Original article

Attenuation of haemodynamic response to different doses of dexmedetomidine during extubation in patients undergoing peripheral vascular surgery

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Abstract:

Backgrounds: Dexmedetomidine being a α_2 agonist provides excellent sedation with minimal cardiovascular instability or respiratory depression, decreases intraoperative requirement of drugs and may also help to facilitate smooth tracheal extubation following surgery.

Material and Methods: Fifty four American Society of Anaesthesiologist grade I-II patients, aged 18-65 years old of either sex, scheduled for peripheral vascular surgery were randomly allocated into Group-I (dexmedetomidine 0.5µ gm/kg), Group-II (dexmedetomidine 1µ gm/kg) and Group –III (control). Anaesthesia techniques were standardized. Heart rate, haemodynamic were recorded at base line, while starting injection, at 5, 10 minutes after starting injection, during extubation, at 1, 3, 5, 10 minutes after extubation. Quality of extubation was evaluated on Likert scale and post operative sedation on Ramsay sedation score. Adverse events were also noted.

Results: Heart rate, systolic and diastolic pressures were significantly higher in Group- III (P<0.001). Majority of patients in Group –I and Group –II were found to have smooth extubation with minimal coughing but most of the patients in Group –III experienced moderate cough. . The incidence of bradycardia and hypotension was found little higher in patients treated with dexmedetomidine than in control group. None of the patients in any group developed respiratory depression, laryngospasm, bronchospasm, undue sedation or desaturation.

Conclusion: Dexmedetomidine 0.5 µg/kg administered 10 minutes before end of surgery stabilizes haemodynamics, provides smooth extubation.

Key words: Hemodynamics, dexmedetomidine, extubation, peripheral vascular surgery.

Introduction

Laryngoscopy as well as tracheal intubation in patients undergoing surgery cause significant changes in hemodynamics.[1]A similar type of hemodynamic derangements has been noticed by various workers during tracheal extubation[2, 3]. These responses may produce myocardial ischemia or infarction in susceptible patients. Various agents like esmolol, lignocaine, opioids, calcium channel blockers, magnesium, clonidine have been shown to attenuate these responses[3, 4, 5, 6] but they all have limitations and side effects.

Dexmedetomidine is a highly specific and selective α_2 adrenergic agonist with α_2/α_1-activity 1620:1 as compared with 220:1 for clonidine [7]. This may result in more potent effects of sedation without unwanted cardiovascular effects from α_1 receptor activation.[8] It has potent hypnotic anaesthetic action in rats, mediated via central adrenoreceptors.[9] In recent studies it has been shown to reduce anaesthetic and analgesic requirements.[10, 11] It also demonstrates a sympatholytic property[11, 12, 13] which can be used to attenuate sympathetic surge associated with tracheal extubation.

Different doses have been used for attenuation of stress responses during tracheal extubation on different groups of patients with controversial results.[14, 15] Therefore, the present study was conducted to observe the effects of two different doses of dexmedetomidine on haemodynamics and recovery characteristics during tracheal extubation and also to evaluate the optimum dose of this drug to attenuate these responses in patients undergoing peripheral vascular surgery.

Materials and methods:

This prospective double-blind, randomized, controlled study was approved by Institutional Ethics committee. After obtaining written informed consent from each patient , 54 patients of 18-65 years old having

ASA (American Society of Anaesthesiologist) grade I and II of either sex ,scheduled for elective peripheral vascular surgery (Table:1) under general anaesthesia, were selected for this study. Enrolled patients were randomly allocated into 3 groups; Group-I, Group-II and Group- III. Patients with cardiovascular or respiratory disorder, diabetes, hypertension, obesity, difficult airway, medications that effect heart rate or blood pressure, pregnant, history of sleep apneoa, hepatic or renal impairment were excluded from this study.

Upon arrival in the operating theatre standard ASA monitors were connected and a radial arterial canulation done to check beat-to-beat change of haemodynamic variables. All patients were premedicated with inj. Glycopyrrolate 4 µg kg^{-1} and received inj. fentanyl 2 µg kg^{-1}before induction. Patients were induced with propofol 1-2.5 mg kg^{-1} till loss response to verbal command and bispectral index (BIS) became 50. After achieving all of these induction criteria, every patient received inj. rocuronium 0.9 mg kg^{-1} and waited until train of four (TOF) became zero. After disappearance of TOF twitch response, all patients were intubated with endotracheal tube of appropriate size. After confirming and securing endotracheal tracheal tube all patients were taken to prone position and position of the tube was reconfirmed.

