Original Article

Comparison of hemodynamic responses to nasal intubation in cancer patients receiving opioid-free general anesthesia versus standard regimen

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Abstract

Background and Aims: Nasotracheal intubation evokes greater hemodynamic responses than oral intubation. We compared the heart rate (HR) and mean arterial pressure (MAP) responses following nasal intubation during opioid-free anesthesia (OFA) using intravenous lignocaine versus standard regimen using morphine in cancer patients undergoing tumor resection.

Material and Methods: This randomized, double-blinded study was conducted in 84 adults. Group A received lidocaine bolus 1.5 mg/kg over 10 min followed by infusion of 1 mg/kg/h. Group B received morphine 0.2mg/kg bolus over 10 min followed by infusion of 2mg/h. Protocols for induction and intubation were similar.

Results: Mean HR and MAP at preinduction, immediately after induction, and at 1, 3, and 5 min after intubation were comparable in groups A and B. Intragroup comparison of preinduction HR with subsequent values in group A showed that the HR values at 1,3, and 5 min after intubation were significantly higher than the preinduction value. HR after induction was comparable. Intragroup analysis in group B showed that preinduction HR was comparable with HR after induction and at 3 and 5 min after intubation. HR at 1 min was significantly higher. Intragroup analysis in group A showed that the MAP values were significantly lower than the preinduction value after induction and at 1,3, and 5 min after intubation. In group B, MAP was significantly lower than the preinduction value after induction and at 3 and 5 min after intubation, with the value being comparable at 1 min.

Conclusion: OFA with lignocaine bolus followed by infusion, as well as morphine did not attenuate the HR responses to nasal intubation in cancer patients. However, both techniques effectively blunted the MAP response.

Keywords: Hemodynamic, lignocaine, morphine, nasal intubation, opioid-free anesthesia

Introduction

Nasotracheal intubation may evoke greater hemodynamic responses than oral intubation secondary to additional nasal and nasopharyngeal stimulation with possibly longer duration of laryngoscopy. Due to concerns of intraoperative opioids favoring metastatic spread during resection of malignant tumors, opioid-free anesthesia (OFA) has emerged as a promising strategy to avoid or minimize opioid consumption. Though bolus intravenous (IV) lignocaine is a well-documented method to blunt the stress response to intubation, in most of the published data, it has been used along with opioids.[1-3]The perioperative analgesic properties and better patient outcome following IV lignocaine in OFA are documented.[4] However, the hemodynamic response to nasal intubation during OFA is an unexplored area.

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The primary objective of the present study was to compare the heart rate (HR) response following nasal intubation with opioid-free general anesthesia using IV lignocaine versus standard regimen using morphine in patients undergoing major head and neck surgeries. The secondary objective was to compare the mean arterial pressure (MAP) response to nasal intubation in these patients.

Material and Methods

This randomized, double-blinded trial was conducted after obtaining approval from the ethics committee (IEC-AIMS-2023-ANES-002 dated 01/20/2023) and informed consent from 84 adult patients. The study was registered in the Clinical Trail Registry India (CTRI/2023/02/063462).

Patients aged 18–70 years, of American Society of Anesthesiologists physical status (ASA PS) 2–3, having head and neck malignancies and undergoing tumor resection surgeries requiring nasal intubation were included in the study. Those with basal HR <60/min, patients on beta-blockers, those having cardiac arrhythmias, heart blocks, congestive heart failure, liver disorders with aspartate aminotransferase/alanine transaminase >2–3 times normal, or renal diseases with estimated glomerular filtration rate <60ml/min/1.73m^2, and those with hypersensitivity to lignocaine or amide-type local anesthetics were excluded.

As there were no previous studies published, we conducted a pilot study with HR at 1 min after nasal intubation as the primary objective in 20 patients who were divided into two equal groups. Group A received lidocaine bolus 1.5 mg/kg over 10 min followed by an infusion 1 mg/kg/h, and group B received morphine 0.2mg/kg bolus over 10 min followed by an infusion 2mg/h. Based on the mean and standard deviation of HR obtained from group A (97.7 ± 12.38) and group B (83.9 ± 20.66) with 80% power and 95% confidence interval, the minimum sample size calculated was 42 per group. Therefore, we conducted our study in 84 patients.

All patients in this study were orally premedicated with metoclopramide10 mg and alprazolam 0.5 mg on the night before surgery after a thorough preanesthetic evaluation. All patients were kept nil per oral 6 h for solids and 2 h for clear fluids. There were two groups of patients: group A received lignocaine bolus 1.5 mg/kg over 10 min followed by an infusion of lignocaine 1 mg/kg/h, while group B received morphine 0.2mg/kg bolus over 10 min followed by an infusion of morphine 2mg/h. Patients were randomized using computer-generated random sequence of numbers. Allocation concealment was done using sequentially numbered, opaque, sealed envelopes.

