A comparison of risk of hypotension using standard doses of remifentanil versus dexmedetomidine infusions in adult patients undergoing surgery under general anaesthesia at the Aga Khan University Hospital, Nairobi

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Abstract

Background: Remifentanil and dexmedetomidine are common agents used in general anaesthesia, monitored anaesthesia care and critical care. When combined with inhaled or intravenous anaesthetic agents intra-operatively, they provide analgesia, lower general anaesthetic requirements and provide sedation and analgesia in the peri-operative period if indicated. Pharmacodynamically, they cause hypotension and bradycardia which are reversible if well managed. Past studies of these drugs have shown a significant proportion of patients with hypotension when compared with similar agents or in isolation. This study compares these two drugs on the effect of hypotension when used as adjuncts to general anaesthesia at low dose standard rate of infusions.

Objective: To compare the proportion of hypotension episodes in a group of adult patients receiving dexmedetomidine infusion at 0.4mcg/kg/hr versus a group receiving remifentanil infusion at 0.2mcg/kg/min, severity of hypotension and physician interventions in each group.

Methods: One hundred and four patients scheduled for elective surgery under general anaesthesia were randomized into two groups:
Control group; received remifentanil infusion at 0.2mcg/kg/min
Intervention group; received dexmedetomidine at 0.4mcg/kg/hr.
General anaesthesia was standardized in both groups. The patients were blinded to the study. Baseline blood pressures of all patients were determined prior to induction. The patient's demographic characteristics were recorded. The number of patients who developed hypotension, the frequency of hypotension and the physician interventions were recorded and analysed.

Results: The age and gender characteristics were different between the two groups (p values <0.023 and 0.05 respectively) however they did not affect the proportion of patients with hypotension. The weight, baseline pressures and ASA status of the patients within the groups were similar. The operative procedures varied within the groups. General surgery did not influence the outcome of hypotension in both arms. The duration of surgery in remifentanil group exceeded that of Dexmedetomidine p value<0.0005 however the time to the first episode of hypotension was similar between the groups. The episodes of hypotension were fewer in the dexmedetomidine arm and the proportion of patients with hypotension were higher in the remifentanil arm, p value<0.001, R.R 0. = 0.5938, 95% C.I= 0.329-0.819 The physician interventions administered were similar between the two groups except the use of ephedrine between the groups.

Conclusion: Among this population, at standard infusion rates, the proportion of patients that risk hypotension was greater in those undergoing elective surgery receiving remifentanil at 0.2mcg/kg/min than in dexmedetomidine at 0.4mcg/kg/hr under isoflurane based anaesthesia.

Keywords: Risk of hypotension, remifentanil versus dexmedetomidine infusions, general anaesthesia, Aga Khan University Hospital, Nairobi.

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Introduction

Balanced anaesthesia is a triad of hypnosis/amnesia, analgesia and muscle relaxation. An ideal anaesthetic agent would be one drug that provides all three which is currently unavailable. With the exception of ketamine and

dexmedetomidine which have analgesic properties, inhaled volatile and intravenous anaesthetic agents have only amnestic/hypnotic properties[1,2].

Balanced anaesthesia is provided by the use of hypnotic agents which could be intravenous or a volatile anaesthetic agent for example propofol and isoflurane, a muscle relaxant which may be used to provide intra-operative paralysis to skeletal muscle and analgesic agents to control pain and add the effect of sedation to the anaesthesia.

Short acting opioids such as remifentanil, fentanyl, alfentanil and sufentanil have been used intra-operatively as infusions for pain control and are combined with volatile inhalational agents or intravenous agents to provide general anaesthesia[3]. Remifentanil is the most common opioid used as an infusion intra-operatively at our hospital. It is associated with deep analgesia, has a fast recovery and deemed useful for patients who have a risk of intra-operative awareness, obstructive sleep apnoea and for patients who require early ambulation post-operatively[4].

Remifentanil can be used as an adjunct with volatile anaesthetics and total intravenous anaesthesia with hypnotic agents[5,6]. At the appropriate doses, it can facilitate endotracheal intubation without muscle relaxant[5]. Remifentanil when used intra-operatively causes chest wall rigidity, hypotension and bradycardia, post-operatively with opioid induced tolerance or hyperalgesia, pruritus, nausea and vomiting which prolong recovery from general anaesthesia and surgery[4,5].

Dexmedetomidine is a classical anaesthetic agent that has been gaining popularity since the early 1990's. It is an alpha 2 selective agonist which provides sedation and analgesia.