Controlled ventilation was done with N_2O and O_2 (2:1).anaesthesia was maintained with propofol infusion guided by BIS (kept within 50-60), intermittent doses of rocuronium guided by TOF (≥1) and inj was administered fentanyl when, BP and HR increased by 20% above baseline value with BIS score <60.

The systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), end tidal CO_2, BIS (Bispectral index), TOF (Train of Four) and body temperature were recorded for each patient during induction and maintenance of anaesthesia.

Propofol infusion was stopped at skin closer and then, the study procedure started. Patients in Group-I received dexmedetomidine 0.5µg kg^{-1} body wt. dissolved in 10 ml normal saline over 10 minutes,

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in Group –II patients received dexmedetomidine 1µg kg^{-1} body wt. in same manner while patients in Group –III received 10 ml of 0.9% normal saline over 10 minutes.

Heart rate, SBP, DBP were recorded at the start of drug injections and thereafter at 5 min. and 10 minutes.

Residual neuromuscular blockade was antagonised with inj. neostigmine and inj. glycopyrrolate when TOF ratio was > 0.8 and when patients' spontaneous respirations were considered sufficient and patients were able to obey simple commands, throat suction was done and trachea was extubated. The anaesthesiologist performing tracheal extubation was blinded to the study drugs.

Heart rate, SBP, DBP was recorded at tracheal extubation and thereafter at1, 3, 5 and 10 minutes.

Time period from starting of the infusion of the study drug to the 1st verbal response and to extubation were also recorded. Occurrence of any adverse event like laryngospasm, bronchospasm, desaturation, respiratory depression, vomiting or undue sedation was noted. Aldrete scoring was also recorded at 30 minutes following extubation before sending the patients to their respective wards.

Hypotension was defined as a decrease of SBP ≥ 20% from base line or SBP < 100 mm Hg and treated with iv fluids and if required inj. mephentermine 3 mg bolus. Any bradycardia with HR <40 was treated with inj. atropine 20 µg kg^{-1}.

The degree of strain on extubation was graded using a six-point Likert scale (0-Extremely smooth, 1- Very smooth, 2-Somewhat smooth, 3-Somewhat strained, 4- Very strained, 5- Extremely strained) by an observer unaware of the study drug used.

The degree of sedation on extubation was evaluated on a six-pointRamsay sedation scale (1-Anxiousor or agitated or restless, 2- Cooperative, orientated and tranquil, 3- Drowsy but responding to commands,4- Asleep , brisk response to light glabellar tap or loud auditory stimulus, 5- Asleep, sluggish response to light glabellar tap or loud auditory stimulus, 6-Asleep and unarousable) [16].

Data obtained in this study were summarized as mean ± Standard Deviation (SD) for numerical variables and count (%) for categorical variables and were compared between groups by one way Analysis Of Variance (ANOVA) followed by Tukey's test as post hoc test. Repeated measures ANOVA followed by Tukey's test was used to asses change in hemodynamic changes in respective groups. For numerical variables that are not normally distributed, corresponding non-parametric tests were used. The Chi-square test, Fisher's exact test were employed for intergroup comparison of categorical variables.

Statistical analysis was performed using, 1. Statistica version 7 [Tulsa, Oklahoma: StatSoft Inc., 2004], 2.GraphPad Prism version 5 [San Diego, California: Graph Pad Software Inc., 2007]. All analysis was too tailed and *P* value < 0.05 was considered statistically significant.

Results

The patients in these three groups were comparable for age , weight, sex distribution, ASA status, duration of surgery and the difference between the groups are not statistically significant(*P* > *0.05*).(Table:2)

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Heart rate of patients allotted in Group –I and Group- II were significantly lower than Group- III from 5 minutes after starting administration of the study drug till 10 minutes after extubation. No significant difference of heart rate was found between Group –I and Group- II. Similarly, systolic blood pressure of patients allotted in Group- III was significantly higher than patients of Group –I and Group- II from 1minute postextubation till 10 minutes postextubation but no significant difference of systolic blood pressure was found between Group –I and Group- II. This study showed a significant difference of diastolic blood pressure between Group –I and Group- II from the starting administration of the agent till 5 minutes postextubation. This parameter showed statistically significant difference between Group –I and Group- III from 1minute postextubation till 10 minutes postextubation (Table: 3).

