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Effects of intravenous dexmedetomidine on perioperative haemodynamics and quality of emergence in patients undergoing head and neck surgery following general anaesthesia—a comparative randomized, double-blind placebo-controlled study

Venugopal Achuthan Nair[1], Divya V. Gladston[1*], Jagathnath Krishna K. M.[2] and Rachel Cherian Koshy[1]

Abstract

Background: Dexmedetomidine is a widely used alpha-2 adrenoreceptor agonist in perioperative patient care. Its postsynaptic activation of the receptors in the central nervous system is responsible for reduced neuronal firing with resultant sedation, anxiolysis, analgesia, hypotension and bradycardia leading to effective stress response attenuation seen during laryngoscopy and orotracheal intubation. Major head and neck surgeries demand nasotracheal intubation which is more stressful than orotracheal as it traverses through the nasopharynx which is very pain-sensitive. This is to protect the airway in the immediate postoperative period from oedema or haematoma in the oral cavity or neck. Though its stress response attenuation, haemodynamic stability during the intraoperative period following orotracheal intubation has been well studied, its role in the prevention of emergence delirium and tube tolerance following nasotracheal intubation in major head and neck surgery is not found in the literature. Our aim was to evaluate whether dexmedetomidine effectively attenuates the stress response following nasotracheal intubation, perioperative haemodynamic fluctuations and quality of emergence in patients undergoing head and neck oncosurgeries.

Methods: A total of 150 patients were randomly assigned to one of the two groups; group D (dexmedetomidine group) and group S (control group with saline). Group D patients received a bolus dose of dexmedetomidine 1 μg/kg in 10 ml saline over 10 mts before induction of GA followed by an infusion at 0.4 μ/kg/h during surgery. Statistical analysis was done using SPSS version 11.0 (SPSS Ltd., Chicago, IL). Categorical data were represented using frequencies and percentages. Continuous variables were represented using mean and standard deviation. The association between categorical variables was assessed using the chi-square or Fisher's exact test, and continuous variables following normality assumption with respect to the two groups were assessed using an independent sample *t*-test. *P* value < 0.05 was considered to be statistically significant.

*Correspondence: divya.gladstone@gmail.com

[1] Department of Anaesthesiology, Regional Cancer Centre, Trivandrum, Kerala, India
Full list of author information is available at the end of the article

Results: Patients in the D group showed statistically significant attenuation of heart rate ($P < 0.05$) and blood pressure ($P < 0.05$) throughout the surgical period compared to saline. Also, there was a significant reduction in blood loss ($P = 0.042$), cough score ($P = 0.001$) and sedation score ($P = 0.001$) in the D group.

Conclusions: We conclude that a bolus dose of dexmedetomidine 1 µg/kg given 10 min before induction of anaesthesia followed by an infusion at 0.4 µg/kg/h during surgery effectively attenuates the haemodynamic responses during nasotracheal intubation and provides smooth emergence as evidenced by reduced coughing, agitation and arousable sedation without respiratory depression which facilitates tube tolerance following major head and neck oncosurgeries. Blood loss was also found to be significantly reduced.

Keywords: Dexmeditomidine, Laryngoscopy and intubation, Stress response, Placebo, Head and neck oncosurgery, Haemodynamics, General anaesthesia

Background

Dexmeditomidine (Dexmed) is a highly selective alpha-2 adrenoreceptor agonist which possesses hypnotic, sedative, anxiolytic, sympatholytic and analgesic properties which makes it a useful anaesthetic adjuvant in routine perioperative patient care (Hall et al. 2000; Kaur and Singh 2011). It produces a dose-dependent decrease in arterial blood pressure (BP) and heart rate (HR) associated with a decrease in plasma catecholamine levels which helps to attenuate stress response during intubation (Ebert et al. 2000). It has an edge over the routinely used drugs for sedation, anxiolysis and analgesia, and its effects on postoperative nasotracheal tube tolerance have been well accepted (Ramakrishnan et al. 2016; Wang et al. 2018).