In the operation theater, on the day of surgery, two IV cannulas were placed and Ringer lactate was started at a rate of 10 ml/kg body weight/h. Preinduction monitors like electrocardiogram, noninvasive blood pressure monitor, and pulse oximeter were attached. The nostril that was more patent was identified and decongested with oxymetazoline drops.

Patients in both groups were preoxygenated, and they received midazolam 2mg and glycopyrrolate 0.2mg IV, followed by propofol 1.5–2mg/kg till loss of response to verbal commands. After ensuring mask ventilation, suxamethonium 2mg/kg was given. After 1 min, laryngoscopy was done and patients were nasally intubated through the decongested nostril after application of a dollop of 2% lignocaine jelly with 6.5 and 7.0-mm nasal Ring–Adair–Elwyn tube for females and males, respectively. Correct tracheal placement of the tube was confirmed by auscultation and appearance of regular square wave end-tidal carbon dioxide waveforms. Then, vecuronium 0.1mg/kg was given and anesthesia was maintained with end-tidal isoflurane 1%–1.5% in air oxygen mixture (1:1). HR and MAP before induction, after induction, and at 1,3, and 5 min after intubation were noted. The number of attempts at intubation, use of Magill's forceps or external neck manipulation during intubation, and time to intubate were also documented. All intubations were performed by anesthetists with more than 5 years of experience in nasal intubation and management of difficult airway.

Any increase in HR or MAP >20% from the baseline was managed with IV propofol bolus 0.5mg/kg and by increasing end-tidal isoflurane to 1.5%–2%. Hypotension was defined as a drop in MAP of >20% from baseline, which was treated with a 250 ml IV fluid bolus, followed by phenylephrine or ephedrine, if there was no response. Bradycardia was managed with IV atropine. Interventions (propofol bolus, increasing isoflurane, use of ephedrine, atropine, or phenylephrine), and incidence of arrhythmias, if any, were documented.

The patient and the outcome assessor were blinded to the test drugs. However, the intubating anesthetist was aware of the drug and dose being administered, so that the patient safety was not compromised. Drug preparation as well as the rates of infusion during bolus and subsequent slow infusion of test drugs were calculated and instructed by the intubating anesthesiologist. The syringes were labeled as test drug only. All the data were documented by a junior resident who was unaware of the type of drug being used.

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 20.0 software (SPSS Inc., Chicago, IL, USA). For presentation of categorical variables, frequency and percentage were used, while mean and standard deviation were used for numerical variables. Kolmogorov–Smirnov one-sample test was used to check the normality of the data. To test the statistical significance of the difference in the mean values of HR and MAP between the two groups, independent sample *t*-test was used and Levene's test was used to test the equality of variance between the two groups. To test the statistical significance of the difference in the proportion of categorical variables between the two groups, Chi-square test was used and for an expected cell count less than five, *P* value corresponding to Yate's correction was taken. Paired sample *t*-test was used to test the statistical significance of the change in each of the hemodynamic parameters from baseline. A *P* value of < 0.05 was considered to be statistically significant.

Results

Data of 84 patients were analyzed [Figure 1]. Mean age, weight, distribution of gender, and ASA PS were comparable [Table 1]. The attempts at intubation and time taken for intubation did not show any statistically significant difference between the groups [Table 1]. The need for increasing isoflurane, use of ephedrine, phenylephrine, use of Magill's forceps, and requirement of external neck manipulation for intubation were comparable in both the groups. The mean HR and MAP at baseline, immediately after induction, and at 1, 3, and 5 min after intubation were comparable in group A and group B ($P > 0.05$) [Tables 2 and 3].

Intragroup comparison of preinduction HR in group A with subsequent HR values at different time points showed a comparable HR after induction. However, HR at 1,3, and 5 min after intubation was significantly higher than the preinduction value. Intragroup analysis of preinduction HR with subsequent values in group B showed that HR after induction and at 3 and 5 min after intubation were comparable. But HR at 1 min was significantly higher than the preinduction value ($P < 0.05$) [Table 4].

Intragroup analysis showed that in group A, the MAP values were significantly lower than the preinduction value at different time points like after induction and at 1,3, and 5 min after intubation. In group B, the MAP values recorded after induction and at 3 and 5 min after intubation were significantly lower than the preinduction value. At 1 min after intubation, MAP was comparable with the preinduction value [Table 5].