Dexmedetomidine is also used in general anaesthesia in various surgeries including major specialties such as cardiothoracic surgery and neurosurgery[7]. Dexmedetomidine has been used as analgesia post-operatively as an infusion for major cardiothoracic surgeries[8,9]. It has been shown to reduce intra-operative analgesic consumption and post-operative induced opioid hyperalgesia by acting centrally in the brain and spinal cord[9,10,11,12,13,14].

Intra-operatively, dexmedetomidine reduces the MAC of inhaled anaesthetic agents as demonstrated by Wong et al and has been used in combination with propofol as total intravenous anaesthesia and patients did not portray any overt signs of intra-operative awareness[10,15,16].
Dexmedetomidine and remifentanil are two different drugs that have a common effect of analgesia, sedation, hypotension and bradycardia. Bradycardia is treated with an anti-cholinergic agent. Hypotension is reduced/ treated by fluid boluses, titration/ discontinuation of the infusions and administration of vasopressors[17,18].

It is established that remifentanil and dexmedetomidine cause hypotension at increasing therapeutic dose ranges. Standard doses which cause adequate anaesthesia/analgesia used are however lower than therapeutic doses and no studies have compared the proportion of patients with hypotension between patients receiving the two drugs under standard isoflurane anaesthesia in oxygen/air mixture at those rates of infusion.
Hypotension is a common side effect encountered during sedative/analgesic infusions administered as adjuncts of inhaled volatile and intravenous agents. Remifentanil infusions have been associated with high incidences of hypotensive episodes when compared to other opioids such as fentanyl[21]. Dexmedetomidine has been shown to have a lower incidence of hypotension when used peri-operatively[22].

Our study question was does the use of isoflurane anaesthesia plus dexmedetomidine infusion in adults undergoing elective surgery result in fewer cases of hypotension compared to isoflurane anaesthesia with remifentanil infusion? We hypothesized that at maintenance doses of 0.4 mcg/kg/hr of dexmedetomidine and 0.2 mcg/kg/min of Remifentanil infusion there is no significant difference in the proportions of patients with hypotension between the two groups.

Our primary objective was to compare the proportion of hypotension cases developing following isoflurane anaesthesia plus dexmedetomidine infusion to isoflurane anaesthesia plus remifentanil at standard doses in adult patients undergoing elective surgery. Our secondary objectives were to compare the severity of the lowest mean

arterial pressure recorded in hypotension among adult patients receiving dexmedetomidine infusion compared to those receiving remifentanil infusion, and to compare the number of physician interventions in each group.

Methodology

The study was performed following approval from the ethical and scientific review Committee at the Aga Khan University, East Africa. The study was registered by the Pan African Clinical Trials Registry registration number PACTR201412000962379. It was a single blinded randomized control trial. The target population included all adults aged between 18 and 85 years who underwent elective surgery at Aga Khan University Hospital, Nairobi. The sample population included 96 ASA I and II patients going to theatre for elective surgery between August 2014 and March 2015. Reasons for exclusion from the study were:

1. Pregnancy
2. Patients with severe liver and renal dysfunction
3. Patients diagnosed to have mental disorders
4. Pre-existing bradycardia and brady-dysrhythmia
5. Cardiovascular insufficiency and valvular heart disease
6. Hypotensive patients clinically diagnosed
7. Patients who declined to participate in the research

A sample size of 96 patients (48 per group) was calculated to be sufficient to demonstrate 27% difference in the proportion of hypotension between the remifentanil and dexmedetomidine group at a 95% confidence level and a power of 80%. A retrospective study looking at the haemodynamic impact of dexmedetomidine administration in 15,656 non-cardiac surgical cases showed a proportion of 26.5% in hypotension and a meta-analysis of 20 studies demonstrated it at 26%[19,20]. Sneyd et al demonstrated a proportion in hypotension of 53% in patients undergoing major abdominal and gynecological surgery using remifentanil infusion at 0.2mcg/kg/min[21].

We therefore hypothesized that there would be no significant difference in the proportion of hypotension between the remifentanil group of patients receiving a standard dose rate of 0.2 mcg/kg/min and the dexmedetomidine group receiving a standard dose rate of 0.4mcg/kg/hr.

