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COMPARATIVE STUDY OF DEXMEDETOMIDINE AND FENTANYL CITRATEAS BOLUS DOSE FOR STRESS ATTENUATION DURING NASAL ENDOTRACHEAL INTUBATION IN ONCOLOGICAL PATIENTS

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ABSTRACT

Background: Various pharmacological agents were used to decrease intubation stress response, with their own limitations.Dexmedetomidine - alpha-2 agonist with analgesic action,less hypotension, better heart rate control and no respiratory depression in post intubation phase than fentanyl. We explore the use of non-opioid analgesic drugs toboth to reduce the risk of developing opioid addictionand its side effects. Objective: It was to compare the hemodynamic effect of dexmedetomidine and fentanyl ininduction techniques and the incidence of side effects in patients scheduled for head and neck cancer surgery. Method: In this prospective randomized, double blinded, control study one hundred patients ofASA physical status I &II, aged 18 to 60, MPG I and IIposted for elective head&neck cancer surgery were included.Before induction of anesthesia, patients were randomly divided into two equal groups. Group D received dexmedetomidine (1 µg/kg) and group F received fentanyl (2 µg/kg) over 10 minutesIV. No stimuli in any form allowed for 10 minutes of induction. Hemodynamic data collected till 15 minutes of induction. Result: In group F, heart rate increased following laryngoscopy and endotracheal intubation and returned back to normal after 10 minutes. The attenuation in systolic, diastolic and mean arterial pressure was significantly better in the groupD than the group F. From3rd minute onwards after intubation,hemodynamic values werelower in group D than group F(p < 0.05). Antihypertensive drug requirement was higher in group F (p value < 0.05). Conclusion: Dexmedetomidine (1mcg/kg) is better than fentanyl for maintenance hemodynamic stability following laryngoscopy and nasal intubation and avoids opioid- related adverse effects, tolerance and hyperalgesia.

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INTRODUCTION

Nasotracheal intubation is a common airway management method used for head and neck onco-surgical procedure. It is easier to fix, out of surgical field and airway security through the small diameter of the nasal pathway.The goal of opioid free anesthesia is to rationalize perioperative opioid use by avoiding intraoperative and post- surgical opioids.

Opioids act as the primary agents of antinociception and decrease arousal by acting on receptors at several levels. [1],[2],[3],[4] They decrease the need for sedative-hypnotics during induction and maintenance.[5]

Sympathetic stimulation during laryngoscopy and endotracheal intubation increases the plasma concentration of catecholamine in turn causing tachycardia and hypertension.[6],[7]Stress induced hypertension generally starts before five seconds of laryngoscopy, peaks in 1–2 min and returns to normal levels in 5 min after [8] This response can increase myocardial oxygen demand and may lead to complications in cardiac individuals [9], [10] Various pharmacological agents like nitroglycerine, beta blocker, and opioids were used forhaemodynamic stability for surgical stress of intubation.

The use of opioid-free analgesic techniques has the propensity to decrease its side effects. Alpha-2 receptor agonists such as clonidine and dexmedetomidine have shown promising results in this *context.*[11]

The benefits of dexmedetomidine (alpha-2 agonist) are anxiolytic, sedation, analgesia and better haemodynamic control without any respiratory depression.[12] It decreases intraoperative opioid and volatile anaesthetic requirements for maintenance of anaesthesia as it decreases MAC of volatile anaesthetics by up to 90%.)[13],[14],[15].It has been shown to provide better heart rate control post intubation than fentanyl when used for intravenous induction. [16]

Fentanyl is a synthetic opioid attenuating the cardiovascular response by its action on opioid receptors and also by decreasing sympathetic outflow.[17].Fentanyl is a potent narcotic with rapid onset, short duration of action and when given in a dose of 2 mcg/kg 5 minutes before laryngoscopy attenuates the haemodynamic stress response of endotracheal intubation.

The aim of this study was to compare the effect of opioid-free (using dexmedetomidine and propofol) and opioid-based (using fentanyl and propofol) induction technique on hemodynamic stability.We had studied non-opioid analgesic drug to both eliminate the risk of opioid addiction and related side effects.

