Comparison of the Relative Efficacy of Fentanyl Premedication and Repeat-dose Propofol in Attenuating the Cardiovascular Response to Endotracheal Intubation.

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SUMMARY

Background: **T**he cardiovascular response evoked by laryngoscopy and endotracheal intubation while causing no harm to majority of patients, could result in fatal consequences, or morbidity, in patients at risk.

Objective: To evaluate the degree of cardiovascular response evoked by laryngoscopy and endotracheal intubation, and compare the effectiveness of repeat-dose propofol and fentanyl premedication in attenuating this cardiovascular response.

Methodology: A total of sixty-nine (69) patients participated in this double-blind, randomized, prospective study. The change in the cardiovascular parameters following endotracheal intubation were evaluated in three groups of patients; Control(Untreated), Repeat-dose propofol and Fentanyl groups. The parameters considered were Heart rate (HR), Systolic arterial pressure (SAP), Diastolic arterial pressure (DAP),Mean arterial pressure (MAP) and Rate-pressure product (RPP).

Results: The untreated group had increase in HR (36.4%), SAP (42.3%), DAP (36.5%), MAP (39.3%), RPP (94.2%) following laryngoscopy and intubation. The fentanyl group had minimal increase in HR (11.6%), SAP (11.64%), DAP (11.42%), MAP (11.35%), RPP (24.6%). Similarly the repeat-dose propofol group had minimal increase in HR (13.6%), SAP (16.63%), DAP (19.5%), MAP (17.2%), RPP (32.8%).

Conclusion: Endotracheal intubation in the untreated group was associated with remarkable increases in all the measured cardiovascular parameters whereas patients in the fentanyl group and repeat-dose propofol groups had significantly less increases in the parameters.

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INTRODUCTION

Laryngoscopy and endotracheal intubation have been known to be associated with tachycardia, increase in blood pressure and sometimes dysrrhythmias[1]. These changes are known as the cardiovascular response to laryngoscopy. The postulation that this phenomenon is a reflex sympatho-adrenal response to stimulation of the upper respiratory tract is supported by the observed concomitant increase in plasma catecholamine levels [2,3] and the absence of the cardiovascular response to laryngoscopy and intubation in patients with thoracolumbar (T1L2) epidural anaesthesia[4]. In anaesthesized patients an average increase of 40–50% in blood pressure and 20% in HR was noted during laryngoscopy and intubation[5] with hypertensive patients showing even higher increases[6].

The cardiovascular response though transient and of little significance in healthy subjects, could have catastrophic consequences in patients with hypertension, Ischaemic heart disease, Pre-eclampsia, Congestive heart failure, intracranial aneurysms and raised intracranial pressure. It is therefore imperative to protect the patients in this risk-group from potential catastrophe by abolishing or attenuating the cardiovascular response to endotracheal intubation.

Intravenous lidocaine has been in common use for this purpose but its efficacy has been challenged by several works[7,8,9]. "Second-dose" Sodium thiopentone[10] has also been credited with limited success. Owing to the reported efficacy of fentanyl premedication[11-14], and repeat-dose propofol[15]; and their relative availability in Nigeria, this study was intended to further verify and compare their efficacy in attenuating the cardiovascular response to laryngoscopy and intubation.

METHODOLOGY

After obtaining approval from the Ethical committee of the hospital, and written consent from the patients, a double-blind, randomized prospective study was carried out on sixty-nine (69) patients between the ages of 12 and 50yrs and of ASA physical status I and II, undergoing gynaecological, maxillofacial, orthopaedic, and general surgical procedures. ASA status III and IV patients, emergency cases, diabetics, hypertensives, cigarette smokers, patients on vasodilator or cardio-depressant drugs and those with history of difficult intubation were excluded from the study.

In the theatre the patients were randomly selected into three groups using a box of colour coded cards. The cards were coloured pink, yellow and grey; each colour twenty three (23) in number and representing either of groups I (control), II (repeat-dose propofol) or III (fentanyl premedication). Each patient was asked to pick a card from the box by balloting. The colour representing each group was known only to the other anaesthetist who assisted in this research. The groups represented by each colour were not revealed to the investigator until the collection of the data was completed. Another assistant

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was responsible for time-keeping and recording of all data in the operating room. Each patient was weighed and routine drugs and equipment check were conducted. Intravenous line was established and monitoring commenced.

Premedication with intravenous glycopyrrolate 5µg/kg was administered to each patient in the theatre, 5 mins before induction of anaesthesia. This anticholinergic premedication was necessitated by the use of suxamethonium chloride for endotracheal intubation. Suxamethonium administration has been associated with bradycardia and asystole, especially when used in conjunction with fentanyl[16,17]. The "RGB Omnicron FT" multichannel monitor was used to monitor HR, SAP, DAP, MAP and Lead II electrocardiogram. The RPP which is an index of myocardial oxygen demand was derived arithmetically in each case later, by the formula; RPP = HR x SAP.

