ORIGINAL ARTICLE

Effect of Single Dose Pre-induction Dexmedetomidine on Anaesthetic Requirement and Pain Profile in Orthopaedic Surgery: A Placebo-controlled Double Blind Randomised Controlled Trial

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ABSTRACT

Introduction: Dexmedetomidine, a selective α^2-adrenoreceptor agonist is an important adjuvant to general anaesthetic practice in view of its potent sedative, anaesthetic-sparing and analgesic effects. We investigated the effect of a single dose pre – induction dexmedetomidine on the anaesthetic requirement during surgery and pain profile. **Methods:** 60 patients who were ASA I - II and planned for orthopaedic procedures under general anaesthesia were recruited. Patients were randomized into 2 groups: Group D received intravenous (IV) dexmedetomidine 1 µg/kg (n=30) preoperatively or Group P received normal saline (n=30) instead. Both groups were induced with standardised IV induction agents and anaesthesia maintained with Sevoflurane, titrated using the bispectral index scale. The expired fraction of sevoflurane and haemodynamic parameters were recorded at 5-minute intervals intraoperatively. Postoperatively, postoperative pain score (VAS) was documented at 30 minutes recovery. **Results:** Our study showed a 27.8% reduction in the intraoperative expired fraction of sevoflurane requirement in group D versus 11.5% reduction in Group P ($p < 0.001$) and a lower mean heart rate in Group D as compared to Group P [mean (CI): 69.20 (64.03, 74.37) versus 82.00 (72.12, 91.87) per minute, $p = 0.00$]. The mean (SD) VAS for 30 minutes postoperative pain was significantly lower in group D when compared to group P [1.507(0.275) vs 2.209(0.403), $p = 0.00$]. **Conclusion:** This study has shown that a single dose of pre-induction dexmedetomidine was able to significantly reduce anaesthetic requirement of sevoflurane and mean heart rate intraoperatively and postoperative pain.

Keywords: Dexmedetomidine, Sevoflurane, Pain, Extubation, Recovery

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INTRODUCTION

Fast track or enhanced recovery after surgery(ERAS) programmes establish a range of perioperative interventions to facilitate postoperative recovery especially after elective surgeries (1). Although traditionally, ERAS was initiated by the colorectal surgeons, nowadays other surgical fields, namely orthopaedic surgery are embracing this new pathway. In 2010, National Services Scotland's Musculoskeletal Audit investigated the outcome of orthopaedic population when the ERAS pathway was implemented. The audit clearly showed the positive benefit of earlier recovery and shorter hospital stay (2).

Amongst the interventions in the consensus guidelines for ERAS were pre-anaesthetic medication. It advocated short acting drugs that should minimise the intraoperative anaesthetic requirement and facilitate earlier recovery and ambulation (1). Aim of premedication in perioperative period are provision of anxiolysis, pain relief, amnesia, and the attenuation of sympathetic response. Dexmedetomidine a highly selective α^2 adrenergic agonist (α^2: α^1 ratio of 1600: 1) provides excellent perioperative haemodynamic stability with decreased intraoperative analgesic consumption (3). In a metanalysis performed in 2013, noted that the use of intraoperative dexmedetomidine lead to lower postoperative pain intensity but was complicated with intraoperative bradycardia (4).

The clinical question in our study was to examine the effect of single dose pre-induction of IV dexmedetomidine to the volatile agent requirement

during anaesthesia, intraoperative haemodynamic changes, and postoperative pain score. If so, it could be something we could adapt in line with the ERAS recovery programme in our institution.

MATERIALS AND METHODS

After obtaining approval from the Human Research Ethics committee Universiti Sains Malaysia (USM/PPSP/Ethics Com./2006(176.3(6)), we performed a prospective, randomized double blind clinical trial involving 60 patients for elective orthopaedic procedures with estimated duration of less than 90 minutes. Inclusion criteria were age between 18 to 60 years, American Association of Anaesthesiology (ASA) status class I or II, scheduled for inpatient procedure associated with postoperative pain and scheduled for at least 24 hours stay in hospital. The exclusion criteria include second- and third-degree heart block, patients on α^2 adrenoreceptor agonist within 28 days before the scheduled surgery, chronic opioid therapy, body mass index (BMI) more than 30kg/m^2, pregnant, and a history of sleep apnoea and allergy.