Method

This prospective randomized, double blinded control study was done in a tertiary medical cancer collegehospital. The patients were kept informed about the study and consent was obtained. One hundred patients undergoing mandibular resection, radical neck dissection and muscular flap reconstruction elective surgical procedures under general anaesthesia with endotracheal intubation were selected for the study.

Approval of the ethical committee and a written informed consent from all the subjects were obtained.ASA Physical status I and II patients in the age group of 18 to 60, weighing between 35 to 70 kg and with airway of Modified Mallampati Grade I and II scheduled for oral cancer reconstructive surgeries were taken.

During patient examination, the presence or absence of a history of epistaxis, condition of teeth, anesthetic problems (e.g., airway disorders, sinusitis, epistaxis, etc.) identified.Patients with refusal, body mass index >35 kg m ^{2}, pregnant, lactating and menstruating women, hepatic, renal and cardiac insufficiency, DM, history of chronic pain, alcohol or drug abuse, psychiatric disease, allergy, contraindication to any of the study drugs were excluded from study.

After receiving the patient in the operation room before induction of anesthesia, large bore intravenous access was secured and all patients were pre-hydrated with 500ml of Ringer's lactate. The patients were randomly divided into two groups of fifty each using sealed envelope method. Group D received bolus of dexmedetomidine 1mcg/kg IV and group F received Inj. Fentanyl citrate 2mcg/kg over 10 minutes in 10 ml normal saline IV. These solutions of 100 ml and 5 ml were prepared by first anesthesiologist. The second anesthesiologist, who was not aware of the groups, administered the drug and monitored the patients recorded vital parameters. The laryngoscopy and intubation were performed by the third anesthesiologist who was also blinded to the drug given.

Oxymetazoline 2 drops were put at both the nasal cavity, xylocaine 10% spray done in both nose in both the groups.After pre-oxygenation (5 l/min for6 minutes), patients were induced with Inj.Glycopyrolate 0.2mg iv, Inj. Propofol 2.0 mg/kg IV over 30 seconds to all patients in both groups and followed by Inj. Vecuronium 0.1mg/kg body weight after confirming a loss of the eyelash reflex. Patients were ventilated with oxygen: nitrous oxide (50%) for 3 minutes. Before ET tube insertion through the nostril, sufficient water-soluble lubricant (lignocaine jelly) is applied so that the tube can smoothly pass through the nasal cavity.Portex endotracheal tube no 7 for female and no 8 for male was chosen for nasal intubation. No surgical stimulation was allowed for 10 minutes after intubation.

Heart rate less than 20%, blood pressure less than 30 % of baseline values was considered as bradycardia and hypotension respectively. Hemodynamic variables were recorded at baseline and 3rd, 5th,7th, 10th and 15th minute interval to induction till 15 minutes. Hypotension (reduction of MAP >20% from baseline) was treated with IV fluid and/or Inj. Phentermine 6 mg IV bolus, repeated, if necessary, after 5 min.

The primary end point was the ease of achieving adequate hemodynamic stability in form of maintaining mean arterial pressure within the desired range of MAP 60-65mmHg during induction period. The secondary end point was to notice the requirement of additional antihypertensive drug in form of Inj.Nitroglycerine 100mg IV bolus dose. At the end of surgery, muscle relaxant was reversed by neostigmine (0.05 mg/kg) and atropine sulphate (0.01-0.02 mg/kg) IV followed by extubation after taking good regular tidal volume. Then the patient was transferred to the post-operative ward.Www.graphpad.com and MedCalc were used to enter data and statistical analysis. Data were presented as mean ± SD, number, and percent.

Comparison between the two groups wasperformed using unpaired student's t-tests for parametric data, P value less than 0.05 was considered as statistically significant.

Normally distributed data were presented as mean and standard deviation (SD) and analyzed using t-test. Categorical data were presented as number of patients and percentage and analyzed using chi square test.

RESULT

The Intergroup & intergroup comparison of heart rate shown in table no 1.

There was no significant difference in basal heart rate and blood pressure and is given in [Table2,3,4]In group D, the mean heart rate decreased after the administration of study drug and did not rise much above basal levels during or after intubation. In fentanyl group, the mean heart rate increased significantly beyond the basal values following intubation.The mean heart rate returned to basal levels at 3rd minutes in dexmedetomidine group while it was at 7th minutes in fentanyl group. Only one patient developed bradycardia in the dexmedetomidinegroup,which responded well to Inj.Atropine 0.3mg IV bolus.