The study participants were recruited from the pre-operative anaesthesia clinic (during the pre-anaesthetic review) and the in-patient surgical ward. All participants received verbal and written explanation on the purpose and procedure of the study from the principal investigator; and written informed consent. The patients who gave written informed consent were enrolled into the study and randomized. Their anaesthesia charts had indication of study patient for ease of identification on arrival in theatres. Simple randomization was done using a computer program which generated a random sequence of numbers. Each of the random numbers was sequentially assigned to either: Group D1; that would be on remifentanil infusion intra-operatively or Group D2; that would be on dexmedetomidine infusion intra-operatively

The patient was blinded to the study. The primary anaesthesia team and the principal investigator were not blinded due to near risk of adverse event of severe hypotension and bradycardia intra-operatively and the different preparation and administration of remifentanil and dexmedetomidine infusions. Dexmedetomidine was recently introduced into the Kenyan market and the anaesthesia team had limited experience with the drug. We sourced this drug for our study from our hospital pharmacy where it had been recently added to the hospital formulary. The recruitment process and patient distribution is illustrated in figure 1.

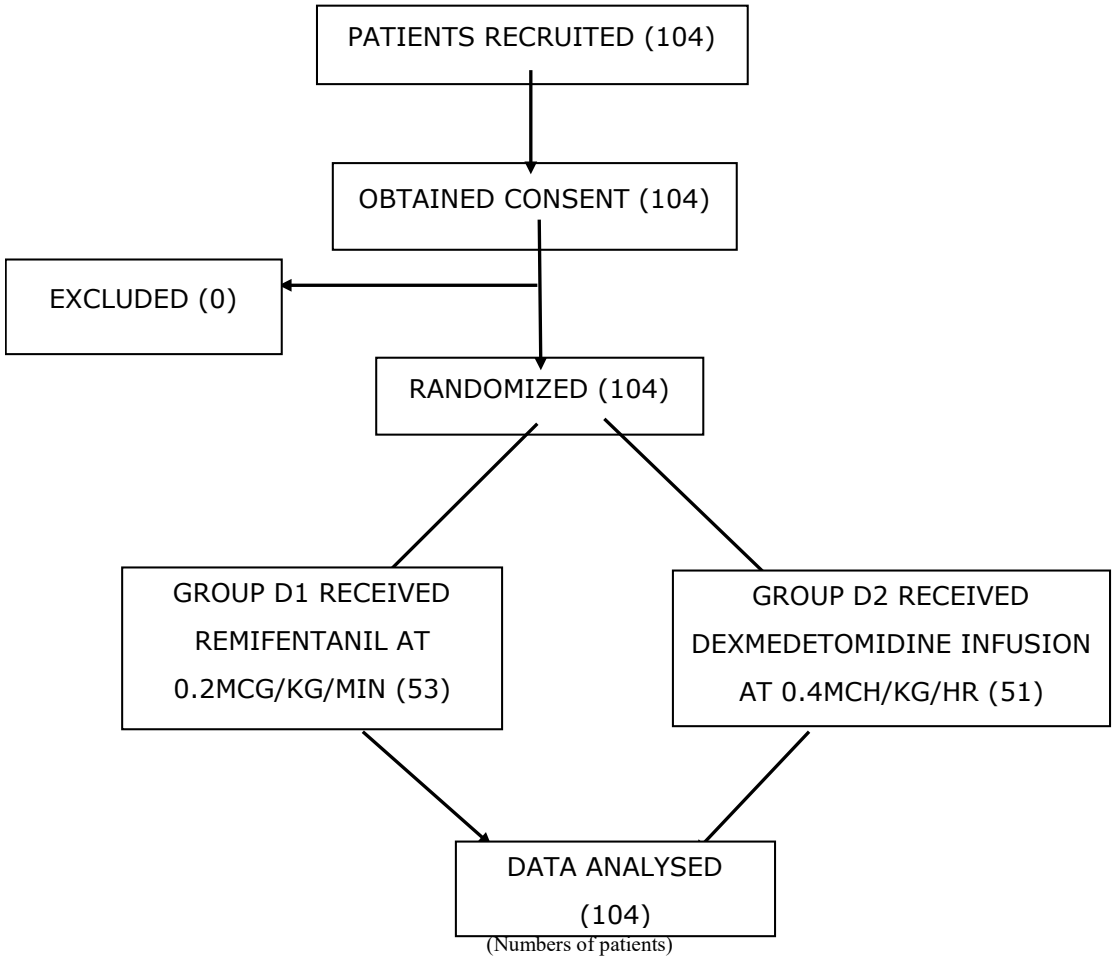


Figure 1: Flow diagram of patient distribution

This study was undertaken at the Aga Khan University Hospital, Nairobi operating theaters.

ASA I or II patients scheduled for elective surgical procedures were received in the pre-operative area. They had been randomized to receive remifentanil 0.2mcg/kg/minute or dexmedetomidine at 0.4mcg/kg/hour after induction as an adjunct to isoflurane maintenance anaesthesia. The anaesthesia team conducting the anaesthesia received the anaesthetic chart with the attached data collection tool. The team included the consultant anaesthetist and the resident. The study drug was prepared by the anaesthesia residents who were not involved in the randomization process.