Head and neck oncosurgeries form a significant subset of malignancies in our centre where the nasotracheal tube (NTT) needs to be retained overnight to secure the airway postoperatively from oedema and haematoma. Moreover, an agitated and restless patient with bucking can contribute to bleeding and accidental self-extubation postoperatively which can make the situation worse. In this context, we decided to study the effects of intravenous (IV) Dexmed on stress to noxious stimuli during NTI, perioperative haemodynamic stability and quality of emergence in patients undergoing major head and neck oncosurgeries following general anaesthesia (GA). Stress to noxious stimuli was assessed by looking at the changes in haemodynamic responses like the HR and BP from baseline frequently for 15 min following NTI and thereafter every 15 min till the end of surgery.

Methods

Patients diagnosed to have head and neck cancers, who underwent surgery under GA with NTI in a tertiary cancer centre during the period 2013 to 2016, were included in the study after getting informed written consent. After prior approval from the Institutional Review Board (reference no. IRB/10-2011 and Human Ethical Committee, reference no. HEC No. 31/2010 dated 25/10/2013), all procedures were performed in accordance with the ethical guidelines of the Declaration of Helsinki. This manuscript adheres to the applicable CONSORT guidelines.

The study included 150 patients of either sex undergoing head and neck surgery aged between 18 and 65 years belonging to ASA-PS 1 and 2 where surgical duration lasting up to 150–180 mts was randomly assigned to the two groups. The exclusion criteria included those unwilling to participate; uncontrolled hypertension and diabetes; those on beta blockers and alpha 2 agonists; morbid obesity; severe hepatic, renal and endocrine diseases and cardiac dysfunction as evidenced by a 2D echo; patients with second- or third-degree heart block; ECG abnormalities; and those receiving opioids for cancer pain. Those with a history of epitasis, surgery or polyps in the nasal cavity and those having difficult airways as assessed by Mallampatti scores III and IV were also excluded. Those with anticipated difficult airway were excluded because the duration of laryngoscopy and intubation may be prolonged or may require multiple attempts at intubation, both of which can be a confounding factor as we are not taking neither the duration nor number of attempts at intubation. Also, in such patients, as our institutional protocol, we go for a short-acting muscle relaxant or plan for an elective fibreoptic awake NTI following topicalisation of the airway. Patients were allocated to group D (dexmedetomidine group) and group S (control group with saline) using a computer generated randomization table, with 75 in each group. Both the observers and patients involved in the study were blinded. On the preoperative day, after explaining the procedure including the need for NTI and the need to retain it overnight, a written informed consent was obtained and nasal patency assessed with the cold spatula test. Group D patients received an IV bolus dose of Dexmed at 1 mcg/kg in 100 ml saline over 10 min using a pump before the induction of GA followed by an infusion of the same drug at 0.4 mcg/kg/h intraoperatively. Group S received

an equal volume of saline in the same manner (CONSORT guidelines, Fig. 1). One patient in group D lost to follow-up since extubation was done following surgery.

The primary outcomes studied were its effectiveness in controlling the stress response to laryngoscopy and intubation and intraoperative haemodynamic stability and quality of emergence. The secondary outcomes were significant hypotension, bradycardia and blood loss following major head and neck oncosurgeries. The efficacy of the drug in effectively controlling the stress response to laryngoscopy and intubation, intraoperative haemodynamic stability and quality of emergence at the time of recovery were assessed and recorded.