Participants were randomized by using computer generated block randomization with equal proportion of intervention to either Group D (dexmedetomidine group) (n = 30) or Group P (normal saline group) (n = 30). The required amount of dexmedetomidine (1µg/kg) was transferred to a 20ml syringe, diluted to 20ml with normal saline and given over 5 minutes through the intravenous catheter 10 minutes prior to induction. The study drug was prepared by a study investigator that played no role in assessing patient's outcome. The study drug was infused by a blinded nurse not involved in the trial. Participants and attending anaesthetist were blinded to the study.

Participants had an intravenous access secured with a 20 Gauge catheter, electrocardiogram (ECG), non-invasive arterial blood pressure (BP), heart rate (HR), pulse oximetry (spO2) and a Bispectral Index (BIS) forehead strip applied at the holding bay. Haemodynamic variables and Ramsey sedation scale were recorded at five-minute intervals but BIS monitoring (BIS monitor Model Aspect Medical Systems, Norwood, MA) was only commenced later in the operating room. Following this, within 10 minutes, induction of anaesthesia was initiated in the operating room. All patients were preoxygenated with oxygen for 3 minutes and induced with intravenous (IV) fentanyl 1.5µg/kg and IV thiopentone 4mg/kg. IV rocuronium 1mg/kg was used to facilitate intubation. Patients were maintained on a sevoflurane: oxygen: nitrous oxide mixture of 2:1:2 at 3L/min of fresh gas flow.

Non-invasive BP, ECG, spO2, end tidal sevoflurane concentration and BIS were monitored every 5 minutes from the point of anaesthetic induction to when the patients were extubated. Heart rate and blood pressure were maintained within 20% of the pre-induction value. Depth of anaesthesia was maintained at 40 to 60. In the event of the BIS going above 60, sevoflurane concentration was increased by 0.25% every 5 minutes till it reached the intended value provided heart rate and blood pressure were maintained within the recommended value. The opposite was done when the BIS score went below 40. In the event of HR and NIBP > 20% despite maintenance of sevoflurane concentration, rescue IV fentanyl 1ug/kg bolus was provided.

Sevoflurane was discontinued once the final stitch of skin closure was applied. Nitrous oxide was discontinued after residual neuromuscular blockade was reversed with neostigmine (50ug/kg) and atropine (20ug/kg). The extubation time, which is the time taken after stopping the sevoflurane to the time of extubation was documented. Participants were sent to the recovery room and pain score Visual Analogue Score (VAS) was documented at 30 minutes in the recovery room. Participants were discharged to respective wards once deemed fit by recovery criteria.

Based on previous study by (5), the sevoflurane requirement was reduced by 33%. A sample size of 60 (n = 30 in each group) were needed to achieve a significant reduction of 25% and power of study of 80%, where $\alpha = 0.05$ (level of significance), M= 1 (ratio between two group), $\delta = 0.4$ and the standard deviation (SD) was taken as 0.5. The calculated sample size according to PS Power and Sample Size calculation Copyright © by William D. Dupont and Walton D. Plummer.

All data analysis and data entry were done using the Statistical Package of Social Science (SPSS) version 20.0 software licensed to Universiti Sains Malaysia. Indepedant t-test was used for analyzing the difference between two groups' means with normal distribution. The Chi-squared (χ^2) test was used to compare the frequencies of two categorical variables. Level of significance (α) was set at 0.05 and p value <0.05 was accepted as significant.

RESULTS

A total of 60 patients were included in this study. 30 patients in Group D and the other 30 in Group P with baseline demographics of the patients that were comparable (Table I).

There was a significant reduction in the end-tidal sevoflurane concentration in Group D compared to Group P from 30 minutes to 90 minutes (Fig. 1). There was a significant reduction in the expired fraction of sevoflurane of 27.8% in Group D in comparison to only 11.5% reduction in the group P ($t = 4.986$; $p < 0.001$) (Fig. 2)

