the objective of offering anxiolysis, sedation and analgesia ensuring rapid recovery without any adverse effects. Local anaesthetic and lengthy immobilisation during surgery necessitate the use of systemic painkillers, which are commonly used to alleviate discomfort. Sedative-hypnotic drugs are used to reduce anxiety and provide intraoperative amnesia thereby making procedures more bearable to the patients and allowing them to relax. Opioids, benzodiazepines, alpha-2 agonists and propofol, are commonly used anaesthetics for sedation and pain relief during middle ear surgery [4-8].

Butorphanol is a synthetic opioid with agonist-antagonist characteristics that is related to levorphanol chemically. It serves as a kappa receptor agonist and mu receptor antagonist that provides excellent analgesia while limiting respiratory depression. Butorphanol has a rapid onset of action (1-2 minutes) with elimination half-life of 2-3 hours. Butorphanol is metabolised by hydroxylation and N-dealkylation reactions to yield hydroxy butorphanol and norbutorphanol with no reported pharmacological consequence. Butorphanol was reported to exhibit some side-effects like nausea, vomiting, dysphoria and respiratory depression and was thus, supplemented with fentanyl 1-2 mcg/kg i.v. as part of balanced anaesthesia [9].

Nalbuphine is lipid soluble opioid with similar agonist-antagonist action as that of butorphanol albeit structurally related to oxymorphone [10]. Along with the rapid rate of clearance, it is reported to exhibit quick onset of action postintravenous injections i.e. 2-3 minutes in comparison to butorphanol (1-2 minutes). Nalbuphine is also less likely to cause side-effects such as excessive sedation, pruritis, urinary retention and respiratory depression. There have been plethora of reports comparing and differentiating the efficacies of various opioids but limited data is available to compare the analgesic efficacy of nalbuphine and butorphanol [11-13]. These reports reveal the superior analgesic efficacy of nalbuphine and butorphanol with better safety profile in separate studies when compared to different analgesic agents.

Thus, the aim of the present study was to evaluate analgesic efficacy of intravenous butorphanol versus intravenous nalbuphine during MAC in patients undergoing tympanoplasty. The study primarily evaluated response to needle prick and onset of pain as a primary outcome. Further, the secondary parameters were haemodynamic changes, sedation, and adverse effects of intravenous butorphanol and nalbuphine administration.

MATERIALS AND METHODS

This randomised clinical trial was conducted at the Department of Anaesthesiology, School of Medicine, D.Y. Patil Deemed to be University, Mumbai, Maharashtra India, from March 2018 to March 2021. The Institutional Ethics Committee had approved the study (IEC Ref No: DYP/IEC/01-010/2019). The purpose, rationale of the study as well as role of the participants were explained to all the patients in the study while obtaining written informed consent, after which the patients were enrolled in the study. Further, an information sheet related to the project work was also given to all the participating patients.

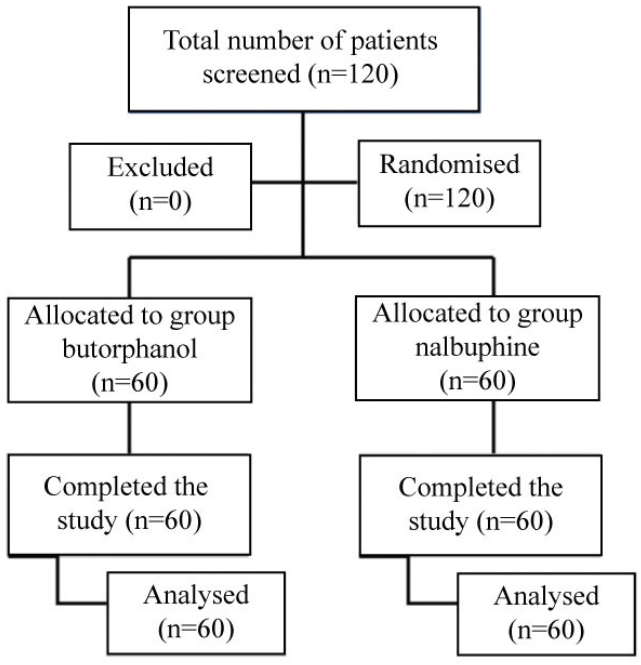
Sample size calculation: Medcalc version 12.0.3 was used for calculation of the sample size guided by: α error=5% (confidence level=95%), β error=5% (power of the test=95%). A total sample size of 54, divided into two equal groups, was found to be sufficient to conduct the study. Finally, a total of 120 subjects were enrolled in the study.