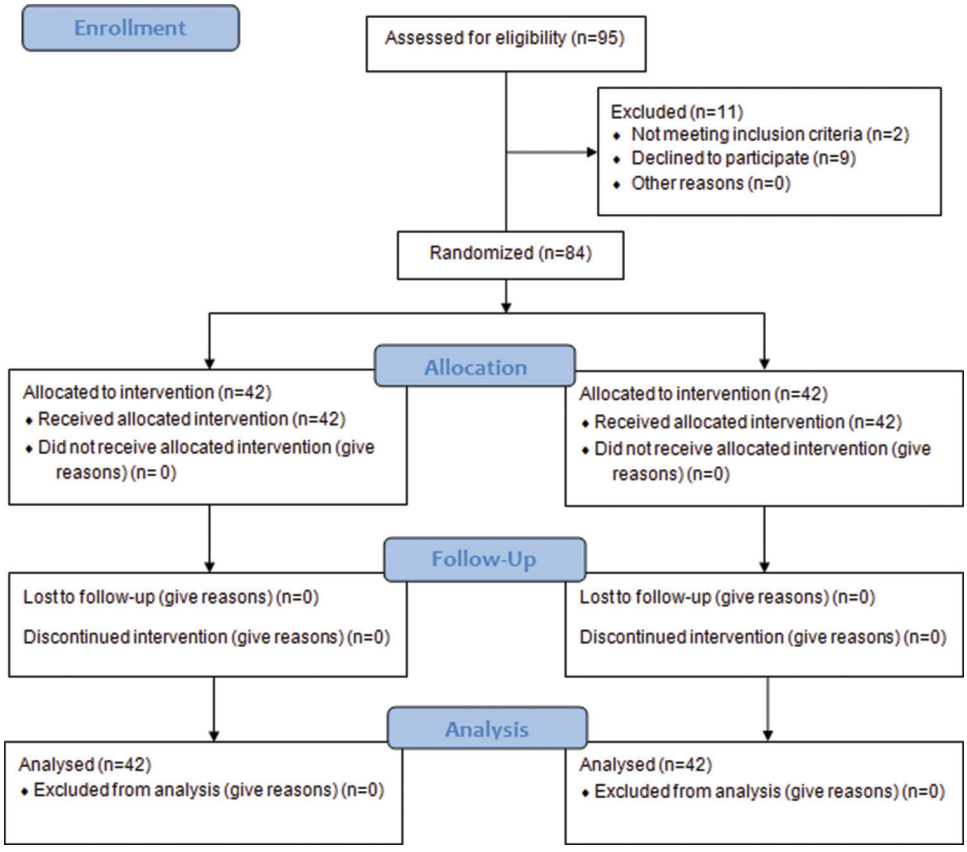

Figure 1: CONSORT flow diagram

Discussion

Surgeries for oral malignancy are usually complex and require nasal endotracheal intubation for better surgical access. Since many recent research works have implied the role of opioids in metastatic spread during cancer surgeries,[5] the practice of OFA has started gaining momentum. However, in the absence of opioids, more stringent measures need to be adopted to attenuate the intraoperative hemodynamic responses, especially in those patients requiring nasotracheal intubation.

Table 1: Comparison of demographic data, ASA PS, number of attempts at intubation, and time to intubate

	Group A		Group B		
Variables	**Mean**	**SD**	**Mean**	**SD**	***P***
Age in years	47.93	16.37	51.93	15.49	0.254
Weight in kg	67.4	12.7	65.2	14.1	0.462
Variables	***n***	**%**	***n***	**%**	***P***
Male	30	71.43	28	66.67	0.637
Female	12	28.57	14	33.33	
ASA PS 2	20	47.6	22	52.4	0.663
ASA PS 3	22	52.4	20	47.6	
One attempt at intubation	34	81	34	81	1.000
Two attempts at intubation	8	19	8	19	
Variables	**Mean**	**SD**	**Mean**	**SD**	***P***
Time to intubate in seconds	60.36	56.100	44.88	45.277	0.394

ASA PS=American Society of Anesthesiologists physical status, SD=standard deviation

Table 2: Comparison of mean heart rate between groups

Time	**Group A**		**Group B**		***P***
	Mean	**SD**	**Mean**	**SD**	
Preinduction	83.8	16.0	84.9	14.8	0.735
After induction	85.4	15.5	82.2	12	0.317
1 min after intubation	92.0	14.9	89.6	14.3	0.448
3 min after intubation	92.4	14.5	89.0	14.8	0.293
5 min after intubation	89.4	13.6	86.4	15.5	0.345

SD=standard deviation

Table 3: Comparison of mean MAP between groups

Time	**Group A**		**Group B**		***P***
	Mean	**SD**	**Mean**	**SD**	
Preinduction	106.74	16.876	108.29	16.371	0.671
After induction	96.71	16.748	94.12	16.383	0.475
1 min after intubation	99.83	23.244	103.52	21.204	0.449
3 min after intubation	92.9	16.341	93.9	15.600	0.775
5 min after intubation	87.26	14.539	89.12	12.611	0.533