Remifentanil Ultiva® 2mg was diluted to 40mls with water for injection to constitute 50mcg/ml and attached to an infusion pump. Dexmedetomidine Dexem® was diluted to 50mls with water for injection to constitute 4mcg/ml and attached to an infusion pump.

The infusion pumps used for the study were Injectomat TIVA Agilia anaesthesia syringe pump by Fresenius Kabi®. Once received into the operating rooms, the patient had standard monitoring equipment attached. These were temperature, non-invasive blood pressure, electrocardiography and pulse oximetry. The baseline cardiovascular and respiratory parameters were established- blood pressure, heart rate, respiratory rate and oxygen saturation.The baseline average mean arterial pressure was determined using mean arterial pressures on anaesthesia review, prior to entry into theater (in the wards) and prior to induction.

Intravenous cannulation was achieved with standard B. Braun Venflow® cannula of Gauge 18. Hartmann's solution was run fully at 15 mls/kg as induction was initiated. No premedication was administered. The patient was then pre-oxygenated for three minutes. The patients randomized to D1 received remifentanil at a loading dose of 1mcg/kg for 60 seconds and received propofol at 1.5 mg/kg thereafter.

The patients randomized to D2 received dexmedetomidine at a loading dose of 1mcg/kg for 10 minutes with propofol administered in the 7th minute at 1.5mg/kg. Isoflurane was initiated after induction. Patients in both groups received Cisatracurium Nimbex® at 0.15-0.2mg/kg to facilitate endotracheal intubation and muscle paralysis.

Maintenance of Isoflurane was targeted at end tidals of 0.8- 1.2% in an oxygen and air mixture at low flow anaesthesia. The infusion rates were targeted at the minimum dose rates in both groups (0.05mcg/kg/min in remifentanil and 0.2mcg/kg/hr in dexmedetomidine) after induction prior to the first surgical stimulation. This was to avoid unnecessary episodes of hypotension prior to surgery.
Group D1 receiving remifentanil infusion had the maintenance rate initiated at 0.2mcg/kg/minute and 0.4mcg/kg/hour for the patients in Group D2 receiving dexmedetomidine infusion at the start of surgical stimulation. Intra-operative intravenous fluid maintenance requirements were calculated using the Holiday- Segar regimen with Hartmann's solution. All patients received antiemetic medication of the anaesthetist choice and when indicated. Blood pressures were recorded as per standard protocol after induction every five minutes up to the end of anaesthesia.

Hypotension was defined as a 30% reduction in the baseline mean arterial pressures. The hypotensive episodes occurring during surgery were noted and recorded on the data collection tool in each group. A fluid bolus of Hartmann's solution at 10mls/kg was given to treat the first episode of hypotension. Subsequent episodes of hypotension were managed by administration of vasopressor boluses and fluid boluses at the anesthetist's discretion. The vasopressors used were either boluses of phenylephrine at 50mcg/ml or ephedrine at 3mg/ml. When hypotension persisted for more than twenty minutes despite physician intervention, the dose was titrated downwards at decrements of 0.05 in remifentanil and 0.1 in the dexmedetomidine infusions. The infusion rate was recorded every 15 minutes.

When hypotension persisted despite vasopressor, fluid support and infusion titration to the minimum dose rate required, the infusions were discontinued and noted. Once mean arterial pressures returned to the baseline, the infusions were recommenced and titrated accordingly with the aim of resuming the standard rates of infusion or maintaining at rates well within the recommended prescriptions that did not yield hypotensive episodes and maintained anaesthesia/analgesia. In the event of hypertension i.e. MAPS that were a 30% increase from the baseline, the rates of both infusions were increased gradually in increments of 0.1 for dexmedetomidine and 0.05 in remifentanil. The maximum therapeutic rate for dexmedetomidine was 0.7mcg/kg/hr. and 0.5mcg/kg/min for remifentanil. Intraoperative bradycardia was treated with 300mcg of atropine intravenously.

