Attenuation of The Cardiovascular Response to Laryngoscopy and Intubation: A Comparison of Dexmedetomidine and Low Dose Fentanyl.
DECLARATION

I declare that this dissertation is my original work and has not been presented for a degree or any other purposes in any institution. Sections copied in whole or in part from any other source are explicitly identified with detailed, complete and accurate referencing.

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To Bakhita; for your unconditional love.
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LIST OF ABBREVIATIONS

α - alpha

β - beta

µ - mu

µg.kg⁻¹ - micrograms per kilogram body weight

ASA - American Society of Anesthesiologist’s physical status classification

BP - Blood pressure

EEG - Electroencephalogram

IV - Intravenous

KNH - Kenyatta National Hospital

MAC - Minimum alveolar concentration

mg.kg⁻¹ - milligrams per kilogram body weight

N₂O - Nitrous oxide

O₂ - Oxygen

SPSS - Statistical Package for the Social Sciences

UoN - University of Nairobi
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1. ABSTRACT

**Background:** Laryngoscopy and intubation are stimuli associated with a transient rise in the heart rate and blood pressure from a sympathetic outflow. Ablation of this sympathetic response would minimize the risks of cardiovascular and/or cerebral events in vulnerable patients. To this end various pharmacological agents have been studied for the attenuation of this response. We set out to compare the effects of fentanyl and dexmedetomidine on the cardiovascular response to laryngoscopy and intubation in our patient population.

**Study Objective:** This study was designed to compare the attenuation response to laryngoscopy and endotracheal intubation between the two drugs fentanyl and dexmedetomidine.

**Study design and site:** It was a comparative cross-sectional study. The study population was drawn from adult patients planned for elective non-cardiac surgery under general anaesthesia at the Kenyatta National Hospital, requiring endotracheal intubation.

**Materials and methods:** We studied 91 consenting adults of ASA class 1 and 2 of either sex. They were studied under one of two arms: Group F (n=45) were those who received a bolus injection of fentanyl 2 µg.kg\(^{-1}\) over 10 minutes before induction of anaesthesia and Group D (n=46) those who received a bolus dose of dexmedetomidine 1 µg.kg\(^{-1}\) over 10 minutes before induction. All patients were induced uniformly using propofol until loss of verbal contact and either atracurium or cisatracurium. Baseline values of the heart rate, systolic, diastolic blood pressures and the mean arterial pressure were measured and recorded prior to administration of the study drug, at the termination of the infusions, during laryngoscopy and tracheal intubation and at minutes 1, 5 and 10 after intubation.
**Results:** Dexmedetomidine at a dose of 1 µg.kg\(^{-1}\) given before induction of anaesthesia significantly prevents an increase in the heart rate from baseline for up to 5 minutes following intubation, compared to fentanyl given at 2 µg.kg\(^{-1}\). The rise in the blood pressure was significantly prevented for up to 10 minutes following intubation.

**Conclusion:** Dexmedetomidine was superior to fentanyl in attenuating the sympathetic response to laryngoscopy and endotracheal intubation.
2. INTRODUCTION

General anaesthesia is the commonest technique applied in the operating room for conduction of most surgical procedures. It will often require laryngoscopy and tracheal intubation as a way of securing the airway. These are among the manoeuvres that provoke marked sympathetic and hormonal responses that may result in hypertension, tachycardia and even cardiac arrhythmias intraoperatively.

Although this response is transient, it may be potentially dangerous in patients with cardiac or cerebrovascular disease[1][2]. The duration of this stress response typically occurs 30 seconds after intubation and lasts for less than 10 minutes[3]. Prevention of hypertensive episodes or tachycardia is therefore a prerequisite for a safe perioperative outcome.

To control this haemodynamic response various pharmacological agents[4][5] and non-pharmacological ones[6] have been studied. The pharmacological agents used prior to laryngoscopy and intubation include low-dose fentanyl, esmolol, lignocaine, clonidine and dexmedetomidine.

This study made a comparison of fentanyl and dexmedetomidine given at induction of general anaesthesia at KNH.

Fentanyl is a phenylpiperidine- derivative synthetic opioid, structurally related to pethidine and an agonist at μ receptors. Due to its high lipid solubility, it is 75-125 times more potent than morphine, the prototype opioid and has a faster onset of action. There is however, a distinct time lag between fentanyl plasma concentration and the slowing on the EEG, reflecting the time to effect-site equilibration. This is 6.4 minutes for fentanyl[7]. It is used as an adjuvant to the
inhalational and intravenous anaesthetic agents to blunt the circulatory responses to direct laryngoscopy and intubation.

Dexmedetomidine is a highly selective, specific and potent agonist at the $\alpha_2$-adrenergic receptor. It is 7-10 times more selective for $\alpha_2$ receptors than clonidine and has a shorter duration of action. Dexmedetomidine given as premedication, attenuates the haemodynamic responses to laryngoscopy and endotracheal intubation. It does so by decreasing the catecholamine levels in plasma. It has also been shown to decrease perioperative requirements for inhaled anaesthetics and opioids.
3. LITERATURE REVIEW

Perioperative myocardial infarction is a principal cause of postoperative morbidity and mortality in normotensive patients due to hypertension and tachycardia\[8\]. There have been varying results in the study of the various pharmacological agents for attenuating the cardiovascular response to direct laryngoscopy and endotracheal intubation. The search for the most ideal agent persists.

It is a well-known fact that hypertension is seen more frequently in the black population and is associated with a higher incidence of cerebrovascular and renal complications\[9\]. In the desire to practice safe anaesthesia, mortalities attributable to anaesthesia could be reduced by controlling the haemodynamic changes that occur during endotracheal intubation. Literature on the black population is fairly scarce. One, conducted in Ghana demonstrated that use of esmolol (2 mg.kg\(^{-1}\)) was effective for the control of haemodynamic responses to laryngoscopy and intubation\[9\]. However, it further recommended the need to investigate the safety and efficacy of use of longer duration of infusions in reducing the risks of myocardial ischaemia after non-cardiac surgery. Use of other classes of drugs for the same indication in this cohort is not mentioned.