Likert scores of patients allocated toGroup – I and Group- II were significantly lower than those in group- III. In present study, most patients in group- I and group- II showed smooth extubation with minimal coughing (Likert scale score 1 and 2 respectively) which were much lower than control group- III, where most patients experienced moderate cough (Likert scale score 3).

In this study patients treated with dexmedetomidine0.5µg kg^{-1} were found to be cooperative, orientated, tranquil (Ramsay Sedation Scale 2) in comparison to higher doses of dexmedetomidine(1µg kg^{-1}) where patients were drowsy but responding to verbal commands (Ramsay Sedation Scale 3) after extubation. Some patients were found restless (Ramsay Sedation Scale 1) in the control group (Figure 1).

The incidence of bradycardia and hypotension, in this study, was found little higher in patients treated with dexmedetomidine than in control group. Only 1 patient in Group -I and 2 patients in Group – II experienced bradycardia(Table: 4). Patients treated with dexmedetomidine, in present study, did not experience any episode of post operative shivering but 4 patients (Chi-square 2-tailed *P value 0.036*) of the control group suffered from it(table: 4). No significant difference in the incidence of vomiting was found between groups. None of the patients in any group developed respiratory depression, laryngospasm, bronchospasm, undue sedation or desaturation (table: 4).

Types of Surgery	Vascular repair			Pseudoaneurysm			Varicose vein		
Drug doses	1µg	0.5µg	control	1µg	0.5µg	control	1µg	0.5µg	control
No. of patients	8	6	7	4	5	4	6	7	7

Table1: types of surgery done in different groups

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variables	Group I (n= 18)	Group II (n= 18)	Group III (n= 18)
Age (years) [mean±SD]	48.72±5.20	53.33±3.50	54±3.85
Weight (kilograms) [mean±SD]	61.72±9.53	60.72±9.58	61.33±10.66
Sex (M:F)	10:8	9:9	10:8
ASA status (I:II)	8:10	10:8	9:9
Duration of surgery (minutes) [mean±SD]	87.12±30.46	76.28±18.99	76.61±25.92

Table 2: Demographic distribution between study groups

		Group-I (Mean±SD)	Group-II (Mean±SD)	Group-III (Mean±SD)	**Group- I vs. Group-II**	**Group- I vs. Group-III**	**Group- II vs Group-III**
HEART RATE	B	89.9±13.79	89.9±14.28	83.4±8.80	*P > 0.05*	*P > 0.05*	*P > 0.05*
	D0	72.2±10.21	76.7±11.04	77.4±6.87	*P > 0.05*	*P > 0.05*	*P > 0.05*
	D5	67.2±10.91	65.2±8.53	74.4±7.46	*P > 0.05*	*P > 0.05*	*P < 0.05*
	D10	64.1±9.62	61.9±10.80	74.6±6.83	*P > 0.05*	*P < 0.01*	*P < 0.001*
	E1	81.8±9.99	82.3±13.40	101.9±8.78	*P > 0.05*	*P < 0.001*	*P < 0.001*
	E3	77.4±10.63	76.2±12.68	95.3±5.67	*P > 0.05*	*P < 0.001*	*P < 0.001*
	E5	73.7±10.57	71.6±12.58	90.1±4.94	*P > 0.05*	*P < 0.001*	*P < 0.001*
	E10	74.2±9.04	69.5±8.39	79.7±6.49	*P > 0.05*	*P > 0.05*	*P < 0.01*
S	B	131.3±12.62	132.7±12.07	136.7±10.25	*P > 0.05*	*P > 0.05*	*P > 0.05*
	D0	113.6±13.85	120.4±12.45	124.4±14.84	*P > 0.05*	*P > 0.05*	*P > 0.05*

B- base line,

D0 -starting of the drug infusion,

D5-at 5 minute after starting the drug infusion,

D10- at10 minute after starting the drug infusion,

E1- at 1 minute after extubation,

E3- at 3 minute after extubation,

E5- at 5 minute after extubation,

E10- at 10 minute after extubation.