Based on a prior study done by Bhattacharjee et al. and assuming 80% power, with 5% significance level (alpha error), 95% confidence interval and with a mean difference of 6.9 and pooled standard deviation of 14.95, the minimum sample required in each group is 73 which has been round off to 75 in each group. Statistical analysis was done using SPSS version 11.0 (SPSS Ltd., Chicago, IL). Categorical data used in our study were body mass index (BMI); ASA-PS were represented using frequencies and percentages. Continuous variables were represented using mean and standard deviation. The association between categorical variables was assessed using the chi-square or Fisher's exact test, and continuous

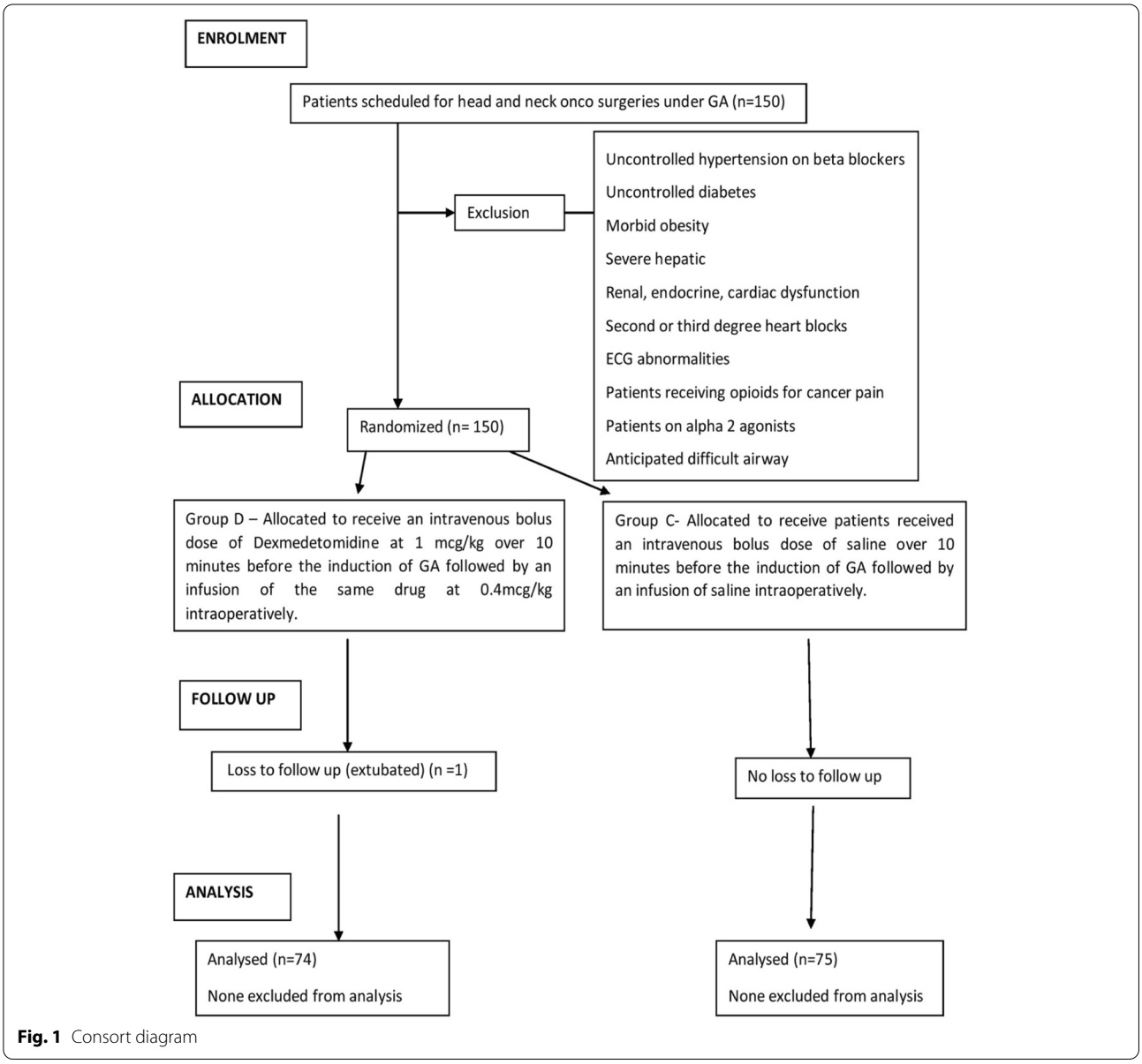

Fig. 1 Consort diagram

variables following normality assumption with respect to the two groups were assessed using an independent sample *t*-test. *P* value < 0.05 was considered to be statistically significant.