Studies looking at different dosages of fentanyl and the optimal time of administration in attenuation of this response appear in various literature\[10][11][12\]. These as expected, have given various results which may be explained by differences in study designs, variations in patient population, ages, racial differences and the dose and timing of fentanyl administration in relation to intubation.
A study by Sawano concluded that it is preferable to administer 2 µg.kg\(^{-1}\) of fentanyl in patients without hypertension and 4 µg.kg\(^{-1}\) in those with hypertension in order to minimize changes in the heart rate, systolic blood pressure and cardiac output associated with tracheal intubation[11].

Feng CK et al showed that low dose fentanyl 3 µg.kg\(^{-1}\) prevented hypertension but not tachycardia, esmolol reliably offered protection against the rise in arterial blood pressure and heart rate, while lignocaine had no effect[4].

Yushi et al, in their study however, concluded that fentanyl 2 µg.kg\(^{-1}\) suppresses the haemodynamic response to endotracheal intubation more than the response to laryngoscopy[13].

Use of 8 µg.kg\(^{-1}\) fentanyl preloading abolished the heart rate and the blood pressure increases related to tracheal intubation. It also prevented an increase of pulmonary capillary wedge pressure during the induction of anaesthesia with thiopental[14].

In a double-blind study, two doses of fentanyl (2 and 6 µg.kg\(^{-1}\)) were evaluated as an adjunct to thiopental induction in normotensive patients, and the large dose of fentanyl completely prevented the increase in pulse rate and arterial pressure[15].

However, fentanyl does produce respiratory depression in a dose-dependent manner. Splinter and Cervenko showed fentanyl-treated patients were at risk of hypotension several minutes after intubation. Large doses (50-100 µg.kg\(^{-1}\)) have been used for cardiac surgery to obtund the metabolic stress response. At such high doses, sedation is profound, unconsciousness may occur
and muscular rigidity of the chest wall may affect ventilation[16]. Fentanyl may also cause postoperative opioid induced ventilatory impairment.

It is therefore preferable to administer the lower dose of fentanyl at 2 µg.kg$^{-1}$ in order to blunt the cardiovascular response to intubation and minimize the adverse effects.

With use of this dose, Ko et al showed that the optimal time for injection of fentanyl in healthy patients to prevent the haemodynamic responses to intubation is consistent with the peak analgesic effect, namely 5 minutes before tracheal intubation[10]. At this dose of 2 µg.kg$^{-1}$ of fentanyl, the number of patients with hypotension or bradycardia was not significantly greater in the fentanyl-treated groups.

Others however differ recommending that fentanyl be administered 10 minutes before intubation. As mentioned earlier, fentanyl requires 6.4 minutes to achieve effect-site equilibrium after an intravenous bolus administration. It is argued that fentanyl may not achieve its peak central nervous effect until 10 minutes after the bolus dose. Thus, the common practice seen among many anaesthesiologists of giving a bolus dose of fentanyl (50-100 µg) concurrently with other induction drugs would not be expected to have any significant effect based on an inadequate dose and inappropriate timing.

Dexmedetomidine, an $\alpha_2$ agonist attenuates both haemodynamic and stress responses to surgery through its sympatholytic effects[17][18]. Dexmedetomidine also has anti-nociceptive, sedative and anti-sialagogue properties.

Dexmedetomidine based anaesthesia has several advantages. It has been shown in many studies to reduce the requirement of isoflurane[19][20][21] and opioid[22][23][24] consumption
intraoperatively. This opioid-sparing effect of dexmedetomidine confers upon it a distinct advantage as a host of opioid side effects are greatly reduced such as nausea and vomiting, ventilatory impairment, pruritus, postoperative ileus and urinary retention.

A recent study by Bilgi et al looking at the effects of dexmedetomidine of intraoperative haemodynamics, opioid consumption and recovery characteristics, strongly illustrates some of these properties. It was a double-blinded controlled study comparing dexmedetomidine with fentanyl for maintenance of intraoperative haemodynamics on hypertensive patients undergoing major surgery. The conclusion was that use of dexmedetomidine infusion intraoperatively controlled the sympathetic response better than fentanyl and provided stable intraoperative haemodynamics. It reduced the dose of thiopentone, requirement of isoflurane and fentanyl boluses. The post-operative analgesia was prolonged and the incidence of post-operative nausea and vomiting was less[25].

A look through literature revealed most studies comparing fentanyl with either the β blockers or the local anaesthetic lignocaine[17][26][27][3]

Only one recent study has compared the drugs dexmedetomidine and fentanyl for the particular indication of attenuating the stress response to direct laryngoscopy and intubation. Dexmedetomidine was given as an infusion of 1 µg.kg\(^{-1}\) over 10 minutes whereas fentanyl was given as a bolus injection at 2 µg.kg\(^{-1}\). Dexmedetomidine was shown to provide consistent and reliable protection against a rise in the heart rate and blood pressure as compared to the fentanyl group[28].
In general, studies on the effect of dexmedetomidine on the haemodynamic responses to laryngoscopy and intubation, concluded that preoperative administration of a single dose of dexmedetomidine resulted in progressive increases in sedation, blunted the haemodynamic response during laryngoscopy and reduced both opioid and anaesthetic requirements[18][29][30][31].
4. RATIONALE OF THE STUDY

Fentanyl is the most commonly used drug in Kenyatta National Hospital to ablate the cardiovascular response to intubation. Even with adequate doses and correct timing, fentanyl is still inferior to other medications when used for this particular indication. Dexmedetomidine has been employed by some anaesthesiologists who have anecdotally expressed the advantages aforementioned, but unfortunately this is not reported. It would be desirable to have documented evidence on the use of either drug for this specific indication.