Table 1
INTRAGROUP & INTERGROUP COMPARISON

TABLE 2 Heart rate changes	**GROUP D**	**GROUP F**	**P VALUE**
BASELINE	80.30 ± 10.12	82.56 ± 10.36	0.2725
INDUCTION	78.30 ± 11.11	80.24 ± 10.96	0.3837
INTUBATION	96.25 ± 12.34	98.25 ± 11.3	0.3977

Table 3 SBP changes	**GROUP D**	**GROUP F**	**P VALUE**
BASELINE	125 ± 17.00	126 ± 16.91	0.7687
INDUCTION	120 ± 16.89	120 ± 16.36	1.00
INTUBATION	146 ± 16.73	144 ± 16.07	0.5435
1 MIN	132 ± 15.01	134 ± 15.83	0.5183
3 MIN	118 ± 13.73	132 ± 14.67	0.0001**
5 MIN	115 ± 12.00	128 ± 14.62	0.0001**
7 MIN	112 ± 11.89	122 ± 13.86	0.0002**
10 MIN	106 ± 10.31	119 ± 13.34	0.0001**
15 MIN	104 ± 09.67	116 ± 12.10	0.0001**

Table 4 DBP changes	**GROUP D**	**GROUP F**	**P VALUE**
BASELINE	84.32 ± 10.97	82.32 ± 10.99	0.3647
INDUCTION	80.62 ± 9.93	79.93 ± 10.61	0.7378
INTUBATION	90.12 ± 9.76	89.94 ± 9.89	0.9272
1 MIN	80.34 ± 8.93	86.64 ± 9.63	0.0010**
3 MIN	78.32 ± 8.01	78.09 ± 8.16	0.0001**
5 MIN	74.31 ± 7.93	77.92 ± 8.47	0.0001**
7 MIN	70.32 ± 7.01	77.54 ± 8.31	0.0001**
10 MIN	68.62 ± 6.97	76.56 ± 7.83	0.0001**
15 MIN	64.62 ± 5.36	75.83 ± 7.62	0.001**

DISCUSSION

This study has showed that there was a significant decrease in HR in Group D at different time intervals during and after nasal intubation compared to baseline parameters (P < 0.001).Airrway maintenance is a challenge in head and neck cancer patients. Hypotension and is usually demanded by the surgeons for better surgical field.

Opioid-free anesthesia as a technique in which no intraoperative opioid is administered via any route, including systemic, neuraxial, or tissue infiltration. The use of opioids in the induction period is associated with respiratory depression, post-operative nausea and vomiting (PONV), pruritus.

'Opioid- paradox': The more the opioids used intraoperatively, the more shall be the requirement postoperatively. This paradoxical phenomenon is due to sensitization of opioid receptor and the tolerance developed which further leads to hyperalgesia. [18]

Jan Paul Mulier in 2012 proposed OFA in obese patients undergoing bariatric surgery and showed improved outcomes.[19]

By including multimodal nonopioid based analgesia, perioperative opioids will no longer be routinely needed as default analgesia. [20] Multimodal analgesic techniques such as use of acetaminophen, pregabalin, nonsteroidal anti-inflammatory drugs, local anesthetics, beta-blockers, dexamethasone either alone or in combination, have been shown to decrease the requirement of opioids intraoperatively.

The ultimate goal is to stop an opioid addiction from developing it from the perioperative period. Unlike opioids, Dexmedetomidine is not associated with significant respiratory depression, PONV, pruritus, constipation, ileus or delirium.[21]

Fentanyl acts on the opioid receptors, mainly μ receptors, for its analgesic action and its ability to reduce sympathetic outflow, it brings about haemodynamic stability. Fentanyl is used routinely as part of general anaesthesia in a dose of 2 mcg/kg and this dose is effective for stress attenuation when given five minutes before laryngoscopy.[22]