Inclusion criteria: Patients within age group of 18-50 years, undergoing elective tympanoplasty surgery, and classified as ASA grade I and ASA grade II were included in the study.

Exclusion criteria: Patients on other opioids, sedatives and psychiatry medications or with a history of alcoholism, drug allergy and history of respiratory problems were excluded from the study.

The study population included 120 patients, randomly allocated into one of the two groups with 60 subjects each, using randomisation table obtained from Rando software 1.2 [Table/Fig-1].

- Group N (n=60): Received 0.2 mg/kg nalbuphine injection
- Group B (n=60): Received 0.02 mg/kg butorphanol injection



[Table/Fig-1]: Consolidated Standards of Reporting Trials (CONSORT) diagram representing the flow of study.

Preoperative Assessment

Careful preoperative anaesthetic check-up was carried out in all patients fulfilling the inclusion criteria. A detailed history was taken, and thorough physical examination was done a day prior to the surgery. All patients were kept nil per oral for eight hours prior to the scheduled surgery. The Visual Analogue Scale (VAS) pain scoring system was explained to all the patients prior to the surgery. On the day of surgery, patients were brought to the operation theatre, intravenous line was secured with 20 G peripheral intravenous cannula. Standard monitors were attached and the baseline parameters were recorded. Premedication was given with 4 mcg/kg glycopyrrolate and 4 mg ondansetron injection intravenously. Further, group N received 0.2 mg/kg nalbuphine injection whereas group B (n=60) received 0.02 mg/kg butorphanol injection. After 10 minutes, response to needle prick given with 26-gauge needle was noted. Response in terms of no pain or tolerable pain was noted as adequate analgesia whereas response as behavioural changes, vocal response or strong grimacing was considered as inadequate analgesia [14]. Further Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), MAP, Heart Rate (HR), Respiratory Rate (RR), Oxygen saturation levels (SpO_2), VAS Score were noted at 0 mins (baseline) and after every 15 minutes post sedation till the end of surgery.

Data collection intraoperatively

- Ramsay Sedation Scale (RSS) was noted as Ramsay 1-6 at 15 minutes interval [15].
- Intraoperative discomforts like intense ear noise, headache, neck pain, backache, positional discomfort, nasal and upper lip itching, claustrophobia, earache as complained by the patient were noted.
- Rescue analgesia was administered to patients who displayed signs of inadequate analgesia i.e. pinprick response as behavioural changes, vocal response or strong grimacing. A 0.5 mcg/kg/hour dexmedetomidine injection and 75 mg diclofenac sodium injection i.v. was used as the rescue agents. Dexmedetomidine was used as a rescue agent for anxiolysis, sedation and analgesia whereas diclofenac sodium was used only as rescue analgesic agent. Injection dexmedetomidine infusion was started at 0.5 mcg/kg/hour directly as the direct maintenance dose and injection diclofenac sodium 75 mg was given as slow intravenous. Since an opioid analgesic was already given in the form of study drug (butorphanol or nalbuphine), dexmedetomidine was preferred.
- Duration of first onset of pain (postsurgery) was noted as complained by patient.