Multimodal analgesia was administered as indicated. These included Paracetamol, non-steroidal anti-inflammatory drug (NSAID) when indicated intra-operatively and an opioid of the anesthetist's preferred choice intra-operatively as a sub-cutaneous injection half an hour to the end of the surgical procedure in the remifentanil group to avoid remifentanil-induced hyperalgesia post-operatively and upon reversal for the dexmedetomidine group to avoid increased sedation post-operatively. Dexmedetomidine was discontinued fifteen minutes before the end of surgery. Remifentanil, air and isoflurane were terminated five minutes to the end of surgery or on the last stitch. Reversal was conducted on appropriate oxygen flows. Atropine was given at 20mcg/kg, glycopyrrolate at 200mcg for each 1mg of neostigmine which was given at 50mcg/kg. Patients were reversed from anaesthesia and transferred to the post-anaesthesia care unit (PACU).
Intra-operative data was collected by the anaesthesia team using the data collection form.

At PACU, the form was verified by the principal investigator to ensure it was filled correctly post-operatively. The collected data material was placed in an envelope and stored in a lockable filing drawer in the supervisor's of-

fice. All the sheets were checked once again to confirm completeness before being filed. The processed data was manually entered and saved in an external portable drive (USB) and copies were kept in the supervisor's office. The collected data were then manually entered by the principal investigator into an MS-Excel data base for analysis.

Data collected was analyzed using SPSS software version 20 by IBM. It was presented in the form of tables and graphs. Mean values with standard deviations were used to describe the patients age, weight and baseline pressures i.e. MAPS, systolic and diastolic pressures, lowest MAP throughout surgery and volume of Hartmann's fluid boluses. Unpaired Student T- test was used to compare means between the two groups. Gender, ASA status, operative procedures and variables such as the use of vasopressors, titrated rate of infusion cessation of infusion were represented as proportions and compared using the Pearson's chi square test or Fischer's exact test.

The proportion of hypotensive cases developing in isoflurane anaesthesia plus dexmedetomidine infusion and in remifentanil respectively were presented and compared using Fischer's exact test. The relative risk ratio was also calculated between the two groups and with confidence intervals. The tests were calculated under the assumption of equal variance. P-values ≤ 0.05 were considered statistically significant. The collected data was kept private and confidential at all times.

Results

One hundred and four ASA I and II patients scheduled to undergo elective surgery were recruited to this study. There was no loss to follow-up of patients during recruitment and pre-operatively. The patient demographics and baseline characteristics are illustrated in table 1.

Student t-test was used to compare age and between the two groups, whereas Pearson's chi square test was used to compare the gender and ASA status. There was no statistical difference in the patient's weight and ASA status between the groups. However significant p values were generated from the age and gender. These statistical significances could influence the outcome of the study despite it being a result of chance from the process of randomization and clinically may be of value.

Table 1: Patient characteristics

	Overall N=104	**Remifentanil Group n=53**	**Dexmedetomidine Group n=51**	**P- value**
Age in Years	36±12.00 (18-75)	36.37±10.34 (18-70)	41.72±13.00 (19-75)	0.023
Sex				
Male	50(48.08%)	31(58.48%)	19(37.25%)	0.05
Female	54(51.92%)	22(41.52%)	32(62.75%)	
Weight in KG	75.16±17.59 (41.5-154)	72.38±11.32 (52-103)	78.04±22.07 (41.5-154)	0.1188
ASA STATUS				
I	61(58.65%)	32(57.4%)	29(56.86%)	0.8692
II	43(41.35%)	21(42.6%)	21(43.14%)	

ASA- American Society of Anaesthesiologists. NS- Not Statistically significant mean, standard deviation, minimum and maximum ranges in brackets are given for Age and weight. Proportions are demonstrated in the ASA status.

More than 50% of the elective procedures were from general surgery and orthopedics. Although the types of surgeries conducted was not analyzed, their nature could have influenced the proportion of hypotension between the groups. This is illustrated in table 2.

Table 2: Operative procedures

	Overall N=104	**Remifentanil Group n=53**	**Dexmedetomidine Group n¹=51**	**P value**
General Surgery	34(32.69%)	10(18.9%)	24(47.1%)	0.084
Gynaecology	24(23.08%)	16(30.2%)	8(15.7%)	
Maxillofacial surgery	6(5.77%)	3(5.7%)	3(5.9%	
Neurosurgery	5(4.81%)	3(5.7%)	2(3.9%)	
Orthopedic surgery	26(25.00%)	14(26.4%)	12(23.5%)	
Plastic Surgery	2(1.92%)	2(3.8%)	0(0.0%)	
Ear Nose and Throat Surgery	5(4.81%)	4(7.5%)	1(2%)	
Urology surgery	2(1.92%)	1(1.89%)	1(1.96%)	

Fisher's exact test was used to compare the distribution of surgical procedures between the two groups.

The duration of surgery was greater in the patients receiving remifentanil infusion compared those receiving dexmedetomidine infusion and was statistically significant as illustrated in table 3. This was a result of the recruitment process. The baseline pressures prior to commencing surgery between the two groups were similar.

