Haemodynamic and anaesthetic advantages of dexmedetomidine

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Abstract

Objectives: The aim of this study was to describe the effect of dexmedetomidine on haemodynamic stability in the intraoperative period, as well as on the pressor response to intubation and extubation and the requirement of inhalation anaesthetics and recovery.

Design: A simple descriptive study.

Settings and subjects: The study was conducted in a tertiary hospital in India from June 2010-June 2011. The 81 American Society of Anesthesiologists classification I and II patients who were enrolled in the study were given a loading dose of dexmedetomidine 1 µg/kg, followed by a continuous infusion of 0.5 µg/kg/hour. Supplementation with end-tidal sevoflurane 1-2% was considered when heart rate (HR) and mean arterial pressure exceeded 20% of baseline values. On completion of surgery, the time taken to discontinue dexmedetomidine infusion and the extubation time were recorded.

Outcome measures: Changes in haemodynamic variables from baseline and a comparison of means were analysed by paired t-test for each time interval.

Results: There was significant reduction in HR and systolic blood pressure following the loading dose of dexmedetomidine (12.31% and 8.82% respectively), in the intraoperative period (17.71% and 16.5% respectively), and during intubation and extubation (p-value < 0.001). None of the patients required supplementary doses of analgesics in the intraoperative period. Only 13 patients required end-tidal sevoflurane of 1% during the study. Seventy per cent of patients could be extubated within five minutes of discontinuing the infusion.

Conclusion: Dexmedetomidine provided a stable haemodynamic profile in the perioperative period and a blunted pressor response to intubation and extubation. With its use, there was a minimal requirement for analgesics and inhalational agents. It had an acceptable recovery profile.

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Introduction

Dexmedetomidine, a highly selective, potent α_2-adrenoreceptor agonist, has sedative, analgesic, anxiolytic and sympatholytic properties that blunt many of the cardiovascular responses in the perioperative period. It has been used widely in anaesthesia as a premedicant analgesic to attenuate a sympathetic response to surgery in the perioperative period, and to potentiate the anaesthetic effects of all intraoperative anaesthetics.

Dexmedetomidine has been used as a sole sedative for noninvasive procedures and as an adjunct for invasive procedures.[1] In one study, dexmedetomidine was used as a sole anaesthetic agent in three patients, but at higher doses.[2]

The purpose of this study was to use intravenous dexmedetomidine as an anaesthetic agent in the intraoperative period at a loading dose of 1 µg/kg for 10 minutes, followed by a continuous infusion of 0.5 µg/kg/hour, and to describe its effect on haemodynamic stability, analgesic and inhalation

anaesthetic requirements, the pressor response to intubation and extubation, and recovery.

Method

The study was conducted in a tertiary hospital in the coastal region of south India from June 2010-June 2011. The study protocol was approved by the hospital ethics committee. Written informed consent was obtained from the patients. A total of 81 American Society of Anesthesiologists (ASA) classification I and II patients aged between 18 and 50 years, who underwent elective surgical procedures under general anaesthesia, were enrolled in the study. Patients posted for emergency surgical procedures, patients with severe pulmonary, hepatic, cardiac or renal disease, and pregnant patients were excluded from the study.

Patients in the study group were given 0.5 mg of alprazolam the night before surgery. On the day of surgery, the patient's baseline values of heart rate (HR), noninvasive blood pressure (NIBP), peripheral oxygen saturation (SpO_2) and end-tidal carbon dioxide ($EtCO_2$) were recorded. An 18-gauge intravenous cannula was inserted and the patient was preloaded with 5 ml/kg of crystalloids. Before induction of anaesthesia, the patients were given a loading dose of 1 µg/kg intravenous dexmedetomidine over 10 minutes, while HR, BP, SpO_2 and the electrocardiogram (ECG) were monitored, followed by a continuous infusion of dexmedetomidine at 0.5 µg/kg/hour until closure of the surgical incision.

Anaesthesia was standard for all the patients. The patients received intravenous doses of 0.02 mg/kg midazolam, 2 µg/kg fentanyl, 0.2 mg glycopyrollate and 4 mg ondansetron before induction of anaesthesia and after the loading dose of dexmedetomidine. Induction was achieved with 5 mg/kg intravenous thiopentone. Intubation was facilitated by 0.1 mg/kg intravenous vecuronium. The lungs were ventilated by maintaining a tidal volume of 7-10 ml/kg, a frequency of 12 breaths/minute and an $ETCO_2$ of 35-40 mmHg in 3 l/minute of fresh gas flow with 66% nitrous oxide in oxygen in a closed circuit. Muscle paralysis was maintained with an intermittent intravenous bolus of 1-2 mg of vecuronium, based on the train-of-four response.