The patients in group I (control) were induced with intravenous propofol 2.5mg/kg and endotracheal intubation facilitated using intravenous suxamethonium chloride 1.5mg/kg. The patients in group II received intravenous propofol 2.5mg/kg for induction, followed by 25% of this induction dose just prior to laryngoscopy. Intubation was similarly facilitated using intravenous suxamethonium chloride 1.5mg/kg. The patients in group III received intravenous fentanyl 4µg/kg as part of premedication 5 mins before induction of anaesthesia. Subsequently, their induction and intubation was facilitated using intravenous propofol 2.5mg/kg and intravenous suxamethonium chloride 1.5mg/kg respectively. In each case the non-invasive monitor was used to directly determine the HR, SAP, DAP, MAP pre-induction, post-induction and post-intubation. The electrocardiogram was also observed for any dysrrhythmia throughout the observation period. The pre-induction (baseline) cardiovascular parameters were taken prior to administration of any drug, including premedicants. The post-induction values were measured 1min after induction of anaesthesia. This was prior to the administration of repeat-dose propofol in group II patients. The parameters were monitored at 60secs (1min),from the commencement of laryngoscopy in each case; and the readings obtained represent the post-intubation values.

Following induction, all patients were ventilated with 100% oxygen using a tight-fitting facemask for a period of 2mins, followed by laryngoscopy and intubation. Laryngoscopy time was taken as the duration from the time the blade of the laryngoscope was advanced beyond the incisors to complete placement of the endotracheal tube, and was measured using a stopwatch. All measured data were recorded immediately on the data form in the theatre. No other anaesthetic agent or adjunct was administered to the patients throughout the period of measurement. Following measurement of the post-intubation parameters, anaesthesia was maintained in all cases with halothane in oxygen as required, while analgesia was provided with either intravenous fentanyl citrate or ketamine hydrochloride. Muscle relaxation was achieved with pancuronium bromide.

Analysis of Results

The cardiovascular response is represented by the difference between the pre-induction and post-intubation cardiovascular parameters. SPSS version 11.0 software was used to determine the mean and standard deviation of the mean of the groups. Comparison of the data was done using the t-test of the software to test for statistical significance; the level of significance being set at value of $P<0.05$. The parameters were also compared among groups. (Tables 4, 5 and 6 show the statistical comparison of the mean cardiovascular parameters of the groups, with the P-values.)

RESULTS

Three of the patients initially recruited did not complete the study. One had failed intubation and was eventually anaesthesized using the LMA, while the other had successful intubation on second attempt. The third patient had rapid desaturation after fentanyl premedication, but prior to induction of anaesthesia. He was discovered to have chest wall rigidity as tight face-mask ventilation with 100% oxygen could neither correct the desaturation nor inflate the lungs in this conscious patient. He was quickly induced with intravenous ketamine hydrochloride (100mg) and endotracheal intubation was facilitated with suxamethonium chloride (100mg). Subsequent ventilation was without any difficulty and routine anaesthesia continued uneventfully. These three did not successfully complete the study and were accordingly excluded from statistical consideration. The table showing patients characteristics (Table 1) reveals similar male: female ratio for all three groups. The mean age distribution was also comparable; 33.77yrs, 35.50yrs and 35.82yrs for groups I, II and III respectively.

Table 2 displays the mean cardiovascular parameters at different times during the study. The pre-induction mean HR in groups I, II and III were 93.41 min^{-1}, 92.41 min^{-1} and 91.64 min^{-1} respectively. After induction (which was preceded by anticholinergic premedication), the mean HR increased by 8.8 min^{-1}, 13.7 min^{-1}, in groups I and II respectively, while in group III the HR decreased by 3.4 min^{-1} compared to baseline values. The SAP, DAP, MAP and RPP were decreased in all three groups after induction of anaesthesia when compared with the baseline obtained in the theatre prior to any premedication. Following endotracheal intubation the mean HR increased to 127.36 min^{-1}, 104.95 min^{-1} and 102.27 min^{-1} in groups I, II and III respectively. The baseline mean RPP was 10,824mmHg min^{-1}, 10,877.6mmHg min^{-1} and 10,903mmHg min^{-1} in groups I, II and III respectively. These increased to 21,020mmHg min^{-1}, 14,447.6mmHg min^{-1} and 13,584.4mmHg min^{-1} following endotracheal intubation. The baseline mean SAP was 115.91mmHg, 118.09mmHg and 119.18mmHg in groups I, II and III respectively. These increased to 164.91mmHg, 137.73mmHg and 133.05mmHg after laryngoscopy and intubation.

