Comparative study of intravenous injection dexmedetomidine and intravenous injection clonidine for attenuation of hemodynamic response during laryngoscopy and intubation

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DOI: https://doi.org/10.33545/26643766.2020.v3.i3a.141

Abstract

Background: Laryngoscopy and tracheal intubation after induction of anaesthesia are nearly always associated with hemodynamic response leading to tachycardia and hypertension which is usually transient and variable. Clonidine and Dexmedetomidine are alpha-2 agonists that can attenuate this pressor response. The present study was designed to evaluate and compare the efficacy of intravenous clonidine in dose of 1.5 mcg/kg and dexmedetomidine in dose of 1mcg/kg in blunting the intubation response.

Methods: 100 adult patients of ASA I/II scheduled for elective surgery under general anaesthesia were randomly divided into two groups C and D. Group C received Inj clonidine 1.5 mcg/kg over 10 minutes and group D received Inj dexmedetomidine 1mcg/kg over 10 minutes. General anaesthesia was administered using standard technique and intubation was done by an expert anaesthesiologist. Laryngoscopy duration more than 15 seconds were excluded from study. Heart rate, systolic, diastolic and mean blood pressure were recorded in pre-operative room (baseline), at start of study drug infusion, at 1,5,10 min of start of drug infusion, after induction, immediately and 1, 3, 5, 10 and 15 min after intubation. An increase in heart rate and/or mean blood pressure by >20% above baseline values during observation period was taken to indicate a positive intubation response.

Results: After propofol induction there was more fall in heart rate in patients of dexmedetomidine group as compared to clonidine group but with statistically non-significant difference (p value>0.05). After laryngoscopy and intubation, hemodynamic variations were more in patients of clonidine group than in dexmedetomidine group with statistically significant difference (p value<0.05).

Keywords: Assess refers to process of the critical analysis and valuation and judgement of the status or quality regarding prevention and home care management of chickenpox in children

Introduction

Endotracheal intubation is the translaryngeal placement of a tube into the trachea via the nose or mouth. It includes laryngoscopy & intubation. The process of laryngoscopy & intubation are noxious stimuli & therefore constitute a period of extreme haemodynamic stress and is associated with intense sympathetic activity marked by tachycardia & hypertension [1, 2]. Normal, healthy person can tolerate this response but in susceptible individuals, this transient sympathetic response can evoke life threatening conditions. Recently Alpha-2 adrenergic agonists i.e Clonidine [3] and Dexmedetomidine [4] have been used for attenuating the sympathetic response. Clonidine and dexmedetomidine are alpha-2 agonist with beneficial effect on the hemodynamic response to laryngoscopy and intubation. A decrease in blood pressure is noted with both as a consequence of alpha-2 mediated central sympathetic effect and decreased peripheral nor epinephrine release. Dexmedetomidine is a more potent alpha-2 agonist with relatively high ratio of alpha-2: alpha-1 activity as compared to clonidine (1620:1 vs 220:1) and thus lesser cardiovascular side effects related to alpha 1 activity such as profound hypotension and bradycardia. Its elimination half-life is also shorter as compared to clonidine (2 hours vs 7.4-11.4 hours) suggesting an advantage if used to obtund the brief intubation response.