Routine monitoring consisted of NIBP, ECG, SPO_2 and $EtCO_2$, recorded every five minutes. The aim was to maintain HR and mean arterial pressure (MAP) within 20% of baseline values. Intraoperative side-effects were defined as bradycardia (HR < 45 beats/minute), hypotension [a decrease in systolic blood pressure (SBP) > 20% from the baseline and/or < 80 mmHg] and hypertension (an increase in SBP of > 20% from the baseline and/or > 150 mmHg), and were also recorded. An increase in HR and/or MAP > 20% from baseline values was treated by increasing the infusion of dexmedetomidine to 0.75 µg/kg/hour. If there was no response within five minutes, sevoflurane was administered at an end-tidal concentration of 1%, and increased to 2% if required. Hypotension was treated with intravenous crystalloids and ephedrine and by reducing the infusion rate of dexmedetomidine by 50%. Atropine 0.6 mg was administered in the event of complicating bradycardia.

On completion of surgery, the neuromuscular blockade was reversed with 0.05 mg/kg intravenous neostigmine and 0.2 mg of glycopyrolate for each milligram of neostigmine. The discontinuation time of the dexmedetomidine infusion was recorded. The standard procedure of extubation was followed and the time of extubation recorded.

Statistical analysis

Statistical tests were performed using SPSS® version 11.05. Demographic data and operation characteristics were evaluated using descriptive statistics. Data were expressed as mean values ± standard deviation (SD). Changes in haemodynamic variables from baseline and a comparison of means were analysed by paired t-test for each time interval. Further analysis was carried out for intervals during which differences from the baseline were statistically significant. A value of p-value < 0.05 was considered to be statistically significant.

Results

A total of 81 patients who underwent elective surgical procedures under general anaesthesia were enrolled in this study. The patient demographics and the type and duration of surgery are shown in Table I. The mean duration of the surgical procedure was 176.56 ± 84.73 minutes. The minimum duration was 55 minutes and the maximum duration was 585 minutes.

The distribution of co-morbid conditions is listed in Table II.

Table I: Patient demographics, type and duration of surgery

Description	Values
Age (years)	**39.43 ± 12.79**
Gender (female/male)	**42/39**
Weight (kg)	**61.23 ± 12.47**
ASA physical status (I/II)	**41/40**
Duration of surgery (minutes)	**176.56 ± 84.73**
Type of surgery	
Oral, maxillofacial and ENT	20 (25%)
General	12 (15%)
Spine	17 (21%)
Brain	5 (6%)
Orthopaedic	2 (2%)
Thyroid	15 (19%)
Laparoscopy	9 (11%)

Values are expressed as mean ± standard deviation or number of patients (proportion)
ASA: American Society of Anesthesiologists, ENT: ear, nose and throat

Table II: Co-morbid conditions encountered in the study

Co-morbid conditions	n (proportion)
Hypertension	24 (30%)
Type 2 diabetes mellitus	4 (5%)
COPD	3 (4%)
Anaemia	2 (2%)
Hypothyroidism	3 (4%)
Hyperthyroidism	1 (1%)
Ischaemic heart disease	2 (2%)
Past history of CVA	1 (1%)