B	D5	117.3±18.69	129.2±17.31	127.1±14.98	*P > 0.05*	*P > 0.05*	*P > 0.05*
	D10	118.3±20.30	129.1±20.67	126.1±12.75	*P > 0.05*	*P > 0.05*	*P > 0.05*
	E1	125.5 ±15.71	134.9 ±12.61	151.9±11.40	*P > 0.05*	*P < 0.001*	*P < 0.01*
	E3	124.7 ±13.83	131.4 ±15.04	148.4±10.36	*P > 0.05*	*P < 0.001*	*P < 0.001*
	E5	120.3±13.09	124.8 ±12.98	140.±9.69	*P > 0.05*	*P < 0.001*	*P < 0.001*
P	E10	112.5 ±11.16	113.7 ±12.49	133.8±8.16	*P > 0.05*	*P < 0.001*	*P < 0.001*
	B	83.2±3.90	85.5±7.87	84.5±5.79	*P > 0.05*	*P > 0.05*	*P > 0.05*
D	D0	73.3±8.68	83.9±11.00	79.7±5.36	*P < 0.01*	*P > 0.05*	*P > 0.05*
	D5	76.4±6.95	87.3±13.43	79.5±6.13	*P < 0.01*	*P > 0.05*	*P < 0.05*
	D10	80.2±7.09	89.2±12.11	78.7±5.74	*P < 0.01*	*P > 0.05*	*P < 0.01*
B	E1	79.3±11.25	92.0±10.39	98.9±6.32	*P < 0.001*	*P < 0.001*	*P > 0.05*
	E	75.8±9.38	85.5±9.79	92.4±7.97	*P < 0.01*	*P < 0.001*	*P > 0.05*
	E5	71.7±8.41	80.2±11.27	89.4±6.62	*P < 0.05*	*P < 0.001*	*P < 0.01*
P	E10	71.6±10.57	73.9±10.25	84.6±7.83	*P > 0.05*	*P < 0.001*	*P > 0.05*

Table 3: Comparison of heart rate (beats/min), systolic blood pressure (mm of Hg) and diastolic blood pressure (mm of Hg) between groups at different time interval

Groups	Bradycardia	Shivering	Respiratory depression	Desaturation/ over sedation	Laryngospasm/ bronchospasm	Postoperative nausea/ vomiting
Group- I	1	0	0	0	0	4
Group- II	2	0	0	0	0	3
Group-III	0	4	0	0	0	4