Table I: Demographic Characteristics

Variables	Group D (n=30)	Group P (n=30)	*t*-values	*p* value
	Mean ± SD			
Age(years)	27.07 ± 9.84	26.60 ± 9.79	-0.184	1.36[b]
Weight (kg)	57.07± 10.61	60.77 ± 10.48	0.86	0.179[b]
Gender				
- Male	86.7 (26)[a]	83.3 (25)	0.131	0.718[c]
- Female	13.3 (4)	16.7 (5)		
Type of surgery				
-Plating of radius/ ulna	23.3(7)	30.0(9)		
-Plating femur	26.7(8)	20.0(6)		
-Removal of implant	23.3 (7)	26.7(8)		
-Arthroscopy surgery	26.7 (8)	23.3(7)		
Duration of surgery (min)	63 ± 20.4	60 ± 23.1	-0.13	1.27[b]
Number of intraoperative fentanyl 1µ/kg given (times)	1.32 ± 0.64	2.19 ± 1.06	-0.10	1.02[b]

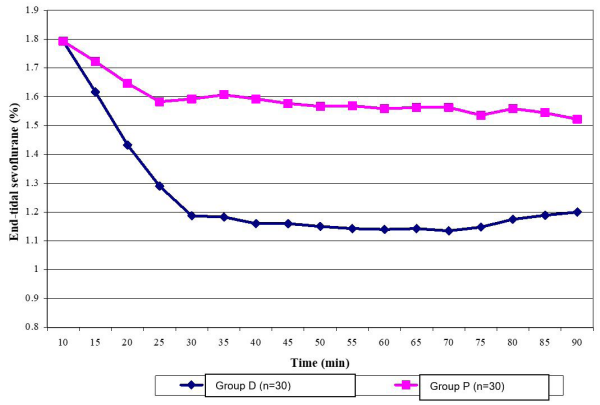

Figure 1: The line graph shows mean expired fraction variation of Sevoflurane (ETsevo) versus time in minutes between group D versus Group P, Blue legend group D (n=30), Pink legend group P (n=30)

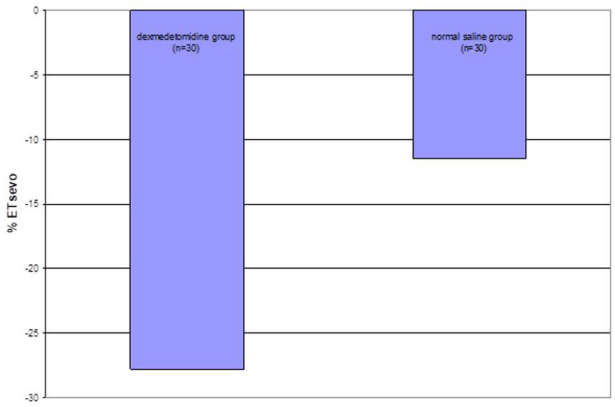

Figure 2: The histogram shows deduction in the expired fraction of sevoflurane (ETsevo) between Group D versus Group P

There was no significant difference in systolic and diastolic BP. However, there was significant lowering of mean HR (CI) in Group D as compared to Group P (mean (CI): 69.20 (64.03, 74.37) versus 82.00 (72.12, 91.87) per minute, p = 0.00) (Fig. 3).

Postoperative mean (SD) VAS at 30 minutes postoperatively was significantly lower in Group D when compared to Group P [mean (SD): 1.507(0.275) vs 2.209(0.403)] (Table II).

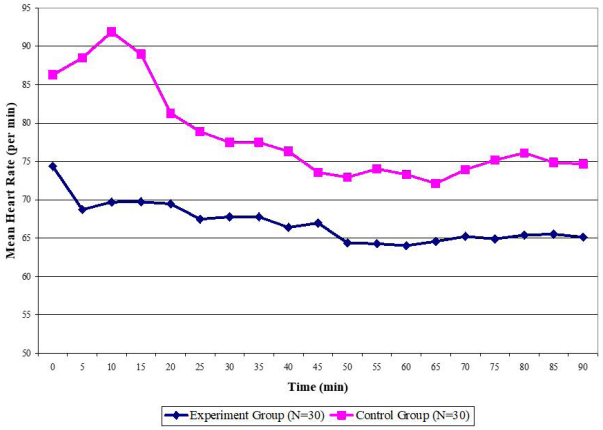

Figure 3: The line graph shows mean heart rate per minute versus time in minutes of Group D versus Group P, Blue legend group D (n=30), Pink legend group P (n=30)

Table II: Postoperative mean Visual Analogue Score at 30 minutes post operation of Group D versus Group P

Variables	Group D (n=30)	Group P (n=30)	*t*-values	*p* value
	Mean (SD)			
Pain	1.507 (0.275)	2.209 (0.403)	6.623	0.000[b]
- Mild pain (≤3 score)	80(24)[a]	20(6)		
- Moderate pain (4 – 6)	20(6)	50(15)	23.66	0.001[c]
- Severe pain (>7-10)	0	30(9)		

DISCUSSION

Our study concluded that single IV premedication of dexmedetomidine of 1 µg/kg was associated with a dose dependent reduction of expired fraction of sevoflurane in patient's undergoing elective orthopaedic procedures. It also shows the analgesic sparing effect of dexmedetomidine as our patients experienced less pain in the immediate postoperative period.