Dexmedetomidine has shown superior qualities in studies done elsewhere. These include reduced anaesthetic and opioid requirements, postoperative analgesia and reduced incidence of postoperative nausea and vomiting. This would imply a gross reduction in the cost of management of surgical patients in the intra- and post-operative periods, and thus economical in a resource limited setting.

It cannot be overemphasized that hypertension, the haemodynamic changes associated with direct laryngoscopy and endotracheal intubation can be controlled and lead to a reduction on anaesthesia-related morbidity and mortality. The scarcity of studies in the black population, that is more vulnerable to hypertension and its attendant complications beg for more research in this cohort.
5. HYPOTHESIS

**Null hypothesis:** There is no difference between low dose fentanyl and dexmedetomidine in attenuating the cardiovascular response to laryngoscopy and intubation.

**Alternative hypothesis:** there is a difference between low dose fentanyl and dexmedetomidine in attenuating the cardiovascular response to laryngoscopy and intubation.

The research problem

To compare the difference in the attenuation of the cardiovascular response to laryngoscopy and intubation between low dose fentanyl 2 µg.kg\(^{-1}\) and dexmedetomidine 1 µg.kg\(^{-1}\).

6. OBJECTIVES

(a) **Broad objective**

To compare the effects of fentanyl and dexmedetomidine on the cardiovascular response to laryngoscopy and intubation.

(b) **Specific objectives**

To determine the difference in the systolic blood pressure, diastolic blood pressure, mean arterial pressure and the heart rate responses to laryngoscopy and intubation between a bolus dose of fentanyl and dexmedetomidine.

(c) **Secondary objective**

To determine the dose of the standard induction agent propofol following administration of either fentanyl or dexmedetomidine.
7. STUDY DESIGN AND METHODOLOGY

(a) Study design

This was a comparative cross-sectional study.

(b) Study area description

The study was conducted at the Kenyatta National Hospital. This is the national teaching and referral hospital.

(c) Study population

Patients recruited into the study were drawn from inpatients admitted in the general wards.

I. Inclusion criteria

- Adult patients scheduled for elective non-cardiac surgery under general anaesthesia
- Aged between 18 and 65 years of age
- They were American Society of Anesthesiologists (ASA) class 1 or 2
- Mallampati class 1 or 2

II. Exclusion criteria

- Any patient with cardiovascular disease including hypertension, coronary artery disease, peripheral artery disease
- Patients on anti-hypertensive medication or sedatives
- Diabetic patients
- Patients requiring more than one attempt at intubation
(d) Sample size determination

This will be a comparative study and the following formula will be used to estimate sample size:

\[
n_1 = n_2 = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 (\sigma_1^2 + \sigma_2^2)}{d^2}
\]

where:

- \(n_1\) – the number of patients required in group 1 (fentanyl)
- \(n_2\) – the number of patients required in group 2 (dexmedetomidine)
- \(Z_{1-\alpha/2}\) – the standard normal deviate for 95% confidence interval = 1.96
- \(Z_{1-\beta}\) – the standard normal deviate for 80% power = 0.845
- \(\sigma_1\) – the standard deviation associated with mean of the parameter of interest in group 1
- \(\sigma_2\) – the standard deviation associated with mean of the parameter of interest in group 2
- \(d\) – clinically acceptable difference in means of the parameters between the two groups = 8

<table>
<thead>
<tr>
<th>Parameter</th>
<th>(\sigma_1)</th>
<th>(\sigma_2)</th>
<th>n in each group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td>10.18</td>
<td>16.49</td>
<td>46</td>
</tr>
<tr>
<td>MAP</td>
<td>11.28</td>
<td>13.17</td>
<td>37</td>
</tr>
<tr>
<td>SBP</td>
<td>11.97</td>
<td>14.45</td>
<td>43</td>
</tr>
<tr>
<td>DBP</td>
<td>11.55</td>
<td>13.04</td>
<td>37</td>
</tr>
</tbody>
</table>
Based on the calculations in the table, the highest sample size was used to estimate the differences of all the parameters between the two groups. Therefore, a minimum of 46 patients in each group (a total of 92 patients) were sampled to estimate a minimum difference of 8 units in the parameters between the two groups with 95% confidence interval and 80% power.

(e) Sampling method

**Figure 1: Flow chart**

- **Enrolment**
  - Assessed for eligibility (n=100)
  - Excluded (n=6)
    - Not meeting inclusion criteria (n=6)

- **Recruited (n=94)**

- **Allocation**
  - Allocated to dexmedetomidine (n=48)
    - Received allocated intervention (n=48)
  - Allocated to fentanyl (n=46)
    - Received allocated intervention (n=46)

- **Analysis**
  - Analysed (n=46)
    - Excluded from analysis (n=2) one patient had 3 attempts at intubation and another received ketamine at induction
  - Analysed (n=45)
    - Excluded from analysis (n=1) patient had 2 attempts at intubation
Convenience sampling was used to include patients into the two groups based on the drug that would be administered to the patients. Patients were recruited consecutively as they were scheduled for elective surgery until the required sample size required in each group was achieved. A total of 94 patients were recruited to the study. However, data from 3 patients was not analysed as two required more than on attempt at intubation and one received ketamine in addition to propofol at induction.

(f) Recruitment and consent

Adult patients admitted for elective non-cardiac surgery, scheduled to undergo general anaesthesia were recruited from the general wards the night prior to surgery and informed written consent obtained.

(g) Data collection

Upon enrolment, a detailed pre-anaesthetic history was obtained, a relevant clinical examination done and patients’ weights taken.

The standard anaesthesia protocol was followed and this entailed:

Obtaining intravenous access once the patients arrived in the operating theatre. An infusion of normal saline or ringers lactate was then initiated as is routine at KNH.