Thus this study is aimed to compare the efficacy of two alpha adrenergic agonist Clonidine and Dexmedetomidine in attenuating the hemodynamic and pressor response during laryngoscopy and intubation.
Material and Methods
This was a prospective double blind randomised study, conducted after obtaining approval of the study protocol by the Institutional Ethical Committee and written informed consent from each patient. The study was carried out on 100 ASA grade I and II patients aged 18 to 60 years belonging to either gender scheduled for elective surgical procedure under general anaesthesia. They were randomly divided into two study groups consisting of 50 patients each:
Patients with history of uncontrolled hypertension, diabetes, ischemic heart disease, renal or hepatic dysfunction or allergy to any of the drug used were excluded from the study. Those with anticipated difficult airway or requiring more than one attempt were also not included in the study. Also pregnant females and patients requiring emergency surgery were excluded from the study.
Baseline (average of three readings) vital parameters of patients including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and oxygen saturation (SPO2) were recorded in the pre-operative room. After 1 hr patients was taken to the operation theatre and routine standard monitors such as pulse oximetry, electrocardiography (ECG) and non-invasive blood pressure was applied and monitoring was started. An IV line was secured with 18-G venous cannula and Ringer's lactate infusion (6 ml/kg body weight) was started. All the patients were uniformly pre-medicated with IV ondansetron 0.08 mg/kg body weight and glycopyrrolate 0.004 mg/kg body weight, 10 min before induction. The study drugs were premixed to a volume of 10 ml and was presented as coded syringes by anaesthesiologists who was not involved in the study. The patients were blinded to the treatment group and all recordings were performed by an anaesthesiologist blinded to the group allocation, thus the study was made double-blind.
The patients were randomly divided into two equal groups of 50 each. Patient in group C received Clonidine 1.5 mcg/kg over 10 minutes and patients in group D received Dexmedetomidine 1.0 mcg/kg over 10 minutes before induction.
The patients were pre-oxygenated for 3 min after study drug infusion. Induction of anaesthesia was performed with Inj. Propofol 2mg/kg body wt. and Inj. Fentanyl 1 mcg/kg and muscle relaxation was achieved with Inj. Vecuronium 0.1 mg/kg body weight administered IV as per standard protocol. The patient's lungs were ventilated manually with 100% oxygen. Laryngoscopy was done 3 minutes after the administration of vecuronium with Macintosh curved blade 3. Laryngoscopy and intubation was limited to 15-20 sec in all patients, failure to intubate within this period was excluded from this study. Anaesthesia was maintained with 50% N₂O in 50% oxygen and sevoflurane to achieve MAC value 1 and intermittent dose of 0.02 mg/kg body weight vecuronium was used for muscle relaxation and maintenance.
At the end of the surgery residual neuromuscular blockade was reversed with neostigmine 0.05 mg/kg body weight and glycopyrrolate 0.008 mg/kg body weight IV and extubated after adequate recovery and then shifted to anaesthesia recovery room and monitored for complications such as pain, respiratory depression, hypertension, hypotension, bradycardia, drowsiness, rigidity, nausea or vomiting and attended appropriately, rescue treatment was also noted during anaesthesia and recovery.

Outcome Measures
Vital parameters such as HR, SAP, DAP and MAP were recorded at baseline, at start of study drug infusion, at 1, 5, 10 min of start of drug infusion, after induction, immediately and 1, 3, 5, 10 and 15 min after intubation. No surgical intervention was allowed throughout the study period of 15 min. The hemodynamic alterations like increase in MAP and/or HR by value of 20% of baseline was taken as an indicative of an intubation response and decrease in MAP greater than 20% below the baseline value or SAP less than 90 mm of Hg was considered as hypotension and treated primarily by increasing the IV fluid infusion rate, reducing sevoflurane concentration and incremental doses of ephedrine 5 mg bolus IV, if required. Decrease in HR (<50 beats/min) was regarded as bradycardia and treated with Atropine 0.6 mg IV. All observations were noted by a blinded anaesthesiologist.

Statistical Analysis
The statistical analysis was done by using SPSS-20 and data was tabulated in Microsoft excel spreadsheet. Mean and standard deviation was calculated. Chi-square test and Unpaired t test were used to calculate the P value and to establish correlation between study groups. A p value < 0.001 was considered highly significant statistically, a p value < 0.05 was considered significant, whereas a p value > 0.05 was considered insignificant. The analysis was further represented by various line graphs and histogram / bar diagram for comparison of various parameters between the study groups.

Results
The two groups were statistically similar with regards to the demographic characteristics age, gender, body weight and ASA grade. There was no significant intergroup difference from the baseline values and found to be statistically non-significant (p >0.05).

Systolic Blood Pressure
The changes in the SBP and their statistical comparison indicates that though there was decrease in SBP in both groups, measured 1 min and 5 min after drug administration, the difference was not significant. However, 10 min after starting drug infusion and post induction decrease in mean SBP was significant from baseline SBP in the group D as compared to group C and difference was statistically significant with p<0.05. Statistically significant difference was observed between group C and group D during intubation and the subsequent assessments at 1, 3 and 15 min. The attenuation of the SBP was highly significant in group D as compared to that in group C (p<0.001 immediately after intubation, at 1 min and 15 min and p<0.05 at 3 min). Mean SBP difference between both group were comparable at 5 and 10 min after intubation (P>0.05). During laryngoscopy and intubation, in group C mean SBP immediately after intubation was 147.36 ± 7.278, representing significant rise from baseline SBP 129.88 ± 8.085 as compared to group D in which mean SBP immediately after intubation was 122.80 ± 7.835 mmHg representing a decrease from baseline SBP value of 129.84 ± 6.576. In group C mean SBP returned to baseline in 3 minutes after intubation however in group D post intubation mean SBP remained below the baseline value even immediately after intubation and throughout the study period of 15 minutes.
Diastolic Blood Pressure