The anaesthesia protocol was standardized for all the patients. They received oral premedication with tab. Pantoprazole 40 mg and tab. Alprazolam 0.5 mg the previous night and at 7 am on the day of surgery. Older age and frail patients received half the dose of alprazolam; 18-G cannula was secured for IV access under local anaesthesia, and Ringer lactate started at 2 ml/kg in the recovery room. After keeping the OT ready, patients were taken, and nasal decongestant 2 to 3 drops applied to both nostrils and IV premedication given to all patients with inj. glycopyrrolate 0.004 mg/kg and inj. midazolam 0.02 mg/kg. All patients were monitored according to the standard ASA monitoring guidelines. Baseline HR, systolic BP (SBP), diastolic BP (DBP), mean arterial BP (MAP), oxygen saturation and temperature monitoring were done and recorded. Inj. fentanyl 2 mcg/kg was given to provide background analgesia. The study drug/saline was given as a bolus for 10 min, and vitals were recorded before induction. After preoxygenation for 3 min, IV lidocaine 1.5 mg/kg and inj. propofol 2 mg/kg, followed by inj. vecuroniun 0.1 mg/kg, were given to facilitate NTI after checking for adequacy of mask ventilation. McIntosh laryngoscope of adequate size was used for laryngoscopy. Patients were ventilated with 50% oxygen in nitrous oxide (N20) and 1% isoflurane during apnoea. The trachea was intubated with an appropriate sized cuffed ETT of polyvinyl chloride which was softened by immersing in warm saline prior to intubation, air entry and tube position confirmed with capnography and secured. Intermittent positive pressure ventilation with N_2O 66%, O_2 33% and inhalation agent isoflurane 1% mixture was used for the maintenance of GA to achieve a MAC of 1. They were put on volume-controlled mode of mechanical ventilation with closed circuit using sodalime. Diclofenac sodium 75 mg or paracetamol 1 g was added to the IV fluid 100 ml to provide analgesia at the start of the case. Vital parameters were monitored 1 min after induction and intubation and thereafter every 5 min till 15 min and every 15 min till the end of surgery.

According to the protocol, in the study group, if bradycardia with heart rate < 50/mt or hypotension with a fall in BP > 20% from baseline occurred, the concentration of agent would be reduced, and if needed, the rate of study drug infusion titrated. If bradycardia still persisted, 0.6 mg atropine is to be given to raise the heart rate or phenylephrine 50–100 μg given to raise the BP. If hypertension with BP > 20% from baseline or tachycardia with heart rate > 100/mts occurred, it will be recorded, and the concentration of the agent and study drug will be increased. If hypertension persisted, propofol is to be given as a titrated infusion. In the control group, the same protocol is carried out except for the study drug dosage titration.

At the end of the surgery, ondansetron 4 mg was given IV to prevent postoperative nausea and vomiting. Study drug infusion was stopped 10 mts prior to reversal and residual neuromuscular blockade reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg when a train of four ratios was > 0.9. NTT was retained overnight to protect the airway considering the chance for oedema and or haematoma around the surgical site. Smooth emergence from anaesthesia as evidenced by the tolerance to NTT with resultant coughing and the level of sedation at recovery and the immediate postoperative period was also assessed using the Modified Minogue Score (Minogue et al. 2004) and observer's assessment of alertness/sedation score (Huncke et al. 2010), respectively (Figs. 2 and 3). Blood loss, oxygen

Outcomes categorization	Grade and severity description	Modified Minogue scale
None to mild	Grade 1 (none)	No coughing or muscular stiffness
	Grade 2 (mild)	Coughing once or twice, or transient cough response to removal of tracheal tube that resolved with extubation
Moderate to severe	Grade 3 (moderate)	≤ 3 coughs lasting 1~2 s, or total duration of coughing last ≤5
	Grade 4 (severe)	≥4 coughs with each lasting > 2 s, total duration of coughing last > 5 s