Measurements of the systolic, diastolic and mean arterial blood pressures as well as the heart rate were taken and recorded preoperatively. These served as the baseline values.

Patients in group F received a bolus infusion of fentanyl 2 µg.kg\(^{-1}\) while those in group D received a bolus infusion of dexmedetomidine 1 µg.kg\(^{-1}\), each over 10 minutes.
Induction of general anaesthesia was done with a bolus dose of propofol 2-3 mg.kg$^{-1}$ titrated to loss of verbal response, then followed by atracurium 0.5 mg.kg$^{-1}$ or cisatracurium 0.2 mg.kg$^{-1}$. Upon adequate relaxation, direct laryngoscopy and endotracheal intubation was done and patients were then put on controlled ventilation with N$_2$O in O$_2$ mixture (66%:33%) with isoflurane 1 MAC. This is the standard practice of inducing patients for general anaesthesia in KNH.

Non-invasive blood pressure and heart rate recordings were done:

- On arrival in theatre as baseline measurement
- At the end of the infusion of either drug
- At laryngoscopy and intubation
- At 1 min, 5 min and 10 min after intubation

For up to 10 minutes following intubation, no surgical stimulation was allowed. No additional medication was administered during this period as well.

(h) Variables

The variables in the study were:

- Heart rate
- Systolic blood pressure
- Diastolic blood pressure
- Mean arterial pressure
8. ETHICAL CONSIDERATION

The study was carried out following institutional approval by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee.

Participation in the study was completely voluntary. An informed and signed consent was obtained from each willing participant. A participant could opt out of the study at any point up till induction of anaesthesia.
9. DATA MANAGEMENT AND STATISTICAL ANALYSIS PLAN

Data was entered and managed in SPSS version 21.0. The population was described using mean age, the ratio of males against females presented as percentages and mean weight of the patients. Heart rate, systolic pressure, diastolic pressure and the MAP were analysed and presented as means with standard deviations. Cardiovascular response parameters and propofol induction doses between the two groups were compared using student’s t test. In addition, the changes from the baseline measurements for each of the parameters were calculated and presented as means and ranges; then compared using student’s t test. Statistical tests were performed at 5% level of significance. Tables and graphs have been used to present findings.
10. RESULTS

10.1 Demographic characteristics

The patients analysed in the study had similar demographic characteristics and baseline variables.

*Table 1: Demographic characteristics: a comparison of dexmedetomidine and low dose fentanyl*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dexmedetomidine</th>
<th>Fentanyl</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>38.8 (14.0)</td>
<td>39.8 (10.5)</td>
<td>0.703</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17 (37.0)</td>
<td>19 (42.2)</td>
<td>0.608</td>
</tr>
<tr>
<td>Female</td>
<td>29 (63.0)</td>
<td>26 (57.8)</td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>63.5 (11.3)</td>
<td>67.8 (15.6)</td>
<td>0.131</td>
</tr>
</tbody>
</table>

As shown in *Table 1*, a total of 91 patients were enrolled, 46 into the dexmedetomidine group and 45 into the fentanyl group. The dexmedetomidine group had a mean age of 38.8 years (SD 14 years) while the fentanyl group had a mean of 39.8 years (SD 10.5 years), p=0.703. The sex distribution was not significantly different with 37% and 42.2% males in dexmedetomidine and fentanyl groups respectively (p=0.608). The mean weight of the dexmedetomidine group was 63.5 kg and in the fentanyl group was 67.8 kg (p=0.131).
10.2 Cardiovascular response

Table 2: Changes in cardiovascular parameters: a comparison of dexmedetomidine and low dose fentanyl

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine</th>
<th>Fentanyl</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>88.3 (17.5)</td>
<td>83.8 (17.0)</td>
<td>0.218</td>
</tr>
<tr>
<td>After intervention</td>
<td>73.2 (14.8)</td>
<td>81.5 (15.9)</td>
<td>0.012</td>
</tr>
<tr>
<td>During laryngoscopy and intubation</td>
<td>96.9 (15.9)</td>
<td>103.1 (21.3)</td>
<td>0.120</td>
</tr>
<tr>
<td>After intubation (1 min)</td>
<td>87.2 (13.9)</td>
<td>95.5 (20.1)</td>
<td>0.024</td>
</tr>
<tr>
<td>After intubation (5 min)</td>
<td>82.9 (12.7)</td>
<td>88.0 (14.0)</td>
<td>0.073</td>
</tr>
<tr>
<td>After intubation (10 min)</td>
<td>81.5 (12.2)</td>
<td>81.6 (16.1)</td>
<td>0.985</td>
</tr>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>133.2 (18.4)</td>
<td>133.1 (15.0)</td>
<td>0.991</td>
</tr>
<tr>
<td>After intervention</td>
<td>122.9 (15.5)</td>
<td>129.3 (16.7)</td>
<td>0.061</td>
</tr>
<tr>
<td>During laryngoscopy and intubation</td>
<td>126.9 (24.6)</td>
<td>138.2 (27.3)</td>
<td>0.040</td>
</tr>
<tr>
<td>After intubation (1 min)</td>
<td>120.0 (24.0)</td>
<td>126.3 (23.2)</td>
<td>0.205</td>
</tr>
<tr>
<td>After intubation (5 min)</td>
<td>104.3 (19.7)</td>
<td>116.7 (20.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>After intubation (10 min)</td>
<td>97.8 (17.8)</td>
<td>109.8 (22.8)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>79.0 (11.6)</td>
<td>78.0 (13.0)</td>
<td>0.712</td>
</tr>
<tr>
<td>After intervention</td>
<td>77.6 (12.8)</td>
<td>75.1 (13.7)</td>
<td>0.372</td>
</tr>
<tr>
<td>During laryngoscopy and intubation</td>
<td>84.8 (20.2)</td>
<td>85.5 (21.7)</td>
<td>0.880</td>
</tr>
<tr>
<td>After intubation (1 min)</td>
<td>74.1 (16.5)</td>
<td>76.8 (17.9)</td>
<td>0.450</td>
</tr>
<tr>
<td>After intubation (5 min)</td>
<td>64.6 (15.3)</td>
<td>71.0 (15.4)</td>
<td>0.049</td>
</tr>
<tr>
<td>After intubation (10 min)</td>
<td>60.1 (13.5)</td>
<td>66.0 (16.4)</td>
<td>0.065</td>
</tr>
<tr>
<td><strong>MAP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>93.8 (14.4)</td>
<td>92.3 (14.1)</td>
<td>0.619</td>
</tr>
<tr>
<td>After intervention</td>
<td>89.9 (12.1)</td>
<td>89.7 (13.7)</td>
<td>0.947</td>
</tr>
<tr>
<td>During laryngoscopy and intubation</td>
<td>96.6 (20.6)</td>
<td>100.7 (24.4)</td>
<td>0.386</td>
</tr>
<tr>
<td>After intubation (1 min)</td>
<td>86.0 (19.3)</td>
<td>90.1 (18.4)</td>
<td>0.312</td>
</tr>
<tr>
<td>After intubation (5 min)</td>
<td>75.6 (16.6)</td>
<td>83.9 (16.7)</td>
<td>0.020</td>
</tr>
<tr>
<td>After intubation (10 min)</td>
<td>69.5 (13.4)</td>
<td>78.7 (17.8)</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Table 3: Mean cardiovascular response; change from baseline: a comparison of dexmedetomidine and low dose fentanyl