COPD: chronic obstructive pulmonary disease, CVA: cerebrovascular disease

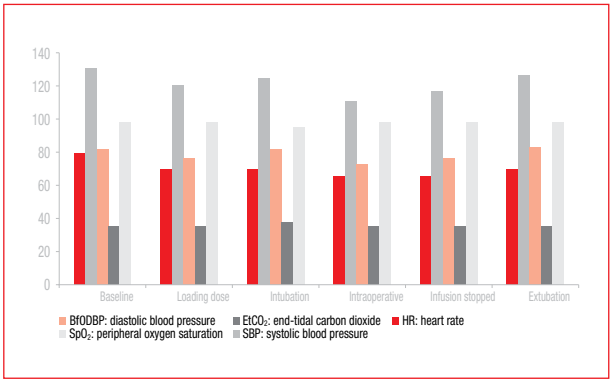

Figure 1: Perioperative hemodynamic variables

Table III: Perioperative haemodynamic variables

Vital	Baseline	Loading dose	Intubation	Intraoperative	Infusion stopped	Extubation
HR (beats/minute)	80.5 ± 15.14	71.4 ± 13.50**	73.4 ± 11.93**	67.1 ± 9.64**	67.5 ± 10.26**	70.9 ± 10.20**
SBP (mmHg)	134.3 ± 18.46	123.8 ± 19.02**	127.4 ± 19.72*	113.6 ± 12.61**	118.8 ± 14.88**	129.4 ± 14.91*
DBP (mmHg)	81.4 ± 10.81	76.0 ± 10.05**	79.9 ± 14.08	73.9 ± 7.18**	76.4 ± 10.60**	82.3 ± 9.53
$EtCO_2$ (mmHg)	33.4 ± 2.88	33.3 ± 2.66	35.9 ± 3.35	32.9 ± 2.81	32.4 ± 4.93	32.6 ± 2.79
SpO_2 (%)	99.7 ± 0.81	99.1 ± 0.19	97.3 ± 0.19	99.9 ± 0.38	99.9 ± 0.11	99.9 ± 0.11

Values are expressed as mean ± standard deviation
Baseline data compared to others: * p-value < 0.05; ** p-value < 0.001
DBP: diastolic blood pressure, $EtCO_2$: end-tidal carbon dioxide, HR: heart rate, SD: standard deviation, SpO_2: peripheral oxygen saturation, SBP: systolic blood pressure

Table IV: Adverse effects (once surgery was deferred)

Adverse effects	n (proportion)
Bradycardia	1 (1.2%)
Hypotension	1 (1.2%)
Hypertension	1 (1.2%)

Twenty-four patients (30%) in the study had hypertension, which was optimised before surgery. Sixteen patients could be maintained with dexmedetomidine alone in the intraoperative period. Of these, two patients required an increase in the infusion dose to 0.75 µg/kg/hour. The remaining eight patients required end-tidal sevoflurane, ranging from 1-2%.

The intraoperative haemodynamic data are listed in Table III and represented in Figure 1. There was a significant reduction in HR (12.31%) and SBP (8.82%) following the loading dose of dexmedetomidine when compared to baseline (p-value < 0.001). In response to tracheal intubation, there was a 9.78% reduction in HR (p-value < 0.001) and a 6.1% reduction in SBP (p-value < 0.05) when compared to baseline. The maximum reduction in HR (17.71%) and SBP (16.5%) was found in the intraoperative period (p-value < 0.001). A significant reduction in HR (17.18%) and SBP (12.51%) was found at the end of surgery on stopping the dexmedetomidine infusion (p-value < 0.001). During extubation, the reduction in HR (12.78%) was more significant (p-value < 0.001) than the reduction in SBP (9.6%, p-value < 0.05). Diastolic blood pressure showed a significant reduction (9.2%) only in the intraoperative period (p-value < 0.001). There was no statistical significance in the results of SpO_2 and $EtCO_2$ values when compared to baseline.

The adverse effects that were seen with dexmedetomidine are listed in Table IV. Bradycardia, noted in one patient in the study, required treatment with 0.6 mg of atropine intravenously. Hypotension, requiring treatment with intravenous crystalloids and ephedrine, was observed in one patient. Surgery was deferred in one patient who developed hypertension that required treatment following the loading dose of dexmedetomidine.

There was no requirement for supplementary doses of opioids or other analgesics in any of the patients during the infusion of dexmedetomidine in the intraoperative period. Two patients required a reduction in the dose to 0.25 µg/kg/hour, and two required an increase in the infusion dose to 0.75 µg/kg/hour. In this study, none of the patients needed the infusion to be stopped.

Only 13 patients (16%) required supplemental end-tidal sevoflurane of 1% during the study, eight of which had a history of hypertension. Three required sevoflurane for a period of less than 30 minutes, six for a period of 30 minutes to one hour, and two for a period of one to two hours. Two patients (2.5%) required end-tidal sevoflurane 1-2% for more than two hours.

Table V: Recovery profiles encountered in the study

Time to extubation after discontinuation of infusion	Number of patients (proportion)
< 5 minutes	56 (70%)
5-10 minutes	20 (25%)
> 10 minutes	4 (5%)

The recovery profiles of the patients after the discontinuation of dexmedetomidine infusion are listed in Table V. Extubation was possible in 56 of the patients within five minutes of discontinuing the dexmedetomidine infusion. Twenty patients (25%) could be extubated between 5-10 minutes of discontinuing the infusion, while four patients (5%) required more than 10 minutes.

Discussion

In this study, a loading dose of 1 µg/kg dexmedetomidine given over 10 minutes, followed by a continuous infusion of 0.5 µg/kg/hour. The following results were found:

- Blunted pressor response to intubation
- Haemodynamic stability in the perioperative period
- Minimal requirements for additional analgesics and sevoflurane during surgery
- An acceptable recovery profile of the patients who were enrolled in the study.