The changes in the DBP and their statistical comparison indicates that though there was decrease in DBP in both groups, measured 1 min and 5 min after drug administration, the difference was not significant. However, 10 min after drug administration and post induction, group D had a significant decrease in DBP compared to group C ($p<0.001$). A significant ($p<0.001$) difference was observed in mean DBP immediate and 1 min after intubation between group C and group D. The mean DBP immediately after intubation in group D was 74.00 ± 6.020 representing decrease from baseline DBP 80.40 ± 6.154 as compared to group C in which mean DBP was 95.64 ± 3.445, representing rise from baseline DBP 78.96 ± 7.242. Dexametomidine was efficient in attenuation of DBP compared to clonidine at all-time intervals however immediate and after intubation at 1 min changes were highly significant ($p<0.001$) and at 3, 5, 10, 15 min results were comparable ($p>0.05$). Group D, mean DBP value remain below the baseline value throughout the study period of 15 min while in group C, mean DBP returned to baseline value in 3 minutes after intubation and remain below baseline value throughout the rest of study period of 15 minutes.
Mean Arterial Pressure
The MAP value at the start of drug infusion was found to be slightly higher than baseline in both groups C and D and the difference was insignificant in both groups (p>0.05). At 1 and 5 min after start of drug infusion values decreased in both groups but difference was found to be insignificant. However, 10 min after drug infusion and post induction, group D had a statistically significant (p<0.001) decrease inDBP compared to group C. A significant difference was observed after laryngoscopy and intubation, in group C MAP was 112.96 ± 3.779, representing rise from baseline MAP 95.92 ± 6.301 while in group D, MAP was 90.46 ± 5.726 representing decrease from baseline MAP 97.06 ± 5.373. Statistical evaluation between group C and group D showed that immediately after intubation and at 1 min, the MAP changes were highly significant (p<0.001); at 3 min, 5 min, 10 min and 15 min after intubation, mean MAP between both the groups were comparable (p>0.05). In group C, the mean MAP returned to baseline value in 3 minutes after intubation however the mean MAP remained below the baseline value throughout the study period of 15 minutes in group D.

Heart Rate
Significant variations in the HR seen in group C and group D before and after the endotracheal intubation. At 1 min after administration of drug, group D had decreased HR compared to group C where HR increased and statistical difference was found to be significant (p<0.05). Heart rate values at 5 min and 10 min after start of drug infusion and post induction decreased in both group C and group D and the difference was found to be significant (p<0.05). Statistical evaluation between group C and group D showed that HR decreased in both groups but there were significant (p<0.05) changes in HR between the two groups immediately after intubation and throughout the study period of 15 minutes and remained below baseline throughout.
Discussion
Reid and Brace, first described the hemodynamic responses occurring during laryngoscopy and intubation in form of elevated blood pressure, tachyarrhythmia, cough reflex, increased intracranial and intraocular pressure [64]. If no specific measures are taken to attenuate these hemodynamic responses, the heart rate can increase from 26% to 66% depending on the method of induction and arterial blood pressure can increase from 36% to 45%. These responses are transient, variable and may not be significant in otherwise normal individuals but in patients with cardiovascular compromise even these transient changes in hemodynamics can result in potentially harmful effects. Attenuation of such responses is of great importance to decrease the periopeative morbidity and mortality.

Dexmedetomidine and clonidine are α2 adrenergic receptor agonist with unique pharmacological profile of sedation, sympatholysis, analgesia and cardiovascular stability without respiratory depression. Dexmedetomidine is highly selective α2 receptor agonist having 8 times more affinity and α2 selectivity compared to clonidine but has shorter duration of action than clonidine.

Dexmedetomidine is used in intravenous doses ranging from 0.25 to 1 mcg/kg for attenuation of hemodynamic response of intubation. A recent study conducted by Sağroğlu AE, Celik M, Orhon Z, Yüzer S, Sen B compared the clinical effects of two different doses of dexmedetomidine (1 mcg/kg and 0.5 mcg/kg) on hemodynamic responses of tracheal intubation and concluded that Dexmedetomidine in dose of 1mcg/kg was more effective than dexmedetomidine 0.5 mcg/kg². In the present study, the dose of Dexmedetomidine 1 mcg/kg was given as infusion over 10 minutes.

Clonidine was initially used as antihypertensive agent, but now it is increasingly used as premedication for its clinical benefit of sympatholysis, sedation, anaesthetic sparing and hemodynamic stabilizing effects during intubation and surgery. Zalunardo MP et al. has shown that intravenous clonidine was better than oral clonidine in attenuating the pressor response. The effects of clonidine on the hemodynamic parameters are dose related. In the present study 1.5 mcg/kg of intravenous clonidine was used to attenuate the pressor response of laryngoscopy and intubation [6].

A total of 100 patients were recruited in two groups of 50 each. The baseline parameters for demography and hemodynamic variables were matched in two groups. Laryngoscopy and intubation was limited to 15-20 sec in all patients and failure to intubate within this period was excluded from this study. After recording baseline values, patients received intravenous infusion of either inj clonidine or dexmedetomidine over 10 minutes and various parameters were recorded.