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine</th>
<th>Fentanyl</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After intervention</td>
<td>-15.1</td>
<td>-50, 53</td>
<td>-2.4</td>
</tr>
<tr>
<td>During laryngoscopy and intubation</td>
<td>8.6</td>
<td>-31, 89</td>
<td>19.3</td>
</tr>
<tr>
<td>After intubation (1 min)</td>
<td>-1.1</td>
<td>-54, 78</td>
<td>11.7</td>
</tr>
<tr>
<td>After intubation (5 min)</td>
<td>-5.5</td>
<td>-57, 77</td>
<td>4.1</td>
</tr>
<tr>
<td>After intubation (10 min)</td>
<td>-6.8</td>
<td>-52, 70</td>
<td>-2.3</td>
</tr>
<tr>
<td><strong>Systolic BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After intervention</td>
<td>-10.3</td>
<td>-61, 30</td>
<td>-3.8</td>
</tr>
<tr>
<td>During laryngoscopy and intubation</td>
<td>-6.2</td>
<td>-72, 54</td>
<td>5.1</td>
</tr>
<tr>
<td>After intubation (1 min)</td>
<td>-13.2</td>
<td>-72, 54</td>
<td>-6.8</td>
</tr>
<tr>
<td>After intubation (5 min)</td>
<td>-28.9</td>
<td>-121, 4</td>
<td>-16.4</td>
</tr>
<tr>
<td>After intubation (10 min)</td>
<td>-35.3</td>
<td>-131, 26</td>
<td>-23.4</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After intervention</td>
<td>-1.3</td>
<td>-83, 47</td>
<td>-2.9</td>
</tr>
<tr>
<td>During laryngoscopy and intubation</td>
<td>5.8</td>
<td>-25, 47</td>
<td>7.5</td>
</tr>
<tr>
<td>After intubation (1 min)</td>
<td>-4.9</td>
<td>-75, 55</td>
<td>7.5</td>
</tr>
<tr>
<td>After intubation (5 min)</td>
<td>-14.4</td>
<td>-12, 81</td>
<td>-7.0</td>
</tr>
<tr>
<td>After intubation (10 min)</td>
<td>-18.8</td>
<td>-82, 75</td>
<td>-12.0</td>
</tr>
<tr>
<td><strong>MAP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After intervention</td>
<td>-3.8</td>
<td>-32, 40</td>
<td>-2.5</td>
</tr>
<tr>
<td>During laryngoscopy and intubation</td>
<td>2.8</td>
<td>-34, 43</td>
<td>8.4</td>
</tr>
<tr>
<td>After intubation (1 min)</td>
<td>-7.7</td>
<td>-41, 48</td>
<td>-2.2</td>
</tr>
<tr>
<td>After intubation (5 min)</td>
<td>-18.2</td>
<td>-52, 43</td>
<td>-8.4</td>
</tr>
<tr>
<td>After intubation (10 min)</td>
<td>-24.2</td>
<td>-56, 33</td>
<td>-13.6</td>
</tr>
</tbody>
</table>
### 10.3 Heart Rate

As shown in Table 2, Fig 2, the heart rates for the two groups were not significantly different at baseline; 86.8 for the dexmedetomidine group and 83.8 for the fentanyl group (p=0.218). A statistically significant difference was recorded after the intervention was administered with the mean heart rate for dexmedetomidine group decreasing to 73.2 compared to 81.5 in the fentanyl group (p=0.012). This is better illustrated in Table 3, where the mean decrease from baseline was higher with dexmedetomidine (-13.5) compared to the fentanyl group (-2.4), p<0.001.