Table 4. Comparison of adverse effects in different groups

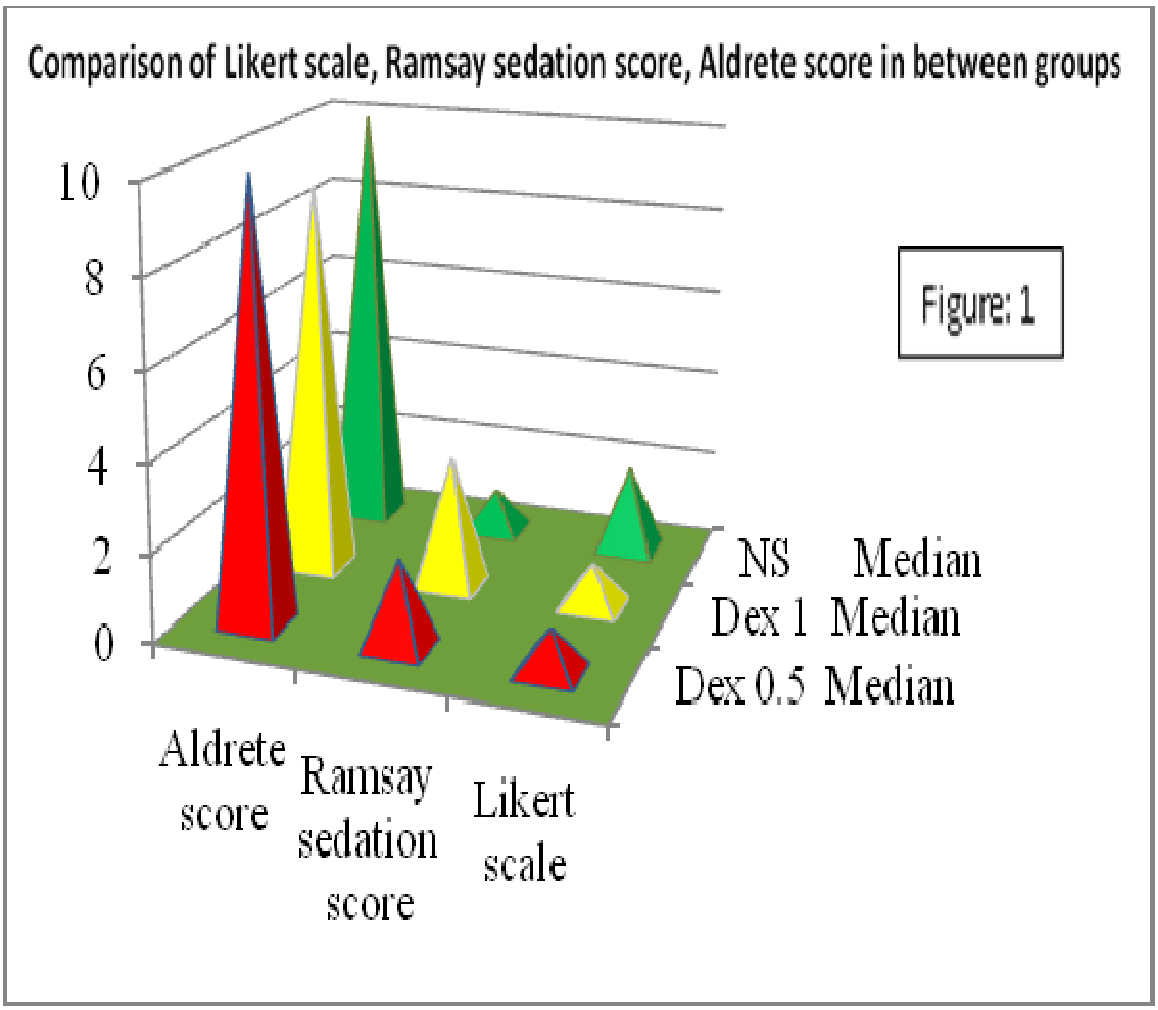

Figure: 1

Discussion

Dexmedetomidine has been successfully used to attenuate the haemodynamic responses to tracheal intubation as it provides sedation, haemodynamic stability and does not depress respiration. These properties might be useful for providing a smooth transition from pre-extubation to post –extubation phase by minimizing the haemodynamic fluctuation.

Standard dexmedetomidine loading dose at a rate of 1 µg kg^{-1} given over 10 minutes period could give rise to hypertensive and hypotensive episodes[17,18,19]. Several studies had been conducted at lower loading dose (0.5µg kg^{-1}) to achieve better haemodynamic stability[14, 20]. Some of those studies had shown significant attenuation of haemodynamics during extubation[14, 21] but one study reported insignificant result[15]. The present study was conducted to evaluate the effect of dexmedetomidine on haemodynamic responses during tracheal extubation as well as to confirm the effectiveness of lower dose (0.5 µg kg^{-1}) for such attenuation.

The present study revealed that two different doses of dexmedetomidine (0.5 µg kg^{-1} and 1 µg kg^{-1})

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effectively attenuated the increase of heart rate, systolic blood pressure and diastolic blood pressure associated with tracheal extubation. It was also observed that diastolic blood pressure was better controlled in the patients treated with dexmedetomidine 0.5µg kg^{-1} than 1µg kg^{-1}. Dexmedetomidine 0.5µg kg^{-1} administered 5 minutes before the end of surgery has been shown to stabilize haemodynamics, allow easy extubation, provide a more comfortable recovery and allow early neurological examination following intracranial operations[14]. In another study, dexmedetomidine 0.5µg kg^{-1}, given 5 minutes before extubation has been found to be more effective than fentanyl 1 mcg/kg in attenuating airway reflex responses to tracheal extubation and maintaining hemodynamic stability without prolonging recovery[22].In patients undergoing vascular surgery, dexmedetomidine (plasma concentrations in the range of 0.18 to 0.35 ng/ml) attenuated the increase in HR and plasma norepinephrine concentrations during emergence from anaesthesia and did not attenuate postoperative increases in HR or BP after emergence from anaesthesia or affect intraoperative anaesthetic or postoperative analgesic requirements[13]. An infusion of dexmedetomidine started 20 minutes before anaesthesia and continued until the start of skin closure in patients undergoing supratentorial brain tumour surgery was found to blunt tachycardic response to intubation and the hypertensive response to extubation[23].