STATISTICAL ANALYSIS

The mean values for the vital parameters, onset of action and ordinal data amongst the group was statistically analysed using unpaired t-test. The data are presented as Mean±SD. VAS and RSS score was compared for differences in the two groups using Mann-Whitney 'U' t-test. Response to needle prick was compared using Chi-square test. Repeat measures Analysis Of Variance (ANOVA) was used for analysis of all measurement data (vitals) and scores (VAS and RSS) with treatment group as the main factor and time as repeat measure with age (years), sex, weight and ASA class as covariates. All testing was done using two-sided tests with alpha 0.05. Data analysis was done using windows based 'MedCalc Statistical Software' version 19.0.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2019). A p-value <0.05 was considered to be statistically significant.

RESULTS

The demographic data suggest a par distribution of the participants in both the groups on the basis of gender, mean age, weight, and ASA grade [Table/Fig-2]. Overall, 50% from group N and 25% of group B showed no response to needle prick. Total 22% and 23% subjects from group N and B, respectively, displayed tolerable response. Vocal response was evident in 8% subjects of group N and 22% of group B participants. This difference in percent of subjects amongst both the groups was revealed to be statistically significant [Table/Fig-2]. On the basis of results obtained from response to needle prick, nalbuphine was found to be more promising than butorphanol.

Preoperative baseline parameters such as SBP, DBP, MAP, SpO_2 and RR were recorded in both the groups. The mean of all parameters of group N at baseline was found to be at par and

Demographic parameters	Group N (n, %)	Group B (n, %)	p-value
Gender			
Male	27 (45%)	26 (43.3%)	0.854
Female	33 (55%)	34 (56.7%)	
Age (years) (Mean±SD)	31.58±10.9	32.16±9.16	0.375
Weight (kg) (Mean±SD)	56.26±9.4	56.08±8.9	0.456
American Society of Anaesthesiologists' (ASA) grade			
Class I	35 (58.3%)	38 (63.3%)	0.575
Class II	25 (41.7%)	22 (36.7%)	
Response to needle prick			
No response	30 (50%)	15 (25%)	0.003
Tolerable	22 (36.7%)	23 (38.3%)	
Vocal response	8 (13.3%)	22 (36.6%)	

[Table/Fig-2]: Demographics of the participants and their response to the needle prick.
p-value <0.05 was considered as statistically significant

statistically non significant when compared to the mean values of the same parameters in group B [Table/Fig-3]. Mean onset of pain (in hours) was recorded to be more in group N (3.16±1.38) than group B (2.63±1.19).

Baseline parameters	Group N (Mean±SD)	Group B (Mean±SD)	p-values
SBP (mmHg)	122.6±13.79	119.93±12.91	0.276
DBP (mmHg)	74.77±10.07	73.43±11.33	0.497
MAP (mmHg)	90.71±7.40	88.93±9.28	0.248
HR (per minute)	77.23±8.65	78.03±9.73	0.635
SpO_2 (%)	98.3±1.92	98.6±1.26	0.467
RR (per minute)	17.08±2.06	17.37±2.17	0.464
Onset of pain (hrs)	3.16±1.38	2.63±1.19	0.027

[Table/Fig-3]: Preoperative baseline parameters in both the groups.
p-value <0.05 was considered as statistically significant

[Table/Fig-4-6] represents mean SBP, DBP and MAP scores recorded at various time points postsurgery in both the groups. The mean difference in SBP, DBP and MAP of both the groups at all the time points was found to be statistically non significant. Also, there was no significant difference in mean change of all parameters from the baseline value in both the groups.