During laryngoscopy and intubation, heart rates rose to a mean of 96.9 in the dexmedetomidine group and 103.1 in the fentanyl group though not significantly different (p=0.120). This was a substantial increase from baseline heart rates with a mean difference of 10.2 in the dexmedetomidine group compared to 19.3 in the fentanyl group (p=0.055) (Table 2,3).
After intubation, the decrease in the heart rate was compared to the readings during laryngoscopy and intubation. The mean heart rate was significantly lower in the dexmedetomidine group (87.2) than in the fentanyl group (95.5) at minute 1 after intubation (p=0.024). The mean difference from baseline was significantly higher in the fentanyl group (p=0.012). Heart rates at 5 and 10 minutes after intubation were not significantly different between the two groups (p=0.073 and 0.985 respectively). There was a mean decrease in the heart rate from baseline (-5.2) at 5 minutes after intubation in the dexmedetomidine group compared to a slight increase (4.1) in fentanyl group (p=0.017). However, the change from baseline at 10 minutes after intubation was not significantly different between the two groups (p=0.438).
10.4 Systolic Blood Pressure

The mean systolic blood pressure was not significantly different between the two groups at baseline and after the intervention (p>0.05) (*Table 2*). There was a reduction in SBP after intervention and the mean decrease was higher in the dexmedetomidine group (-10.3 mmHg) compared to the fentanyl group (-3.8 mmHg), *p*=0.041 (*Table 3*). However, the dexmedetomidine group had significantly lower SBP (mean 126.9 mmHg) during laryngoscopy and intubation than the fentanyl group (mean 138.2 mmHg), *p*=0.040. There was mean reduction of SBP (-6.2 mmHg) from baseline during laryngoscopy and intubation in the dexmedetomidine group, compared to the fentanyl group where there was a mean increase (5.1 mmHg), *p*=0.031. The SBP after intubation showed no significant difference in the two groups at minute 1. However, there was a continued decrease which was higher in the dexmedetomidine group than the fentanyl group.
showing significant differences at 5 and 10 minutes. The mean decrease from baseline at minute 1 and minute 5 after intubation was not different between the two groups (p>0.05) but was significantly higher for the dexmedetomidine group (-37.3 mmHg) at minute 10 than in the fentanyl group (-23.4 mmHg), p=0.011.
10.5 Diastolic Blood Pressure

The mean diastolic blood pressure was not significantly different between the two groups at baseline (p=0.712), after intervention (p=0.372) and during laryngoscopy and intubation (p=0.880) (Table 2). There was a decrease in the diastolic blood pressure after intubation but showed no difference between the two groups at 1 minute (p=0.450). The mean DBP changes from baseline were not significantly different between the two groups after intervention (p=0.995), during laryngoscopy and intubation (p=0.693) and 1 minute after intubation (p=0.169) (Table 2). However, a significant difference was seen at 5 minutes where the mean DBP was 64.6 mmHg in the dexmedetomidine group compared to a mean of 71 mmHg in the fentanyl group (p=0.049). The difference was not significant at 10 minutes after intubation (p=0.065).
The mean DBP changes from baseline were significantly higher in dexmedetomidine group compared to the fentanyl group at 5 minutes (p=0.008) and 10 minutes (p=0.007)
10.6 Mean Arterial Pressure (MAP)

![Figure 5: Changes in MAP: a comparison of dexmedetomidine and low dose fentanyl](image)

The MAP was not significantly different between the two groups at baseline, after intervention and during laryngoscopy and intubation ($p>0.05$) *(Table 1)*. MAP dropped after intubation but with no significant difference between the two groups after 1 minute. The mean change of MAP from baseline was not significantly different between the two groups after intervention ($p=0.330$), during laryngoscopy and intubation ($p=0.101$) and after intubation ($p=0.062$) *(Table 2)*. However, MAP was significantly lower for the dexmedetomidine group than fentanyl group at minute 5 (75.6 vs 83.9 respectively, $p=0.020$) and minute 10 (69.5 and 78.7 respectively, $p=0.007$). The same was seen when the mean reduction of MAP from baseline was significantly higher for the dexmedetomidine group than the fentanyl group at minute 5 ($p=0.005$) and minute 10 ($p=0.003$).
10.7 Average dose of propofol

Table 4: Average dose of propofol: a comparison of dexmedetomidine and low dose fentanyl

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dexmedetomidine</th>
<th>Fentanyl</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of Propofol (mg/kg)</td>
<td>1.78 (0.41)</td>
<td>1.96 (0.59)</td>
<td>0.107</td>
</tr>
</tbody>
</table>

Although the average dose of propofol for induction was lower in the dexmedetomidine group, mean 1.78 mg kg⁻¹ compared to a mean of 1.96 mg kg⁻¹, it was not statistically significant (p value 0.107).
**11. DISCUSSION**

Direct laryngoscopy and endotracheal intubation are often employed for patients undergoing surgery under general anaesthesia. This stimulates a profound sympathetic response with attendant rise in blood catecholamine levels. This acute, albeit transient rise in the heart rate and blood pressure may lead to adverse cardiovascular or cerebrovascular events in vulnerable patients. The quest for the ideal pharmacological agent that would abolish this response continues to dominate research in the pursuit of provision of safe anaesthesia.

This study compared the difference in the attenuation response to laryngoscopy and endotracheal intubation between a bolus dose of dexmedetomidine and low dose fentanyl.

Dexmedetomidine is a potent $\alpha_2$ adrenergic agonist. $\alpha_2$ agonists produce hyperpolarization of adrenergic neurons and suppression of neuronal firing in the locus ceruleus in the brain stem. This leads to decreased systemic noradrenaline release, resulting in attenuation of sympathoadrenal responses and haemodynamic stability during laryngoscopy and tracheal intubation.

Dexmedetomidine has been shown to reduce the requirements of isoflurane\cite{19,20,21} and opioid\cite{22,23,24} consumption intraoperatively. This opioid-sparing effect of dexmedetomidine confers upon it a distinct advantage as a host of opioid side effects are greatly reduced such as nausea and vomiting, ventilatory impairment, pruritus, postoperative ileus and urinary retention.