MAP=mean arterial pressure, SD=standard deviation

OFA is essentially the practice of conduct of general anesthesia without the use of opioids. It is postulated that use of intraoperative opioids weakens the cell-mediated immunity and could be associated with an increased tumor recurrence rate after cancer surgery.[6,7] After establishing these adverse effects of opioids, there is now a change in the unwarranted usage of opioids.[8] Though opioids are postulated to aid in tumor progression, it is also known that the stress of surgery and pain can also produce the same effects,[9] stressing on the importance of providing optimum analgesia during OFA. The suppressant action of local anesthetics on tumor spread during surgery has been investigated, and it was found that lidocaine might exhibit some antitumor effect. This antiproliferative action could be through the epidermal growth factor receptor.[10]

In our study, we observed that IV lignocaine was not effective in blunting HR response to intubation. Though multiple previous trials[11-15] have shown similar findings, the major difference of our study was that our patients underwent nasal intubation, whereas the patients of many previous trials were intubated orally. Either fentanyl[14,16-18] or morphine[15,19] was used along with lidocaine in these trials, whereas in our study, opioids were not used in the OFA group. Majority of the previous studies have used IV lignocaine as bolus, which was administered at different time points before intubation,[11,14,17,18,20,21] while we used a bolus followed by an infusion.

On intragroup analysis of changes in the mean arterial blood pressure from baseline within each group, we observed that the blood pressure responses were effectively attenuated by both morphine and IV lignocaine. Similar observations were made in many previous trials as well.[14,22]

Though various drugs like dexmedetomidine,[23] clonidine,[24,25] and low-dose ketamine[25] are being used to provide OFA during cancer surgeries, we opted for lignocaine due to its additional protective effect in preventing metastatic spread

Table 4: Intragroup comparison of preinduction HR with subsequent values in each group

	Group A			Group B		
Time	**MeanHR**	**SD**	***P***	**MeanHR**	**SD**	***P***
Preinduction	83.89	16.080		84.93	14.75	
After induction	85.36	15.498	0.352	82.21	12.99	0.152
1 min after intubation	92.05	14.949	0.000	89.62	14.25	0.047
3 min after intubation	92.38	14.547	0.001	89.00	14.75	0.121
5 min after intubation	89.40	13.617	0.031	86.38	15.49	0.590

HR=heart rate, SD=standard deviation

Table 5: Intragroup comparison of preinduction MAP with subsequent values in each group

	Group A			Group B		
Time	**Mean MAP**	**SD**	***P***	**Mean MAP**	**SD**	***P***
Preinduction	106.74	16.87		108.29	16.37	
After induction	96.71	16.74	0.016	94.12	16.38	0.000
1 min after intubation	99.83	23.24	0.028	103.52	21.20	0.099
3 min after intubation	92.90	16.34	0.000	93.90	15.60	0.000
5 min after intubation	87.26	14.53	0.000	89.12	12.61	0.000

MAP=mean arterial pressure, SD=standard deviation

during such surgeries.[26] We used lignocaine in the dose of 1.5 mg/kg as used in many previous trials.[11,13,22,27,28] Higher doses like 2 mg/kg as bolus[1] and higher rates of infusion like 2 and 3 mg/kg/h[27,29] were used in some previous trials, as opposed to 1 mg/kg/h used in our study. We used a lower dose of lignocaine to reduce the risk of drug toxicity, since we did not monitor plasma levels of the drug intraoperatively. Moreover, a pilot study with a higher dose of lignocaine did not show any added advantage in terms of intraoperative analgesia or in hemodynamic parameters.

The major limitation of our study was that though doses of lignocaine bolus, infusion, and morphine bolus were calculated as per body weight, we used a fixed dose of morphine for infusion, that is, 2mg/h, irrespective of body weight. This might have affected the depth of anesthesia and hence the hemodynamic responses to intubation as well. We intubated the patients 10 min following morphine bolus. As IV morphine takes 15–20 min for its peak action, if we had given the drug earlier, we could have obtained optimal drug action during intubation. There was a lack of assessment of plasma concentration of lignocaine, and intraoperative depth of anesthesia was assessed with hemodynamic parameters only. Use of bispectral index (BIS) monitoring would have provided more reliable data on the depth of anesthesia.

The observation of our study that morphine and IV lignocaine produce similar effects in attenuating blood pressure response to nasal intubation implies that opioids can be avoided in cancer surgeries without much concern regarding hemodynamic responses to intubation. However, further evaluation is needed to determine whether it provides adequate intraoperative analgesia.

Conclusions

It is concluded that opioid-free general anesthesia using IV lignocaine bolus followed by an infusion, as well as IV morphine did not attenuate the HR responses to laryngoscopy and nasal intubation in head and neck cancer patients. However, both techniques were effective in blunting the MAP response to nasal intubation.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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