Tracheal extubation is not only associated with alteration of haemodynamic parameters but it can also invite complications like coughing, bronchospasm etc. These complications are usually transient and well tolerated by most patients, but may be deleterious in certain subgroups. $Alpha_2$ stimulation can cause smooth muscle relaxation thereby preventing bronchoconstriction[15]. Dexmedetomidine being an α_2 receptor agonist can also attenuate airway reflexes during extubation[21].It had been shown in previous studies that single dose dexmedetomidine 0.5µg kg^{-1} given as bolus before tracheal extubation decreased agitation and cough scores during extubation with no difference between the groups in the incidence of breath holding or desaturation.

Central stimulation of parasympathetic outflow and inhibition of sympathetic outflow from the locus coeruleus in the brainstem plays a prominent role in the sedation and anxiolysis produced by dexmedetomidine. Decreased noradrenergic output from the locus coeruleus allows for increased firing of inhibitory neurons including the ɤ-amino butyric acid system resulting in anxiolysis and sedation[15]. One study had shown dexmedetomidine when given just before end of the surgery, might increase the time to emergence and extubation[24]. Another study using dexmedetomidine infusions on ICU[25] patients' described successful extubation without agitation and significant sedation within a mean time of 28 minutes (range 20-50 min). In present study the average time of extubation was found to be 28 minutes (range 16-37 minutes) without any significant intergroup variations but the time interval between the appearance of 1st verbal response and the time of successful extubation was increased in patients treated with dexmedetomidine 1µg kg^{-1}.

Dexmedetomidine is known for conscious sedation with minimal respiratory depression[26,27] and dexmedetomidine 0.25 µg $kg^{-1}hour^{-1}$ when used for

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sedation during mechanical ventilation in paediatric patients were found to be as effective as midazolam 0.22 mg/kg/hour[28]

The activation of α2 adrenoceptors, imidazoline-preferring receptors, or both in the ventrolateral medulla and especially in the solitarius nucleus tract by dexmedetomidine causes bradycardia. Dexmedetomidine 2.5 μg kg^{-1}followed by 0.2□2.5 μg $kg^{-1}hour^{-1}$has been found to reduce HR in patients[25]. The incidence of bradycardia and hypotension, in this study, was found little higher in patients treated with dexmedetomidine than in control group. A higher frequency of postoperative hypotension had been reported in the patients when dexmedetomidine was administered via patient controlled analgesia[29]. No significant difference in the incidence of vomiting was found between groups. However, others had found a higher, though not statistically significant, prevalence of adverse events (i.e., hypotension, bradycardia, and perioperative nausea and vomiting) with use of dexmedetomidine[30].

The α-2 receptor agonists are also known to prevent shivering to a moderate extent without any associated respiratory depression as with other antishivering drugs like meperidine[31,32]. Dexmedetomidine reduces shivering by lowering vasoconstriction and shivering thresholds[32, 33].

None of the patients in any group developed respiratory depression, laryngospasm, bronchospasm, undue sedation or desaturation. Similar findings had been reported by Guler and his associates[27].Dexmedetomidine use in morbidly obese patients had been found that there was no respiratory depression induced at clinical doses[34]. All patients of all groups were shifted to the ward from recovery room within 30 minutes as all of them achieved ≥ 9 score when examined with Modified Aldrete scoring scale.

In this study, lower dose of dexme-detomidine (0.5μg kg^{-1}) had effectively reduced extubation strain and attenuated haemodynamic surge following tracheal extubation. Dexmedetomidine is known for conscious sedation with minimal respiratory depression[26, 27], even central apnoea had been reported when dexmedetomidine was continued through extubation[35]. So, the priority of attenuating the haemodynamic response would therefore need to be balanced against the risk of delayed awakening and even the risk of apnoea after extubation.

Conclusion

So, to conclude single loading dose of dexm-edetomidine 0.5μg kg^{-1} when infused over 10 minutes at the time of skin closer of the surgeries was found to attenuate haemodynamic surge of extubation successfully without any significant adverse cardio-respiratory effects. It was also found that 0.5μg kg^{-1}dose was better tolerated by the patients with less sedation than infusion of higher loading dose 1μg kg^{-1}.

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