The use of an intraoperative infusion of dexmedetomidine lowers the anaesthetic requirements of isoflurane by 47-90% in healthy patients\cite{32,21,33}. We noted in our study that following induction of anaesthesia in the patients who received a pre-induction bolus of
dexmedetomidine, the anaesthesiologist had to dial down the isoflurane concentration to as low as 0.6 MAC to maintain stable haemodynamics. The lowering of the MAC values of volatile anaesthetic agents is attributable to dexmedetomidine’s inhibition of the central noradrenergic receptors.

Activation of these central α2 receptors as well as those found in the dorsal horn of the spinal cord have the additional effect of sedation and analgesia. The analgesic properties go well into the post-operative period[25] [34].

In this study, a pre-induction bolus dose of dexmedetomidine at 1 µg.kg⁻¹ was seen to attenuate but not completely obliterate the cardiovascular response to laryngoscopy and intubation after induction of general anaesthesia. A similar finding was reported by Arpita[18]. In their study however, they included patients with controlled hypertension and ischaemic heart disease. We excluded these from our study.

Following the administration of dexmedetomidine and up to five minutes post tracheal intubation, there was a statistically significant decrease in the heart rate from baseline compared to the fentanyl group. Sellamuthu and Laha found statistically significant decreases in the heart rate for up to ten minutes after endotracheal intubation following administration of dexmedetomidine[28][18]. In their study, Sellamuthu used a universal dose of propofol at 2.5 mg. kg⁻¹ on all patients who received either a bolus dose of dexmedetomidine or fentanyl. We titrated our propofol dose to loss of verbal response and this was therefore variable. It may also explain this slight difference in the duration of time seen with the other study as the higher
dose of propofol may have augmented the cardiovascular effect given that dexmedetomidine has been shown to lower anaesthetic requirements of induction agents.

It is argued that fentanyl may not achieve its peak central nervous effect until 10 minutes after the bolus dose. Thus, the common practice seen among many anaesthesiologists of giving a bolus dose of fentanyl (50-100 µg) concurrently with other induction drugs would not be expected to have any significant effect based on an inadequate dose and inappropriate timing. This informed our decision to give the fentanyl over 10 minutes to coincide with its peak central nervous system effect.

Following this, there was a significantly higher rise in the heart rate in the fentanyl group as compared with the dexmedetomidine group. This is consistent with Feng’s study where he showed that a dose of fentanyl at 3 µg.kg⁻¹ prevented the rise in blood pressure more than the heart rate[4].

The systolic blood pressure was significantly lower following dexmedetomidine administration before, during and up to 10 minutes following tracheal intubation.

The mean diastolic blood pressure on the other hand was not statistically different at baseline, after intervention with either drug and during laryngoscopy and intubation. A significant difference was only noted at minute 5 following tracheal intubation.

The mean arterial pressure was only recorded at being significantly lower for the dexmedetomidine group as compared to the fentanyl group from 5 minutes up to 10 minutes following intubation.
Two previous studies showed that the attenuation in the systolic, diastolic and mean arterial pressures was significantly better following dexmedetomidine administration[18], [28]. In this study, a better attenuation of the mean systolic blood pressure was demonstrated. The dose of dexmedetomidine used in these studies was identical to the one used in our study.

It is important to note however that whereas a bolus injection of fentanyl was used in the prior study by Laha et al [28] at 5 minutes before induction, in this study, it was administered as an infusion over 10 minutes before induction.

A secondary objective in this study was to determine the dose lowering effect of dexmedetomidine on the induction dose of propofol. Scheinin showed it reduced the need for thiopentone and perioperative fentanyl[29].

In our study, though the induction dose of propofol per kg body weight was lower in the dexmedetomidine group than in the fentanyl group, it was not statistically significant.
12. CONCLUSION

In this study, dexmedetomidine at a pre-induction dose of 1 µg.kg⁻¹, compared to fentanyl 2 µg.kg⁻¹ was better at attenuating the sympathetic response to laryngoscopy and endotracheal intubation.

13. LIMITATIONS

Lack of randomization introduced the risk of observer bias. This was countered by the fact that the variables being measured were objective.

There was no actual measurement of blood catecholamine levels.

We were also not able to measure the actual depth of anaesthesia following induction and prior to laryngoscopy and endotracheal intubation.

14. RECOMMENDATIONS

A greater uptake of the use of dexmedetomidine in attenuating the cardiovascular response to laryngoscopy and intubation. This will probably be more useful for the vulnerable patients with cardiovascular disease where the sympathetic response may be detrimental.

A future randomised study to minimise bias would be invaluable in validating the results of our study.
15. REFERENCES


APPENDIX I: DATA COLLECTION TOOL

Attenuation of The Cardiovascular Response to Laryngoscopy and Intubation: A Comparison of Low Dose Fentanyl and Dexmedetomidine.

<table>
<thead>
<tr>
<th>Serial number</th>
<th>Date</th>
<th>Age</th>
<th>Sex</th>
<th>Weight</th>
<th>Diagnosis</th>
<th>Procedure</th>
<th>Premedication (if any)</th>
<th>Intravenous induction agent and dose</th>
<th>Muscle relaxant and dose</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th><strong>Vital parameters</strong></th>
<th><strong>Baseline</strong></th>
<th><strong>After intervention</strong></th>
<th><strong>During laryngoscopy and intubation</strong></th>
<th><strong>After intubation (minutes)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate</td>
<td></td>
<td></td>
<td></td>
<td>1 5 10</td>
</tr>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX II: CONSENT FORM

Attenuation of The Cardiovascular Response to Laryngoscopy and Intubation: A Comparison of Low Dose Fentanyl and Dexmedetomidine.

Principal Investigator: Dr Abuya C. Moraa, University of Nairobi
Supervisors: Dr. Mark Gacii, University of Nairobi and Dr. George Njogu, Kenyatta National Hospital

Background: The researches named above are carrying out a research to compare the effects of two drugs: fentanyl and KNH with dexmedetomidine in blunting the cardiovascular stress response to direct laryngoscopy and intubation. This is a necessary manoeuvre carried out in theatre for patients scheduled to undergo surgery under general anaesthesia.