Time points (mins)	Group N (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	101.9±22.43	105.9±18.85	0.289
15	119.8±13.11	120.0±14.01	0.930
30	128.4±27.20	129.9±30.67	0.775
45	115.8±12.47	113.7±12.45	0.366
60	113.7±11.42	112.4±9.46	0.504
75	112.3±11.64	110.1±11.06	0.306
90	113.9±10.13	112.4±9.69	0.419
105	120.8±18.90	118.8±18.57	0.547
120	119.4±13.80	116.0±11.85	0.152

[Table/Fig-4]: Mean Systolic Blood Pressure (mmHg) recorded at various time points postsurgery in both the groups.
p-value <0.05 was considered as statistically significant

Time points (mins)	Group N (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	87.68±16.79	88.33±18.74	0.842
15	76.75±11.73	73.48±11.81	0.131
30	74.88±14.63	75.08±11.16	0.933
45	73.72±12.46	73.37±11.52	0.873
60	73.98±11.36	72.27±11.99	0.422
75	74.53±13.02	73.30±13.44	0.611
90	73.27±12.24	73.35±13.05	0.971
105	75.29±12.78	73.23±12.31	0.373
120	73.52±12.88	70.60±12.88	0.217

[Table/Fig-5]: Mean Diastolic Blood Pressure (mmHg) recorded at various time points postsurgery in both the groups.
p-value <0.05 was considered as statistically significant

[Table/Fig-7-9] represents mean Heart Rate (HR), SpO_2 and Respiratory Rate (RR) recorded at various time points postsurgery in both the groups. The mean difference in HR, SpO_2 and RR of both the groups at all the time points was found to be statistically non significant except for 15th min in case of HR (p-value <0.05). Likewise, there was no significant difference in mean change of all parameters from the baseline value in both the groups except for the 15 min in case of HR.

Time points (mins)	Group N (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	92.43±12.42	94.21±14.68	0.475
15	90.70±8.29	89.01±9.19	0.291
30	92.72±12.96	93.42±12.0	0.763
45	87.76±9.79	86.76±9.37	0.573
60	87.52±8.89	85.46±9.28	0.220
75	87.13±9.85	85.59±9.66	0.391
90	86.82±8.57	86.39±9.59	0.798
105	89.65±12.0	88.43±10.7	0.560
120	88.64±10.56	85.67±10.7	0.132

[Table/Fig-6]: Mean mean arterial pressure (mmHg) recorded at various time points postsurgery in both the groups.
p-value <0.05 was considered as statistically significant

Time points (mins)	Group N (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	76.63±12.5	79.07±12.1	0.284
15	77.50±9.38	73.87±10.5	0.048
30	80.10±9.80	80.55±11.0	0.814
45	77.78±10.7	76.73±9.20	0.567
60	77.15±7.97	78.03±9.77	0.588
75	78.20±15.8	75.63±12.7	0.330
90	74.82±14.0	72.67±13.5	0.394
105	74.38±16.6	72.70±21.5	0.632
120	72.82±6.70	73.45±8.11	0.642

[Table/Fig-7]: Mean heart rate (per minute) recorded at various time points postsurgery in both the groups.
p-value <0.05 was considered as statistically significant

Time points (mins)	Group N (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	99.38±0.76	99.40±0.79	0.906
15	99.50±0.65	99.50±0.62	1.000
30	99.78±0.42	99.77±0.43	0.829
45	99.82±0.39	99.78±0.42	0.651
60	99.95±0.22	99.90±0.30	0.302
75	99.95±0.22	99.93±0.25	0.700
90	99.95±0.22	99.93±0.25	0.700
105	100±0.00	100±0.00	1.000
120	100±0.00	100±0.00	1.000

[Table/Fig-8]: Mean SpO_2 recorded at various time points postsurgery in both the groups.
p-value <0.05 was considered as statistically significant

The VAS score for intent to treat was recorded. A significant difference in the mean value was observed at 15th and 30th min time point for

Time points (mins)	Group N (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	17.08±2.06	17.36±2.17	0.284
15	14.15±1.49	14.08±1.49	0.807
30	13.85±1.29	13.88±1.47	0.895
45	13.55±1.14	13.68±1.22	0.539
60	13.46±1.19	13.5±1.18	0.878
75	13.55±1.17	13.63±1.22	0.703
90	13.48±1.22	13.6±1.16	0.594
105	13.6± 1.21	13.58±1.07	0.936
120	13.55±1.18	13.61±1.15	0.755

[Table/Fig-9]: Mean RR recorded at various time points postsurgery in both the groups.
p-value <0.05 was considered as statistically significant

VAS scores. A significant difference was also observed in the mean RSS value of both groups specifically at 15th min. Rest of the data remained non significant when compared to the other group [Table/Fig-10,11]. The mean change of VAS score from baseline was also found to be significantly different at these time points.