Dexmedetomidine, a newer alpha 2 adrenergic agonist, is a suitable agent. It helps in maintaining stable hemodynamics thus reduces blood loss. Dexmedetomidine became agonist of choice, due to its greatest affinity (8 times greater than clonidine). [23]Bradycardia is the major dose limiting side effect and this responds readily to atropine. Premedication with Dexmedetomindine obtunds the autonomic pressure responses due to laryngoscopy and endotracheal intubation when used as an adjuvant to general anesthesia. [24],[25],[26]

Dexmedetomidine, leads to dose-dependent decrease in heart rate and blood pressure. This is due to decrease in central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the brainstem the locus coeruleus.[27]

Several studies have highlighted that the use of dexmedetomidine in a dose of 0.5mcg/kg to 1mcg/kg , dexmedetomidine 0.6mcg/kg, 0.6mcg/kg) [28],2mcg/kg,

[15] 0.5mcg/kg, [29]. 1mcg/kg is effective in obtunding haemodynamic stress response following laryngoscopy and intubation.

Dexmedetomidine useful in blunting the increase in systolic BP preoperatively. [30]In our study, there is less fluctuation in SBP and DBP and MAP in group D in comparison to group F with p-value <0.05 after intubation. Similar findings were observed by Patel CR (34) et al., who found lesser increase in SBP (6% vs 23%), DBP (7% Vs 20%) after intubation with dexmedetomidine 1 go/kg as compared to fentanyl 2 μg/kg when given as loading dose prior to induction.

Vaswani JP, showed the effect of Dexmedetomidine Vs. Fentanyl on hemodynamic response in patients undergoing elective laparoscopic surgery and noticed that there was no statically difference between both groups regarding PACU discharge time.

In 2015, Mondal et al. compared the low dose of dexmedetomidine (1 μcg/kg) with a higher dose of fentanyl (2 μcg/kg), and they found that this higher dose of fentanyl caused more airway obstruction and consequent oxygen desaturation; however, still dexmedetomidine provides a more desirable tolerance to intubation in the form of less cough scores.In our study same dose regime,we reported fentanyl induced cough in 2 pts,respiratory depression(Resp rate 10/min) in one patient only.Keniya VM et al., who reported that with 1 μg/kg of dexmedetomidine, more chance of bradycardia. The cases of bradycardia (HR, <50) two cases in group D while none in group Fin our study.

In the present study, heart rate was significantly decreased in the group D when compared to group F, there was statistically significant reduction in heart rate from 3rd min after intubation in the group D. In groupF, heart rate increased following laryngoscopy

and endotracheal intubation and returned back to normal only after 7th minutes. The attenuation in systolic, diastolic and mean arterial pressure was significantly better in the group D than the group F. This finding was also observed by [31]

Laha et al.concluded that administration of dexmedetomidine not only attenuates the rise in mean heart rate, systolic blood pressure after intubation at 1, 2, 3 and 5 min but also significantly reduces the requirement of adjuvant anaesthetic drugs. The dose of dexmedetomidine used and the results were similar to our study.

Lawrence et al., performed a study with a single dose of 2mcg/kg of dexmedetomidine before induction of anaesthesia and observed that it attenuated the hemodynamic response to both intubation and extubation.Bradycardia was observed at the 1st and 5th min after administration and this might have been due to bolus administration of a large dose when compared to our study(1mcg/kg). In our study, bradycardia was noticed in only 2 patients (4%) (p value>0.05).

One of the limitations of our study is that we did not measure plasma catecholamine levels, which was not feasible in our institute.

Preclinical evidence and uncontrolled studies suggested that opioids can increase cancer recurrence by inhibiting the function of natural killer cells and by their effect on angiogenesis and tumor cell signaling pathways. [32] A large (n = 2,108) multicenter randomized controlled trial, concluded that there was insufficient evidence to recommend any particular analgesic technique for patients undergoing cancer surgery.[33] So, we should focus on minimizing opioid use with known, safe, feasible options, adapted to individual patient needs. In best interest of patient safety, we had compared opioid free anesthesia to routine anesthesia protocol.

CONCLUSION

"Concluded that bolus injection of dexmedetomidine 1mcg/kg given intravenously over 10 minutes prior to nasal intubation attenuated the pressor response during laryngoscopy and nasal intubation when compared to fentanyl 2mcg/kg."

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