Dexmedetomidine is a highly selective α_2 agonist. It has potent sympatholytic, anxiolytic, sedative and analgesic properties mediated through α_2-adrenoreceptors in the central and peripheral nervous system. Dexmedetomidine has an α_2:α_1 adrenoreceptor ratio of approximately 1 600:1, which is seven to eight times higher than that reported for clonidine. This ratio favours the sedative and anxiolytic actions, rather than the haemodynamic actions, seen in the same class of α_2-adrenoreceptor agonists, such as clonidine.[3,4] However, systemic administration of dexmedetomidine can produce moderate decreases in blood pressure and HR.[5-8] Its primary site of action is the α_2-adrenoreceptors in the locus coeruleus, a predominant noradrenergic nucleus of the brainstem, which is an important modulator of vigilance.[9,10]

Dexmedetomidine-induced sedation qualitatively resembles normal sleep from which patients can easily be aroused. This type of sedation is termed as co-operative or arousable, to distinguish it from sedation that is caused by drugs acting on γ-aminobutyric acid receptors, such as benzodiazepines or propofol, which reduce consciousness.[9]

Numerous studies have shown that dexmedetomidine reduces the analgesic and anaesthetic requirements in the perioperative period.[11-14] In the present study, dexmedetomidine was used as an anaesthetic agent in the intraoperative period as a continuous infusion, supplemented by sevoflurane only during significant haemodynamic fluctuations which may have caused concern about awareness in the intraoperative period. But studies have shown that dexmedetomidine has a lower bispectral index (BIS) or measure of awareness, when compared to propofol or sevoflurane.[11,15-18] Hall et al found the BIS score to reduce by 30% following infusion of dexmedetomidine at 0.2 µg/kg/hour in healthy volunteers.[11] Elbaradie et al evaluated the degree of sedation with dexmedetomidine using the Ramsay Sedation Score (RSS) and BIS in their study.[15] They found that both propofol and dexmedetomidine had an equal RSS of four, but that dexmedetomidine at an infusion dose of 0.2-0.5 µg/kg/hour had a lower BIS score of 60 when compared to propofol, with a BIS score of 64. Kaskinoro et al recorded the lowest BIS values for dexmedetomidine (BIS 62) when compared to propofol (BIS 73) and sevoflurane (BIS 70).[16] Venn et al reported comparable sedation between propofol and dexmedetomidine, but a lower BIS score with dexmedetomidine (BIS 46) than with propofol (BIS 53).[17] Kasuya et al compared the sedative effect of dexmedetomidine and propofol using BIS and the Observer's Assessment of Alertness and Sedation score (OAA/S). They concluded that, at comparable OAA/S, BIS was significantly less with dexmedetomidine than with propofol.[18] Based on these studies, it was decided to give dexmedetomidine at a loading dose of 1 µg/kg over 10 minutes, followed by a continuous infusion of 0.5 µg/kg/hour in the intraoperative period.

Dexmedetomidine has been used as a sole sedative for noninvasive procedures and as an adjunct for invasive procedures. Ramsay et al have used dexmedetomidine as the sole anaesthetic agent in three patients, although at high doses. Dexmedetomidine was given at a loading dose of 1 µg/kg for 10 minutes, followed by a continuous infusion of 0.7 µg/kg/hour, which was further increased to achieve satisfactory anaesthesia. These authors found that the attributes of dexmedetomidine, namely sedation, analgesia and no respiratory depression, appeared to be sustained at anaesthetic doses. In their study, no patient experienced hypotension or severe bradycardia. There was no evidence that vasoconstriction led to hypertension. Even though the recovery of the patients was from two to three hours with the high dose employed in their study, this is not significantly prolonged when compared to many conventional anaesthetic techniques.[2]

Co-administration of midazolam, fentanyl, propofol or sevoflurane enhances the sedative effect of dexmedetomidine.[13,19] Midazolam (0.02 mg/kg) and fentanyl (2 µg/kg) were used during induction in all the patients. This might have enhanced the sedative effect of dexmedetomidine, but these agents have a short duration of action and are unlikely to enhance the sedative effect of dexmedetomidine for more than two hours. The duration

of 78% of the surgical procedures in our study exceeded two hours. There was no requirement for subsequent supplementary doses of opioids or other analgesics in all the patients, because of the infusion of dexmedetomidine in the intraoperative period. Only four patients (5%) required sevoflurane 1% for more than two hours, which means that the majority of the patients could be maintained on dexmedetomidine without the use of a potent inhalation anaesthetic in the intraoperative period. Our results support the findings of Dawson et al, who proposed that in settings where dexmedetomidine is being administered, a potential clinical advantage may be realised through the addition of nitrous oxide as, together, these two agents provide a synergistic action once tolerance to nitrous oxide has developed.[20] Fukuhara et al reported that clonidine, which is a less selective α_2-adrenoreceptor agonist than dexmedetomidine, also enhanced the analgesic effect of nitrous oxide.[21]