Time points (mins)	VAS (0-10) (Intent to treat)		
	Group N (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	5.10±1.28	4.95±1.14	0.500
15	2.85±0.63	3.23±1.01	0.012
30	2.41±0.53	2.65±0.65	0.017
45	1.73±0.82	1.85±0.87	0.22
60	1.57±0.65	1.58±0.62	0.886
75	1.25±0.44	1.28±0.45	0.683
90	1.17±0.38	1.13±0.34	0.613
105	1.10±0.30	1.07±0.25	0.513
120	1.03±0.18	1.00±0.00	0.156

[Table/Fig-10]: Mean VAS score recorded at various time points postsurgery in both the groups.
p-value <0.05 was considered as statistically significant

Time points (mins)	Group N (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	4.32±0.66	4.22±0.86	0.521
15	4.25±0.68	4.00±0.69	0.048
30	4.00±0.55	3.92±0.56	0.414
45	4.00±0.96	3.90±0.97	0.571
60	4.12±1.06	3.82±1.10	0.130
75	4.03±0.96	3.90±0.97	0.450
90	4.02±0.79	3.92±0.85	0.506
105	3.93±0.78	3.87±0.87	0.660
120	3.80±0.78	3.68±0.78	0.393

[Table/Fig-11]: Mean RSS recorded at various time points postsurgery in both the groups.
p-value <0.05 was considered as statistically significant

Further the patients showing need for rescue analgesic was recorded with parallel monitoring of any adverse events in both the groups. Only 7 patients (11.6%) from group N and 12 patients (20%) from group B required the rescue agent. Total 41 patients in group N and 22 patients in group B had nausea and vomiting, the difference of which was found to be extremely statistically significant (p-value <0.001). Total 17 and 37 patients of group N and B, respectively did not report any adverse event whereas itching was noted in two patients who received nalbuphine and one patient who received butorphanol. There was not a single case of respiratory depression in both the groups [Table/Fig-12].

Variables	Group N (n, %)	Group B (n, %)	p-value
Rescue required	7 (11.66%)	12 (20%)	0.211
Rescue not required	53 (88.33%)	48 (80%)	
No adverse effects	17 (28.3%)	37 (61.7%)	0.001
Nausea/Vomiting	41 (68.3%)	22 (36.7%)	
Itching	2 (3.3%)	1 (1.7%)	

[Table/Fig-12]: Need for rescue analgesic and adverse effects.

DISCUSSION

More effective pain-relieving drugs have become accessible to the world in the last few decades owing to our superior understanding about physiology of pain but still postoperative pain is not adequately addressed. Opioids are the primary treatment for postsurgical pain and associated under utilisation of opioids in postoperative conditions is possible for a variety of reasons, including a lack of understanding about appropriate dose range and action time, apprehension over side-effects, and their addictive potential. For managing postoperative pain, opioid agonist-antagonist drugs have proven to be efficient and promising [16]. Thus, the study attempted to evaluate analgesic efficacy of intravenous butorphanol versus intravenous nalbuphine during MAC in patients undergoing tympanoplasty.

In the present study, 86.6% and 63.3% patients in group N and B, respectively, had adequate analgesia whereas 13.4% patients in group N and 36.7% patients in group B had inadequate analgesia. A significant difference was seen amongst the group when patients were evaluated for response to needle prick. The data indicates that nalbuphine showed better analgesia effect.