Purpose of the Study: to determine the most suitable drug for ablating this cardiovascular response in our population.

Voluntariness of participation: Note that participating in this study is completely voluntary and you are free to discontinue your participation at any point in the study.

Benefits: Participating in this study will neither cost you anything nor will you receive any form of reimbursement. We hope that this study will increase our knowledge locally in how we respond to the two different medication and better inform us on the appropriate choice of medication to use.

Risks: We do not expect you to have any adverse effects with the recommended doses we will be using for the study. But should any occur, we will immediately cease the administration of the drug and treat you accordingly. What you should expect however, is a feeling of sleep or sedation.

Confidentiality: If you agree to participate in the study, a thorough medical history will be obtained from you through an oral interview and a relevant physical examination performed. Your pulse rate, blood pressure and weight will be taken and noted down.
Once in theatre, observations will be taken as is routine in KNH and then undergo induction of anaesthesia. Your information will be treated with utmost confidentiality and your name will not appear in any document as serial numbers will be employed.

**Right to withdraw:** participation being entirely voluntary, you have the right to opt out of the study at any point with no consequence to you.

If you have further questions or concerns about participating, please call or send a text message to the researchers at the numbers provided below.

For questions about your rights as a research participant you may contact the Kenyatta National Hospital Research and Ethics Committee at 2726300 ext. 44355/44102.

For more information, contact Dr. M. Abuya at 0721-518931 at any time,

Dr. M. Gacii at 0733-709953 from 8 am to 8 pm

Dr. G. Njogu at 0722-712207 from 8 am to 8 pm
**APPENDIX III: IDHINI YA KUSHIRIKI**

**Mazingira:** Watafiti walotajwa hapo juu wanafanya uchunguzi ili kulinganisha athari ya dawa mbili: fentanyl na dexmedetomidine, zinazo tumiwa KNH katika kukabiliana na madhara kwenye moyo na mishipa wakati wa kuitazama zoiloto (laryngoscopy) na kutia kifaa kinachosaidia kupitisha hewa wakati wa kupasuliwa (intubation).

**Madhumuni ya utafiti:** Ni kutumbua ni dawa ipi iliyo bora zaidi kwa kukabiliana na madhara yaliyotajwa kwa waafrika. Ni matumaini yetu kuwa watafiti huu utaongeza ufahamu wetu humu nchini kuhusu athari ya madawa haya na kutuelekeza juu ya uchaguzi sahihi wa dawa itakotumika na manufaa zaidi.

**Ushiriki ni kwa hiari yako:** Tunahitaji idhini yako ili kushiriki katika utafiti huu. Hakuna atakaye kukulazimisha ili ujumishwe.

**Faida:** Kushiriki katika utafiti huu haitakugharimu chochote, wala usitajajie kupokea malipo ya aina yoyote.

**Hatari:** Hatutarajii wewe kuwa na madhara yoyote mbaya na dozi zilizopendekezwa kwa ajili ya utafiti. Lakini shida itakapotokea, tutasitisha madawa haya na kukupa madawa ipasavyo. Hata hivyo, unapaswa kutarajia hisia ya usingizi au utulivu.

**Usiri:** Tutayatibu maelezo utakayotupa kwa siri mkubwa na jina lako halitaonekana katika hati yoyote, kwani nambari maalum zitatumika kwa washirika wote. Ijapo utakubali kushiriki katika utafiti, yafua tayo yataokea: Tutachukua historia ya kina kuhusu matibabu yako kwa njia ya mahojiano, na kufanya uchunguzi wa kimwili uliolengwa. Kiwango cha mbio wa moyo, shinikizo la damu na uzito wako zitachukuliwa na kurekodiwa.

Utakapofika kwenye chumba cha matibabu, mapimo yatachukuliwa tena kisha utapewa madawa ya kulala kufuatilia itifaki ya KNH.
**Kujiondoa:** Kumbuka kwamba kushiriki katika utafiti huu ni kwa hiari yako na uko na uhuru wa kutatisha ushiriki wako wakati wowote wa huu utafiti.

Jihisi huru kuuliza maswali yoyote kuhusu madhumuni na mwenendo wa masomo haya.

Kama una maswali zaidi au jambo lolote kuhusu kushiriki, tafadhali piga simu au tuma ujumbe mfupi kwa watafiti katika nambari zinazoonekana hapa chini.
APPENDIX IV: Participants Consent/ Assent Form

If you decide you want to be in this study, please sign your name

........................................................................... Date...........................................

I also understand that participation is voluntary.

**Investigators declaration**

I declare that I have explained to the participant about this study and have understood the purpose, objectives, benefits, risks and their rights in agreeing to participate.

........................................................................... Date...........................................
APPENDIX V: **Idhini ya kushiriki**

Kama umeamua unataka kuwa katika utafiti huu, tafadhali tia sahihi yako.

........................................................................................................ Tarehe........................................

Naelewa pia ushiriki ni wa hiari.

**Tamko la mtafiti**

Nkiri kwamba nimemwelezea mshiriki kuhusu utafiti huu na amelewa malengo, faida, hatari na haki zake katika kukubali kushiriki.

........................................................................................................ Tarehe........................................

Kwa maswali kuhusu haki zako kama mshiriki katika huu utafiti unaweza kuwasiliana kamati ya maadili na utafiti wa hospitali kuu ya Kenyatta katika 2726300 ext. 44355/44102.

Kwa habari zaidi, wasiliana na Dk Abuya katika 0721-518931 wakati wowote,

Dk M. Gacii katika 0733-709953 kutoka saa 8 asubuhi hadi saa 8 usiku

Dk G. Njogu katika 0722-712207 kutoka saa 8 asubuhi hadi saa 8 usiku