The haemodynamic effects of dexmedetomidine are due to a combination of its central sympatholytic and peripheral vasoconstrictive effects. The bolus of 1 µg/kg results in a transient increase in blood pressure and a reflex decrease in HR, which can be prevented by slow infusion over 10 minutes. This initial response lasts for five to 10 minutes and is followed by a decrease in BP of 10-20% below baseline and stabilisation of HR below baseline values.[9,22] A decision was made to give the loading dose of 1 µg/kg over 10 minutes. A 12.31% reduction in HR, and a 8.82% reduction in SBP from baseline values, was noted.

There was a 9.78% reduction in HR and a 6.1% reduction in SBP during intubation. This implies that dexmedetomidine attenuates the sympathetic response to endotracheal intubation. The results are comparable to those of Ozkose et al, who also found that at a loading dose of 1 µg/kg dexmedetomidine was effective in controlling the haemodynamic response to tracheal intubation.[22] Jakkola et al reported that dexmedetomidine significantly reduced the blood pressure and HR response to intubation at a dose of 0.6 µg/ kg only.[23]

In the present study, a maximum reduction of 17.71% in HR and 16.5% in SBP was seen in the intraoperative period. One patient (1.2%) had bradycardia, while another (1.2%) had hypotension that required treatment. Our results are comparable to those of Bekker et al, who reported that dexmedetomidine, given at a similar dose, was effective in blunting the increase in SBP perioperatively, although it did not increase the incidence of hypotension or bradycardia.[24] Hogue et al reported that dexmedetomidine preserves baroreflex sensitivity and that patients had a normal HR response to blood pressure. The noted slowing of the HR is mostly from sympathetic withdrawal and not due to enhanced vagal activity.[25]

In the present study, two thirds of patients who were hypertensive had a stable haemodynamic profile with dexmedetomidine infusion only. One patient required antihypertensive treatment following the loading dose of dexmedetomidine.

After intravenous infusion, dexmedetomidine has a rapid distribution phase, with a distribution half-life of approximately five minutes and a terminal elimination half-life of approximately 120 minutes.[24] Talke et al reported that the plasma concentration of dexmedetomidine was halved within 20 minutes after continuous infusion for 60 minutes at the rate of 1.15 mg/hour.[12] Even though the elimination half-life of dexmedetomidine is 100-150 minutes, extubation was found to be rapid as 70% of patients could be extubated within five minutes of discontinuing infusion, and 25% could be extubated within 10 minutes of discontinuing infusion. The results are comparable to those in the study by Ozkose et al, who supplemented desflurane in the intraoperative period to maintain BIS at 40-60 and recorded a mean extubation time of four minutes following the discontinuation of dexmedetomidine infusion.[22] Although sedative premedication was not administered in their study, there was a significant reduction in the requirement for desflurane and faster recovery in patients who received dexmedetomidine. Venn et al have stated that dexmedetomidine can be continued safely over the extubation period.[17] In the present study, of the four patients in whom recovery was prolonged, one had hypothyroidism and three patients required end-tidal sevoflurane of 1-2% for surgery that exceeded six hours.

Limitations of the study

A limitation of this study was that there was a lack of BIS monitors to monitor intraoperative awareness and the role of dexmedetomidine in ensuring haemodynamic stability in patients with hypertension. Although 24 patients in our study had hypertension, they were optimised before being taken for surgery. End-organ damage, due to hypertension, was not evaluated in the present study. Hence a conclusion could not be reached regarding the effect of dexmedetomidine in ensuring hemodynamic stability in patients with hypertension.

Conclusion

The loading dose of 1 µg/kg dexmedetomidine, followed by a continuous infusion of 0.5 µg/kg/hour, provided a stable haemodynamic profile in the perioperative period and effectively blunted pressor response to intubation and extubation, leading to minimal requirements for analgesics and potent inhalational agents. There was also an acceptable recovery time with its use. Therefore, dexmedetomidine may provide an effective alternative to currently used anaesthetic regimens for patients in various surgical settings.

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