Table 3 shows the change in cardiovascular parameters associated with laryngoscopy and intubation. Following intubation the mean HR in group I increased by 33.95 min^{-1} (36.4%), while groups II and III showed increases of 12.54min^{-1} (13.6%) and 10.63 min^{-1} (11.6%) respectively. Following intubation the mean SAP of groups I, II and III increased by 49mmHg (42.3%), 19.6 mmHg (16.6%) and 13.87 mmHg (11.64%)

respectively. The post-intubation mean DAP of groups I, II and III increased by 26.5mmHg (36.5%), 14.77 mmHg (19.5%) and 8.78mmHg (11.42%) respectively. Analysis showed the post-intubation DAP in groups II and III to be significantly different from group I; P = 0.00. The post-intubation DAP in groups II and III were also significantly different from each other; P = 0.04. Following intubation, the mean MAP in groups I, II and III increased by 36mmHg (39.3%), 16.32mmHg (17.2%) and 10.87mmHg (11.35%).

The post-intubation increase in mean RPP was 10196 mmHg min^{-1} (94.2%), 3570mmHg min^{-1} (32.8%), and 2680.6 mmHg min^{-1} (24.6%) in groups I, II and III respectively. The groups of patients treated with fentanyl premedication and repeat-dose propofol exhibited significantly less increase in all the measured cardiovascular parameters. (HR, SAP, DAP, MAP, RPP), compared to the untreated group.

Table 1: Table showing patients characteristics

Group	I	II	III
No. of patients	22	22	22
ASA grade: I	15	18	15
II	7	4	7
Sex (M:F ratio)	12:10	11:11	10:12
Mean age (yr) (+ σ)	33:77 (+ 12.2)	35.50 (+ 12.4)	35.82 (+ 10.5)
Mean weight (kg) (+ σ)	66.95 (+ 12.2)	71.32 (+ 14.1)	72.23 (+ 11.7)
Mean intubation time(sec)	18.9 (+ 5.3)	16.5 (+ 3.9)	19.4 (+ 5.1)

Table 2: Table showing mean cardiovascular parameters .

Cardiovascular parameter	Group I	Group II	Group III
HR(min-1):			
Pre-induction	93.41 (+ 4.8)	92.41 (+ 6.7)	91.64 (+ 5.6)
Post-induction	102.2 (+ 8.0)	106.1 (+ 5.3)	88.2 (+ 9.0)
Post-intubation	127.36 (+ 10.5)	104.95 (+ 7.9)	102.27 (+ 7.2)
SAP (mmHg):			
Pre-induction	115.91 (+ 7.1)	118.09 (+ 8.9)	119.18 (+ 8.2)
Post-induction	109.2 (+ 3.0)	112.4 (+ 5.2)	104.21 (+ 6.0)
Post-intubation	164.91 (+ 7.2)	137.73 (+ 10.9)	133.05 (+ 11.9)
DAP (mmHg):			
Pre-induction	72.64 (+ 5.2)	75.68 (+ 8.9)	76.86 (+ 7.3)
Post-induction	62.31 (+ 6.3)	64.72 (+ 3.6)	56.82 (+ 5.4)
Post-intubation	99.14 (+ 4.1)	90.45 (+ 5.8)	85.64 (+ 8.6)
MAP (mmHg):			
Pre-induction	91.68 (+ 5.3)	94.91 (+7.08)	95.77 (+ 7.1)
Post-induction	76.34 (+ 4.2)	78.39 (+8.4)	70.42 (+ 6.1)
Post-intubation	127.68 (+ 4.6)	111.23 (+ 7.5)	106.64 (+ 9.2)
RPP (mmHg min-1)			
Pre-induction	10824 (+816.6)	10877.6 (+188.8)	10903.8 (+771.7)
Post-induction	11156 (+6024.2)	11880.4 (+644.3)	8976.5 (+1018.6)
Post-intubation	21020 (+2145.2)	14447.6 (+1522.9)	13584.4 (+1338.4)

Table 3: Table showing change in cardiovascular parameters following intubation.

Cardiovascular parameter	Group I	Group II	Group III
HR (min-1):	33.95 (36.4%)	12.54 (13.6%)	10.63 (11.60%)
SAP (mmHg):	49 (42.3%)	19.64 (16.6%)	13.87 (11.64%)
DAP (mmHg):	26.5 (36.5%)	14.77 (19.5%)	8.78 (11.42%)
MAP (mmHg):	36 (39.3%)	16.32 (17.2%)	10.87 (11.35%)
RPP (mmHg min-1):	10196 (94.2%)	3570 (32.8%)	2680.6 (24.6%)

DISCUSSION

In this study, laryngoscopy and endotracheal intubation evoked an increase in HR of 33.95min^{-1} (36.4%), increase in SAP of 49mmHg (42.3%), increase in DAP of 26.5mmHg (36.5%), increase in MAP of 36mmHg (39.3%) and increase in RPP of 10196mmHgmin-1 (94.2%) in the untreated patients. Ebegue[10] had reported a HR increase of 30.9min^{-1}, SAP increase of 37.5mmHg, DAP increase of 42.5mmHg, MAP increase of 42mmHg and RPP increase of 8440.0mmHgmin^{-1} in the untreated patient group. Similarly in the study by Ko and colleagues[18] on the attenuation of the cardiovascular response to tracheal intubation, patients in the untreated group showed HR increase of 39.4%, SAP increase of 33.6%, DAP increase of 43.4% and MAP increase of 38.7%.