Table 3: Duration of surgery

	Overall N=104	**Remifentanil il Group n=53**	**Dexmedetomidine Group n¹=51**	**P value**
Duration of Surgery in minutes	101.54±51.35	121.75±54.45	80.54±38.27	<0.0005
BASELINE MAPS (mmHg)	88.89±12.94 (60-120)	72.38±11.33 (65-120)	78.04±22.08 (60-114)	0.1011
BASELINE SYSTOLIC PRESSURE (mmHg)	119.40±15.78 (100-145)	119.00±11.64 (100-144)	121.68±11.53 (100-145)	0.2279
BASELINE DIASTOLIC PRESSURES (mmHg)	74.13±10.10 (50-101)	73.77±11.10 (50-101)	74.51±9.04 (54-95)	0.7107

MmHg- millimeters of Mercury, minimum and maximum values are in brackets.
The means of the pressures between the two groups was compared with unpaired t-test.

The use of NSAIDs when compared between the two groups did not yield any statistical significance. Paracetamol was used in all recruited patients. Morphine was the most common opioid analgesic preferred by the anaesthesia team. There was greater administration of morphine in patient's receiving remifentanil. This was based on the preference of the anaesthesia team and was statistically significant. This is illustrated in table 4.

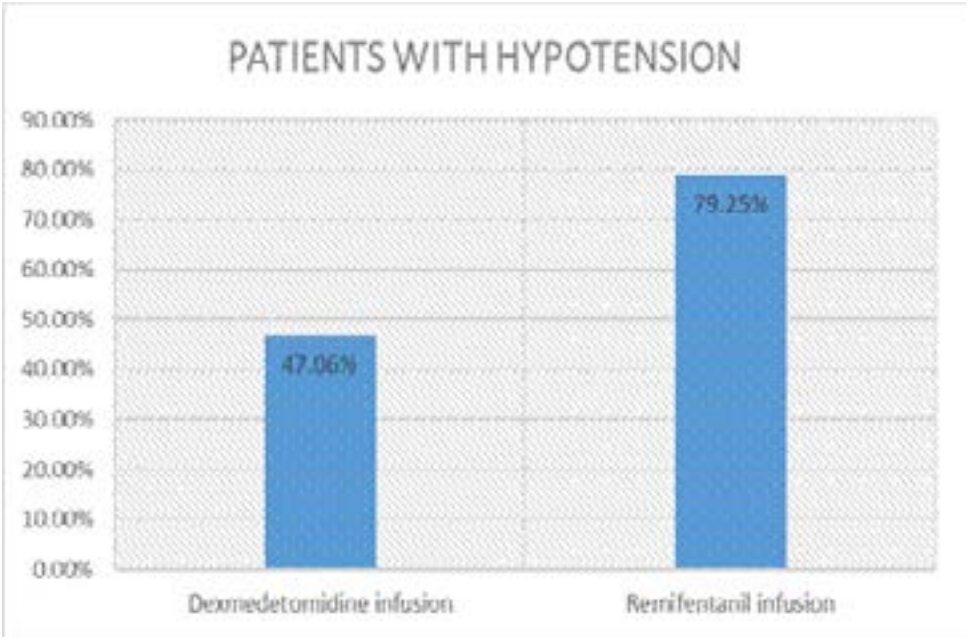
Table 4: Analgesia administered in the operating room

ANALGESIA				
	Overall N=104	**Remifentanil Group n=53**	**Dexmedetomidine Group n[1]=51**	**P value**
Paracetamol	104(100%)	53(100%)	51(100%)	1
NSAIDs	89(85.58%)	44(83%)	45(88.2%)	0.449
NSAIDs Avoided	15(14.42%)	9(17%)	6(9.8%)	
OPIOID USE				
Morphine	90(86.54%)	51(96.22%)	39(76.47%)	0.2365
Pethidine	3(2.88%)	1(1.89%)	2(3.92%)	
Tramadol	4(3.85%)	0(0.00%)	4(7.84%)	
None	7(6.73%)	1(1.89%)	6(11.6%)	

Pearson's uncorrected Chi square test was used to compare the use of analgesia between the two groups.

The proportion of hypotension episodes developing between patients receiving dexmedetomidine infusion and remifentanil infusion is illustrated in the figure 2 and table 5.

Figure 2 showing the proportion of patients who developed hypotension between the two groups.