Fig. 2 Modified Minogue Score

Definition	Score
Responds easily to name spoken in a normal tone	5
Responds only after mild prodding or shaking	4
Responds only after name is called loudly and/or repeatedly	3
Lethargic response to name spoken in normal tone	2
Does not respond to mild prodding or shaking	1

Fig. 3 Observer's assessment of alertness/sedation score

saturation and adverse effects of the drugs were also analysed. The amount of intraoperative blood loss was assessed by looking at the suction bottle and soaking of the gauze and pads, and the assessment was mainly visual and approximate. We considered a loss of more than 250 ml as significant in major head and neck surgeries.

The vitals were monitored in the ICU with supplemental oxygen via T piece and intraoperative Dexmed providing adequate arousable sedation and resultant tube tolerance in the immediate postoperative period. IV morphine 3–4.5 mg was given 6th hourly and as required to provide excellent analgesia and tube tolerance as the pain following major head and neck surgeries is difficult to control with non-steroidal anti-inflammatory agents and nerve blocks difficult to perform. These patients were extubated only the next day under the supervision of the surgeon, and Dexmed was avoided to prevent overdose due to its prolonged infusion.

Results

The demographic data were found comparable with respect to their age, sex and BMI. Regarding ASA-PS, significantly more patients were in ASA II in both groups (P value 0.002) which did not affect our test results in any way. We observed significant attenuation of haemodynamic parameters in D group with respect to the S group. There was a statistically significant reduction in heart rate ($P < 0.05$) from 1 min after induction till the end of surgery (graph 1) (Fig. 4). SBP and DBP were found significantly less in the D group ($P < 0.05$) from 1 min of intubation till the end of surgery (Graph 2 and 3 respectively) (Figs. 5 and 6). MAP also showed significant attenuation in group D ($P < 0.05$) from 10 mts of induction till the end (graph 4). In the S group, 5 patients had a cough score of 1, 9 had a score of 2, 45 patients had a score of 3 and 16 had a score of 4, whereas in group D, 23 patients had a cough score of 1 and 51 had a cough score of 2 with none having scores of 3 and 4 (Table 1) which shows that there was a statistically significant reduction