Dexmedetomidine has ideal properties as a perioperative adjuvant agent which are mediated by its potent effects on the α^2 adrenoceptors in the central and peripheral nervous system. Under the influence of dexmedetomidine, patients are easily rousable with clear headedness and minimal respiratory depression as it exerts its natural sleep like action through central

activation of α^2-receptors within the locus coeruleus (6).

In line with ERAS, we are seeking to facilitate the lower usage of anaesthetic dose while ensuring safe anaesthetic depth by means of appropriate adjuvant agents (7). Several authors had already reported a reduction in the inhalation anaesthetic agent consumption after a loading dose followed by maintenance infusion of dexmedetomidine but in this study only a loading dose of 1 ug/kg was given 10 minutes before induction. Our study is unique as it is BIS guided and haemodynamics are monitoring as well to show the anaesthetic sparing effect of dexmedetomidine.

The usage of premedication dexmedetomidine at 1 µg/kg also shows lesser haemodynamic disturbances within the intraoperative period. The greater sympathetic response to tracheal intubation and extubation was attenuated in the dexmedetomidine group as was intraoperative heart rate variability in the study by Lawrence (8). There were even studies looking at even lower doses of dexmedetomidine at 0.5 ug/kg but that showed less efficacy in controlling the sympathetic response to stimulation (9).

Similarly, another study by Lawrence et al studied single preinduction dose of 2 µg/kg on anaesthetic requirement and perioperative haemodynamic stability. It was found that the isofluorane requierement were reduced however at the expense of hypotension and bradycardia in the interventional group (10).

Interestingly, single dose preinduction dexmedetomidine of 0.5 µg/kg also was able to improve recovery in ambulatory care patients. Study by Shariffuddin shows that higher resumption of daily activities by 48 hours in subjects treated by preinduction dexmedetomidine (11). There are also studies that examine different routes of admimistration of preinduction dexmedetomidine especially intravenous versus intranasal routes. This study showed a higher sedation score in patients receiving single dose preinduction intravenous dexmedetomidine 0.5 µg/kg compared to intranasal 1 µg/kg (12).

Dexmedetomidine inhibits pain signals to the brain by inhibiting the release of norepinephrine, which in turn induces hyperpolarization at the central pre and postsynaptic α^2-receptors. Dexmedetomidine an analgesic adjuvant helps to modulate the release of nitric oxide by initially releasing of acetylcholine from spinal interneurons as well (13).

Dexmedetomidine has shown excellent opioid sparing effect which is vital in our aim to promote ERAS in our institution. Studies have postulated that patient's benefit from earlier recovery not due to suppression of inflammatory stress response to surgery but rather the opioid sparing effect that it provides. Despite being a single and small dose as premedication, the significant reduction of pain translates into better quality recovery and shorter hospital stays (14).

Various authors have also studied the antinociceptive action of dexmedetomidine at a single bolus dose of 1 ug/kg compared to 0.2–0.7 µg/kg/h infusion(15). It found that single doses of 1 ug/kg were able to provide superior pain control in the postoperative period up to 24 hours. However, in our study we were able to establish that despite similar dosage requirement of fentanyl was used in the intraoperative period, the recovery profile was better in terms of VAS up to 30 minutes postoperatively.

Limitations of our study was that patient's that were recruited were in-patients as opposed to day-care patients that may have benefited more in this study in line with ERAS. We could have investigated other parameters to assess quality of recovery in day-care patients. Notably, our research question should have been lengthened to include opioid requirements post-surgery as well.

CONCLUSION

Dexmedetomidine given preoperatively as a single dose could benefit patients by reducing intraoperative requirement of sevoflurane and obtund the haemodynamic response to surgery. It also offers opioid sparing effects that translates into better recovery profile as well.

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