P value using Fischer's exact test <0.001

Table 5: Relative risk ratio for having at least one hypotensive episode

	Hypotension	**Normal Blood Pressure**	**TOTAL**
Dexmedetomidine infusion	24(47.06%)	27(52.94%)	51
Remifentanil infusion	42(79.25%)	11(20.75%)	53
R.R= 0.5938			
95% C.I= 0.329-0.819			

R.R- Relative Risk ratio, C.I-Confidence interval

There was a greater proportion of hypotension in patient's receiving remifentanil versus patients receiving dexmedetomidine (79.25% against 47.06 %) at standard rates of 0.2mcg/kg/minute versus 0.4mcg/kg/hour.

The proportion of patients with a hypotensive episode between each group was statistically significant (p value <0.0001). The risk ratio being less than 1 implied the likelihood of hypotension developing in patients receiving remifentanil infusion at 0.2mcg/kg/minute was 59.38%.

There were more episodes of hypotension in the remifentanil arm (3.04 per patient) than in the Dexmedetomidine arm (2.08 per patient) as illustrated in table 6.

Table 6: Number of hypotensive episodes in patients with hypotension during surgery

	EPISODES OF HYPOTENSION
Remifentanil n=42	128
Dexmedetomidine n[1]= 24	50

Comparison of the lowest hypotensive MAP was done using independent student t test.

The lowest hypotensive mean arterial pressures between the two groups recorded were similar and not statistically significant as shown in table 7. This is clinically satisfactory.

Table 7: The lowest hypotensive MAP recorded during surgery

	Overall N=66	**Remifentanil Group n=42**	**Dexmedetomidine Group n[1]=24**	**P- value**
MAPs of the lowest episode of hypotension in mmHg	53.81±7.48	53.34±7.22	54.63±7.98	0.5040

MmHg- Millimeters of mercury

The management required variable physician interventions which included: -

1. Administration of Hartmann's solution boluses.
2. The administration of vasopressors.
3. Titration of infusions.
4. Termination of the infusions.

These were options left to the discretion of the team. They were used as single or combined treatments. Forty five patients from both arms received Hartmann's fluid bolus. 65.96% of the patients who experienced hypotension were in the remifentanil arm against 48.15% in the Dexmedetomidine arm. Volumes received in both arms of the study is illustrated in table 8.

Table 8: Volume of Hartmann's fluid boluses administered to treat the patients with hypotension

	Overall N=45	**Remifentanil Group n=31**	**Dexmedetomidine Group n¹=14**	**P value**
Volume of Hartmann's boluses given in mls	181.81±106.25 (100-500)	187.1±111.78 (100-500)	169.23±94.73 (100-400)	0.6064

The means of the volume of Hartmann's fluid bolus of the two groups were compared with unpaired t-test.

The mean volume infused in the dexmedetomidine group was less compared to the remifentanil arm but there was no statistical significance. 19.70% of the patients who developed hypotension received ephedrine and 28.78% received phenylephrine. The use of ephedrine between the groups was significant as illustrated in table 9. Fisher's exact test was used to compare the two groups. The proportion of patients requiring the infusion rates to be titrated downwards was similar between the two groups at 79.17 % in the dexmedetomidine group and 85.71% in the remifentanil group. The minimum rate of infusion in each group remained in the recommended dose ranges suitable for anaesthesia in patient's undergoing surgery.

Table 9: Use of vasopressors in patients with hypotension during surgery

	Overall N=66	**Remifentanil l Group n=42**	**Dexmedetomidine Group n¹= 24**	**P value**
Ephedrine	13(19.7	4 (9.52 %)	9(37.5 %)	0.036062
	Overall N=66	**Remifentanil Group n=42**	**Dexmedetomidine Group n¹= 24**	**P-value**
Phenylephrine	19 (28.78%)	13(30.10 %)	6(25.00 %)	0.0

The proportion of patients requiring termination of the infusion was higher in the remifentanil arm at 11.90 % while the dexmedetomidine group had none. This was statistically insignificant following comparison of the two study arms with Fischer's exact test p= 0.1499. The average rate of infusion of remifentanil and dexmedetomidine in the patients recruited in this study was 0.154mcg/kg/minute (S.D±0.05) and 0.39mcg/kg/hour (S.D±0.13) respectively.

Discussion

Intra-operative hypotension remains a common side effect of inhaled and intravenous anaesthetics agents used in general anaesthesia. This study demonstrated that there was a significantly higher proportion of patients receiving remifentanil infusion who developed hypotension than those on dexmedetomidine. Among patients in either group who developed hypotension, the hypotensive episodes were also more frequent in the patients receiving remifentanil infusion.