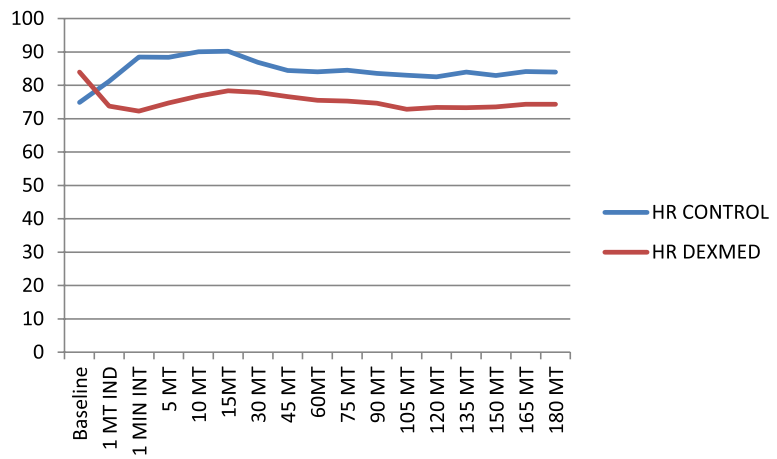

Fig. 4 Heart rate response with the control and dexmeditomidine groups

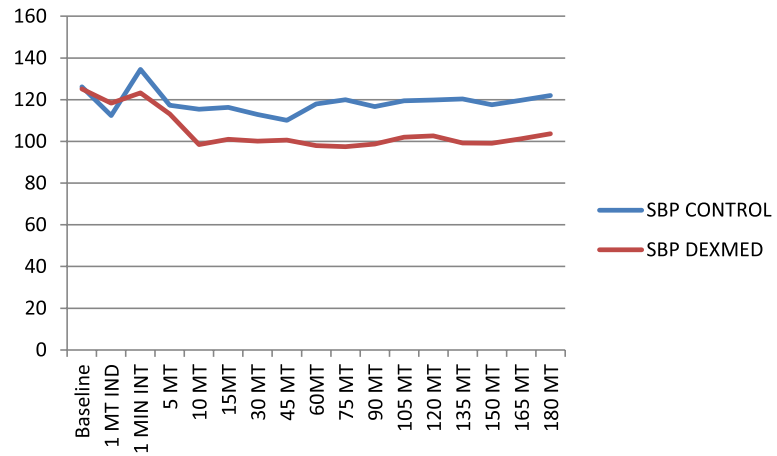

Fig. 5 Systolic blood pressure response with the control and dexmeditomidine groups

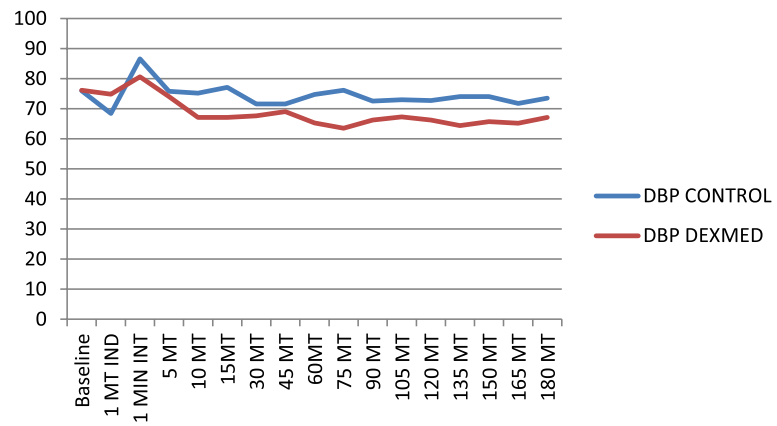

Fig. 6 Diastolic blood pressure response with the control and dexmeditomidine groups

Table 1 Demographic data

Group		Mean	Std. deviation	Std. error mean	*P* value
Weight	(S)	60.92	11.109	1.283	0.940
	(D)	61.05	10.597	1.232	
Height	(S)	159.21	8.669	1.001	0.883
	(D)	159.00	8.970	1.043	
BMI	(S)	24.185	4.965	0.573	0.876
	(D)	24.310	4.754	0.553	

in coughing ($P = 0.001$). Comparing the sedation scores, it was observed that patients in group D (P value $= 0.001$) were calm, resting, sedated but arousable (Table 2). As the haemodynamic parameters were well maintained in the D group, blood loss was also found significantly less ($P = 0.042$) (Table 3). Two patients in the D group had significant bradycardia which went below 50/mts and

Table 2 Cough and sedation score

	Group	(S) 0	(D) 1	Total	*P* value
Cough score	1 (no cough)	5	23	28	0.001
	2 (mild)	9	51	60	
	3 (moderate)	45	0	45	
	4 (severe)	16	0	16	
	Total	75	74	149	
Sex	F	41	43	84	0.672
	M	34	31	65	
	Total	75	74	149	
Sedation score	5	0	5	5	0.001
	4	0	56	56	
	3	10	13	23	
	2	38	0	38	
	1	27	0	27	
	Total	75	74	149	

Table 3 Blood loss

Group	Mean	Std. deviation	*P* value	
Blood loss	No	113.33	52.847	0.042
	Yes	97.91	37.663	

improved after a single dose of 0.6 mg atropine. Oxygen saturation was found maintained well in both groups.