In this study, pretreatment with α2-adrenergic agonist dexmedetomidine 1 mcg/kg attenuated the cardiovascular and catecholamine surge responses to laryngoscopy and tracheal intubation after induction of anesthesia and all values remained below the baseline throughout the study period of 15 min. After administration of dexmedetomidine and clonidine before intubation there was a fall in mean HR statistically significant in case of dexmedetomidine at 5.10 min and post induction (p<0.05) as compared to clonidine. During laryngoscopy and intubation and immediately after it, the rise in the HR was seen but it remained below baseline. Statistical evaluation between group C and group D showed that there were significant (p<0.05) changes in HR in between the two groups, immediately after intubation and throughout post intubation period of 15 minutes and Dexmedetomidine was highly effective in attenuating the HR response due to intubation. This finding was in agreement with those of the studies which were done by Arora S, Parikh H in 2014 who concluded that dexmedetomidine in dose of 1 mcg/kg was more effective in attenuating HR response to intubation as it resulted in only 4.7% rise in heart rate from baseline post intubation as compared to clonidine in dose of 1 mcg/kg which resulted in 9.59% rise in heart rate with statistically significant difference (p<0.05) between the two drugs [7].

In our study we observed that SBP, DBP and MAP values increased after intubation from baseline in group C compared to Dexmedetomidine where SBP, DBP and MAP values increased after intubation but remained below baseline and it was found to be statistically significant (p<0.05). During laryngoscopy and intubation, the maximum rise of only by 6%, 8% and 7% in SBP, DBP and MAP values respectively was seen with Dexmedetomidine as compared to clonidine where values of SBP, DBP, MAP increase by 13%, 21% and 17% respectively. Agarwal S, Gupta K, Singh VP, Sharma D, Pandey MN conducted a study with dexmedetomidine and clonidine in dose of 1 mcg/kg intravenously as premedication and observed that SBP, DBP, MAP show hemodynamic variations in form of more increase in patients of clonidine group than in Dexmedetomidine group with statistically significant difference (p value<0.05). In the dexmedetomidine group blood pressure and hemostatic values remain below baseline throughout the study period of 15 min while in the clonidine group, this return of blood pressure and heart rate towards baseline after 3 min [8]. Mondal S, Mondal H, Sarkar R, Rahaman M also observed that clonidine in dose of 2 mcg/kg and dexmedetomidine in dose of 1 mcg/kg significantly attenuate cardiovascular and catecholamine response which was more significant with dexmedetomidine with quicker return to baseline as compared to clonidine [9]. The hemodynamic effects of dexmedetomidine probably resulted from peripheral and central mechanism, α2-adrenoceptor agonists show a biphasic, dose-dependent, blood pressure effect. At low doses, the dominant action of α2-adrenoceptor agonist activation results in reduction of sympathetic tone, mediated by a reduction of norepinephrine release at the neuroeffector junction, and an inhibition of neurotransmission in sympathetic nerves [10]. The net effect of Dexmedetomidine action is a significant reduction in circulating catecholamines with a slight decrease in blood pressure and a modest reduction in HR [11].

The present clinical study concluded that in patients with no drugs to attenuate the sympathetic response to laryngoscopy and intubation, the maximum increase in HR and SBP, DBP were significantly high as compared to pre induction values. Dexmedetomidine significantly attenuate the sympathetic response to laryngoscopy and intubation in dose of 1 mcg/kg with values below baseline throughout and without any significant side effects. Clonidine also reduces the pressor response but it cannot completely attenuate the hemodynamic changes occurring during laryngoscopy and intubation in dose of 1.5 mcg/kg.
Conclusion
The pressor response to laryngoscopy and intubation is a sympathetic reflex phenomenon provoked by stimulation of oro-laryngopharynx and leads to transient and variable tachycardia and hypertension.
Various pharmacological methods such as inhalational agents, lidocaine, narcotic analgesics, topical anaesthetics, vasodilators etc are evaluated to attenuate this pressor response.
The present study compared two alpha-2 agonists i.e, Dexmedetomidine and Clonidine in attenuating the hemodynamic response and from present study we concluded that:
1. Dexmedetomidine at dose of 1µg/kg body weight given IV over a period of 10 minutes prior induction and Clonidine at dose of 1.5 µ/kg body weight IV bolus prior induction were effective in controlling the heart rate after laryngoscopy and intubation.
2. However Dexmedetomidine stands better due to its more effective control of systolic, diastolic and mean arterial pressure after laryngoscopy and intubation without any side effects as compared to clonidine.

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