Salman and his colleagues compared remifentanil to dexmedetomidine at similar infusion rates in females undergoing ambulatory laparoscopic gynecological procedures[23]. The loading dose during induction was ten minutes in each group whereas in this study, remifentanil was loaded for one minute as prescribed.

Their baseline characteristics including duration of surgeries were similar between the two groups. The population in this study had both gender and heterogeneous operative procedures. They used BIS monitoring to ensure standardized depth of anaesthesia which was not used here. They noted the systolic blood pressures between the two groups were similar and did not report hypotension throughout surgery. The results in the current study have shown that hypotension does occur at these rates of infusion and is frequent 2.7 vs 2.1 per patient in remifentanil and dexmedetomidine respectively. The current study demonstrated that despite the occurrence of hypotension, the lowest mean arterial pressure readings during surgery between the two groups was clinically acceptable. No adverse cardiovascular events were reported requiring resuscitation which is similar to Salman's findings.

Jung et al compared the haemodynamic profile of remifentanil and dexmedetomidine infusions at varying infusion protocols and the blood pressures were significantly lower in patients on dexmedetomidine[24]. This is different from the current results. Although infusion rates were well within the recommended doses, their infusion rates were as high as 0.7 mcg/kg/hour, which is higher than the 0.4mcg/kg/hour used in the current study. Thus, it is possible that the higher rates of hypotension were due to their higher infusion rates. The lowest mean arterial pressure during surgery was similar between the two groups revealing the safety profile of both drugs during surgery and there were no cardiac adverse events and significant blood loss reported.

The females enrolled in the study were slightly greater than males and did not influence the outcome of proportion of patients with hypotension between the groups. This was a result of the recruitment process. The proportion of patients with hypotension between the sexes was not significant (p = 0.8023). Women physiologically have an active parasympathetic system, higher estrogen levels and a lower center of gravity which would influence blood pressure as demonstrated by Cheng and his colleagues[25] but Sachin Kheterpal et al demonstrated that gender was not a predictor of cardiac adverse events peri-operatively in patients undergoing elective surgery[26].

The average infusion rate of dexmedetomidine was 0.39mcg/kg/hour indicating better hemodynamic stability in the population selected for the study. The average infusion rate of 0.154mcg/kg/min in remifentanil showed this could be the rate of infusion that provides haemodynamic stability in our population as opposed to 0.2mcg/kg/min in this study.

The volume of Hartmann's solution administered as boluses was similar between the two groups. There was a greater preference in using phenylephrine than ephedrine in both arms. Using weight based infusions and calculating the percentage increase from the mean arterial pressure could have been a better measure of the value of volume boluses and managing hypotension. Ephedrine was commonly used to raise blood mean arterial pressures in the dexmedetomidine arm (37.5% vs 8.51%; p = 0.007). The mode of managing hypotension was at the discretion of the anaesthetist. Comparing a single agent for example phenylephrine at 100mcg and determining the time period before the next hypotensive episode may have demonstrated the value of the vasopressors in managing episode between the two arms.

No study has determined the equipotent doses of remifentanil and dexmedetomidine. It would be very valuable but costly as laboratory tests are necessary for each patient. This would then enable us to induct studies in the same setting to yield better and accurate results.
This study has demonstrated the average rate of infusions required in remifentanil and dexmedetomidine in the Kenyan population undergoing surgery. It has also raised awareness on dexmedetomidine as an adjuvant to inhaled anaesthetic agents and its use peri-operatively.

The use of dexmedetomidine intra-operatively as a substitute to remifentanil infusion would result in a lower proportion of patients getting hypotension and fewer episodes during surgery. Other studies have shown it also reduces the risk of apnoea, nausea, vomiting and opioid induced hyperalgesia during recovery. The effect of lower sedation scores may be suitable in patients requiring sedation post-operatively. Termination of its infusion is very important in patients requiring prompt ambulation for example day care surgery

Limitations

Limitations to the study include the use of simple randomized sampling. We did not use Bispectral index (BIS) monitoring to ensure standard depth of anaesthesia and eliminate the probability of the inhaled anaesthetic agent contributing to the hypotension in patients. BIS monitoring is available at our hospital but is very costly. It would be unethical to extend the cost to the patient and the budget allocated for the study was short of covering the cost. Lastly our study had single blinding and this could have been a potential source of bias.

Conclusion

The conclusion to this study is that at standard infusion rates, the proportion of patients and risk hypotension is greater in patients undergoing elective surgery receiving remifentanil at 0.2mcg/kg/min than in dexmedetomidine at 0.4mcg/kg/hr. under isoflurane anaesthesia.

Conflit of interest

None.

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