Discussion

Dexmed is an imidazole derivative like clonidine with potent alpha 2 adrenergic receptor agonistic activities. Clonidine has a specificity of 220:1(α-2:α-1), while Dexmed has 1620:1 which is 7 times more (Giovannitti et al. 2015). Through postsynaptic alpha 2 receptors, it inhibits pontine locus cerulrus thereby increasing conductance through potassium channels and acts through the endogenous sleep-promoting pathways, generating natural sleep pattern (Giovannitti et al. 2015). Its role in day care surgery as an anaesthetic adjuvant to provide mild sedation is well established (Mahmoud and Mason 2015). It offers dose-dependent sedative, hypnotic, analgesic and anxiolytic effects without significant respiratory depression (Ramakrishnan et al. 2016). Dexmed was found to have a useful role in the multi-modal approach in the management of postsurgical patients especially in the surgical intensive care unit (ICU) (Ramakrishnan et al. 2016). Its role in opioid-sparing effects, arousable sedation stable haemodynamics without respiratory depression has been exciting (Martin et al. 2003; Khan et al. 1999; Manne et al. 2014; Gerlach and Dasta 2007). There is a progressive decrease in heart rate and cardiac output which requires close monitoring and should be cautiously used along with vasodilators, cardiac depressants and drugs causing bradycardia (Bhana et al. 2000). Emergence delirium following surgery can lead to a dissociative state with altered cognitive perception, excitation and agitation where Dexmed infusion during surgery was found effective (Kim et al. 2013; Garg et al. 2018). Though it is observed more frequently in the paediatric age group, in adults, its incidence ranges from 4.7 to 21.3% including PACU (Vlajkovic and Sindjelic 2007; Lepousé et al. 2006). Factors such as pain, inhalation anaesthetics, preoperative benzodiazepine use, male gender, age, preoperative anxiety and type of surgery have been implicated for emergence agitation (Yu et al. 2010). Premedication with Dexmed can also effectively control emergence agitation (Kim et al. 2019).

Our study results very well correlate with other studies where the sympatholytic property of Dexmed was found responsible for stable haemodynamics during intubation, surgical stimulation and at extubation (Bhattacharjee et al. 2010; Tanskanen et al. 2006; Patel et al. 2012; Tufanogullari et al. 2008). The initial increase in arterial blood pressure which we also observed is probably due to the vasoconstrictive effects of the drug (Fig. 7). Its effects on the sparing of opioids and reduced requirement of inhalational anaesthetic agents following infusion of Dexmed have also been well studied (Ramakrishnan et al. 2016; Manne et al. 2014; Tufanogullari et al. 2008; Keniya et al. 2011). In a recent RCT on patients undergoing robotic-assisted laparoscopic oncosurgeries, intraoperative Dexmed infusion resulted in reduced anaesthetic agent and postop opioid requirements significantly (Bakshi et al. 2020). Extensive resection and reconstruction in some of the head and neck oncosurgeries demands NTT to be retained postoperatively in order to secure the airway in case oedema, bleeding or haematoma makes reintubation difficult for the anaesthesiologist

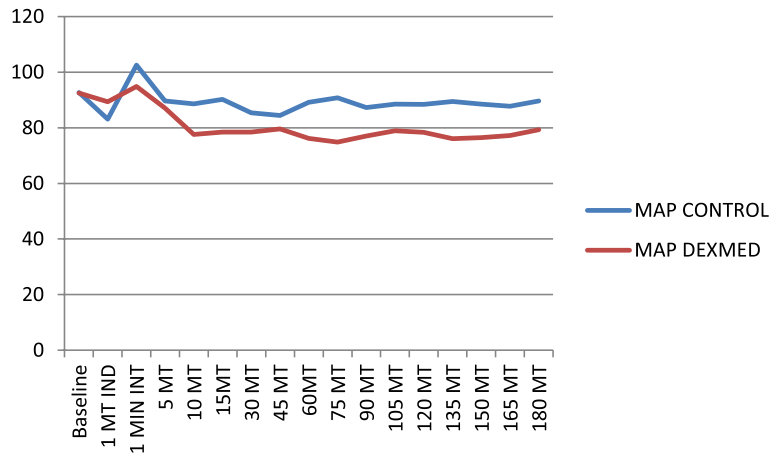

Fig. 7 Mean arterial pressure response with the control and dexmeditomidine groups