These results corroborate with the previously published works [17,18]. Another report concluded that the analgesic and sedative effects of butorphanol adequately modified the pain perception (VAS ≤30 mm) by patients for the jugular cannulation as compared to placebo group [19]. A comparative study between midazolam and butorphanol reported that almost all patients in both the groups perceived needle pricks of local anaesthetic injection as mild discomfort [20].

A study compared changes in pulse rate, SBP and DBP, SpO_2, and ECG intraoperatively between nalbuphine and pentazocine at 5 minutes after giving drug and 15 minutes interval thereafter. No significant changes were noted in this study between the two groups [14]. A similar observation of non significant difference in both groups of our study was recorded when assessed for SBP, DBP, MAP, SpO_2 and RR. As opposed to this observation, a significant difference in HR at 15th minute was revealed followed by the mean change of HR from the baseline value at 15th minute.This might be attributed to the sympatholytic, vagotonic and baroreflex sensitivity reducing effect of analgesic agent. A study reported a significant fall from baseline in butorphanol and dexmedetomidine group as compared to patients in group dexmedetomidine (p-value <0.05). After 20 mins, there was greater fall in HR and MAP with no depreciation in SpO_2 [21]. A significant fall in HR and MAP from baseline in group nalbuphine with dexmedetomidine as compared to group dexmedetomidine (p-value <0.05) is also established [22]. A different study, comparing butorphanol to placebo, showed that there was significant lower oxygen saturation in butorphanol group [19].

The present data suggests a significant difference in the mean value of both the groups as well as mean change from baseline at 15th and 30th min time point for both VAS scores thereby presenting nalbuphine as a better candidate in pain management in comparison to butorphanol. This is comparable to other studies where nalbuphine exhibited better pain control in comparison to tramadoland dexmedetomidine groups separately [22,23]. On the contrary, a study supported butorphanol premedication to exhibit better pain control than placebo group [19]. A study observed mean RSS more in nalbuphine and dexmedetomidine group as compared to dexmedetomidine alone (p-value <0.001) [21]. Whereas, other

group of researchers, Panjabi DG and Tank PR, did not observe any significant difference in fentanyl and nalbuphine groups even though patients sedated were higher in number in nalbuphine group [23].

In the present study, 7 patients (11.66%) in group N with 12 (20%) in group B required rescue analgesia and the difference remained statistically non significant. Other reports have revealed four patients in dexmedetomidine group and none in group dexmedetomidine and butorphanol who required rescue analgesia [21]. A comparative study mentioned that 42 patients in group dexmedetomidine and eight patients in dexmedetomidine and nalbuphine group demanded analgesia [22].

In the present study, the mean onset of pain was more in group N as compared to group B suggesting longer duration of action of nalbuphine. This observation is in agreement with other reports suggesting prolonged action of nalbuphine over fentanyl and tramadol in separate studies [23,24]. Also, reports presenting nausea and vomiting cases in patients administered with nalbuphine are available which is evident in our study as well [12,24]. Butorphanol groups as well are reported to cause nausea and vomiting [19,25].

Limitation(s)

Limitations of the study encompasses sedation assessment by Ramsay sedation score due to unavailability of BIS monitoring. Further, frequent mobilisation of the patient from Operating Room to the Recovery Room and wards hampered the assessment of sedation score.

CONCLUSION(S)

The analgesic efficacy of intravenous nalbuphine is better in providing pain relief with longer duration of action than butorphanol. It has the advantage of postoperative sedation owing to its longer duration of action. Also, due to high incidence of nausea and vomiting seen in nalbuphine, it is necessary to administer antiemetics to avoid patient discomfort. On the other hand, intravenous butorphanol has the advantage of being haemodynamically superior to intravenous nalbuphine. Existing clinical and laboratory evidence indicate that nalbuphine may be an advantageous addition to a practitioner's repertoire of opioids.

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