The group of patients treated with fentanyl premedication 4g/kg showed effective attenuation of the cardiovascular response with only 11.6%, 11.64%, 11.42%, 11.35% and 24.60% increases with respect to HR, SAP, DAP, MAP and RPP respectively. Ko and colleagues in their study using fentanyl premedication 2g/kg administered 5mins before laryngoscopy found this smaller dose to be equally efficacious; only 14.9%, 6.7% and 11.2% increases in HR, SAP and MAP respectively were noted. They however observed that this same dose administered at 1min and 10mins before laryngoscopy failed to attenuate the response. Right timing of the administration of low-dose fentanyl would thus achieve similar efficacy as poorly-timed high-dose premedication, with less adverse effects. High dose fentanyl provides cardiostability and would prevent the increase in heart rate and blood pressure that is associated with laryngoscopy but may cause worrisome respiratory depression, bradycardia and hypotension or chest wall rigidity as reported in one of the study patients.

In the patients treated with repeat-dose propofol HR, SAP, DAP, MAP and RPP post-intubation were all significantly lower than in the untreated group (P =0.00). Another study by Sood et al[15] demonstrated similar efficacy with repeat-dose propofol in respect of SAP, DAP and MAP (P< 0.01). Many patients are at risk of myocardical ischaemia during laryngoscopy. Edwards and colleagues[19] reported myocardial ischaemia in more than 11% of patients undergoing tracheal intubation. The RPP remains a good indicator of myocardial oxygen demand [20]; hence it is a useful tool for assessing potential risk of angina. However since myocardial ischaemia and angina result from the imbalance in myocardial oxygen demand and supply, RPP alone does not determine the risk of myocardial ischaemia and angina. Factors that affect oxygen supply such as the state of the coronary arteries, haemoglobin concentration, oxygen saturation, blood pressure, viscosity and HR (determinant of duration of diastole and coronary flow) also play influential role in determining risk. Comparatively, while RPP is suggestive, electrocardiographic monitoring of appropriate leads remains the diagnostic tool for myocardial ischaemia. The increase in RPP in the three treatment groups following intubation were 10196 (94.2%) Vs 3570(32.8%) Vs 2680.6(24.6%) respectively in the untreated, repeat-dose propofol and fentanyl groups. Anticholinergic premedication may have contributed to the relatively high RPP values in all the groups, even prior to laryngoscopy.

The cardiovascular changes at 1min after intubation were recorded. This was meant to obtain the maximum change in the parameters, as previous work5 has shown that the peak occurs 30-45secs after intubation. Amadasun[21], also found in his study that maximum haemodynamic response occurred in 1min post intubation. Strikingly no dysrrhythmia was observed in any of the sixty-six (66) patients studied. This is contrary to expectation, since laryngoscopy and intubation trigger a sympathetic surge and the latter is known to be sometimes associated with dysrrhythmias[1]. In the study by Ko and colleagues[18], out of the 155 patients investigated for the optimal timing for the administration of fentanyl to attenuate the cardiovascular response to endotracheal intubation, dysrrythmia occurred in seven patients. Catecholamines enhance atrio-ventricular nodal transmission and reduce the refractory period of the impulse transmission pathways, hence their arrhythmogenicity.

Fentanyl causes chest wall rigidity in some patients and may thus interfere with respiration. This peripheral effect is in addition to the central depressant effect of opioids on the respiratory centre. One of the patients that participated in the study manifested severe oxygen desaturation due to chest wall rigidity, and had to be quickly paralysed and intubated. He was later identified, at the end of the study, to have received fentanyl premedication. Fentanyl is among the opioids implicated in this occasional phenomenon.

CONCLUSION

Laryngoscopy and endotracheal intubation elicit strong cardiovascular response which was most marked in untreated patients. Both fentanyl premedication and repeat-dose propofol effectively attenuate the cardiovascular response, to the same extent, though fentanyl attenuated the rise in DAP better than repeat-dose propofol.

Owing to the very poor power supply situation in many resource- poor countries, propofol storage which requires “cold chain facilities” may present a problem to its usage. Fentanyl also offers a cost advantage as the dose required to attenuate the cardiovascular response in a patient costs only 10% that of propofol, for same patient. Being a controlled substance, little hiccup may sometimes be encountered with fentanyl procurement, however.

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