where Dexmed offers better tube tolerance with less agitation at recovery (Ramakrishnan et al. 2016; Hassani and Bhananker 2006). It can be either continued postoperatively or can be managed with narcotics in the PACU. Blood loss in such surgeries is a major concern where Dexmed can keep it minimum as observed from our study. Regarding sedation, in the D group, 5 patients responded easily to a name spoken in normal tone, and 56 patients responded to mild prodding or shaking and rest 13 responded when their name is called out loudly shows the effect of conscious sedation by Dexmed with decreased narcotic requirements for tube sedation at recovery. The saline group patients on the other hand required more narcotics at emergence for tube tolerance with 10 patients responding only after name is called loudly and/or repeatedly; 38 patients lethargic response to name spoken in normal tone and 27 patients do not respond to mild prodding or shaking. Dexmed sedation has been used safely to preserve respiration in patients with compromised airways and during difficult awake fibreoptic intubation (Bergese et al. 2007). The narcotic sparing effect of it can decrease the risk of respiratory depression particularly who are sensitive to narcotics as seen in the study done by Huncke et. al. (Huncke et al. 2010) In a meta-analysis done by Lee et al., it was found that systemic Dexmed resulted in significant reduction in surgical time, intraoperative blood loss and emergence agitation (Lee et al. 2018). Also, intraoperative Dexmed infusion was found to reduce blood loss following FESS surgery and spinal surgery as seen in our study (Fazel et al. 2020).

Regarding limitations, we selected patients in whom surgery may last approximately for 150–180 mts for a major head and neck oncosurgery with flap reconstruction in order to analyse the effects of the study drug well. In those cases which extended for more than 3 h, we excluded the variables for statistical analysis for uniformity but continued the infusion in the study group for its desired effects. We also could not look into the postoperative narcotics or other analgesic requirements and any re-explorations in our study. Also, we could not quantify the blood loss that occurred intraoperatively, and it was a visual and approximate calculation.

Conclusions

Dexmed when given as an IV bolus followed by an infusion at 0.4 mcg/kg/h can effectively attenuate the stress response during intubation and throughout the surgical duration, less bleeding, provides arousable sedation without respiratory depression with a smooth emergence and provides better tube tolerance in head and neck oncosurgeries.

Abbreviations

ASA-PS: American Society of Anaesthesiologist-Physical Status; BMI: Body mass index; BP: Blood pressure; D: Dexmedetomidine group; DBP: Diastolic BP; ETT: Endotracheal tube; GA: General anaesthesia; HR: Heart rate; ICU: Intensive care unit; IV: Intravenous; MAC: Minimum alveolar concentration; MAP: Mean arterial BP; NTT: Nasotracheal tube; PACU: Postanaesthesia care unit; RCT: Randomized control trial; S: Control group with saline; SBP: Systolic BP.

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Authors' contributions

VAN, DVG, JKKM, and RCK done the concepts, design, definition of intellectual content, literature search, clinical studies and manuscript editing. VAN, DVG, JKKM done the experimental studies, data acquisition, data analysis, statistical analysis and manuscript preparation. DVG, JKKM and RCK done the manuscript review and are guarantors. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Approval obtained from Institutional Review Board, Regional Cancer Centre Trivandrum (reference no. IRB/10-2011) and Human Ethical Committee, Regional Cancer Centre Thiruvananthapuram (reference no. HEC No. 31/2010 dated 25/10/2013). Informed written consent to participate in the study was provided by all the participants.

Consent for publication

Informed written consent was taken from the individuals for publication.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Anaesthesiology, Regional Cancer Centre, Trivandrum, Kerala, India. [2]Division of Cancer Epidemiology and Biostatistics, Regional Cancer Centre, Trivandrum, Kerala, India.

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