Original Research Article

Comparative study of desflurane requirement and recovery characteristics in entropy guided general anaesthesia with or without dexmedetomidine infusion

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Abstract

Background: Newer anaesthetics such as desflurane have smaller blood-gas partition coefficient than older ones like halothane. Desflurane is preferred because it leads to faster onset of anaesthesia and faster emergence from anaesthesia. However, desflurane is considered to be more expensive than other volatile anaesthetics. Highly selective alpha two adrenoceptor agonists like Dexmedetomidine reduce anaesthetic requirements. Hence this study was designed to compare the effect of Dexmedetomidine infusion on desflurane consumption and recovery characteristics under entropy guided general anaesthesia. **Materials and Methods:** Fifty patients aged between 18-55 years belonging to ASA I and II scheduled for elective surgeries under general anaesthesia were randomly divided into two groups. Group D patients received a loading dose of inj Dexmedetomidine 1 µg/ kg, over 10 minutes before the induction of anaesthesia, and 0.5 µg/ kg/ hour infusion following induction of anaesthesia till the end of surgery. Group P patients received similar volumes of normal saline as bolus before the induction and maintenance infusion till the end of the surgery. Desflurane concentration was adjusted to maintain response entropy values between 40 to 60 and based on clinical variables like heart rate (HR), and mean arterial pressure (MAP). Muscle relaxation was guided by TOF count. HR, NIBP, MAP, SPO2, ENTROPY values were recorded. The total desflurane consumption was recorded from Anaesthesia gas module of GE Datex-Ohmeda S 5 Advance system. At end of surgery, desflurane was discontinued and patient extubated after adequate recovery and when TOF ratio was more than 0.9. Time to eye opening, extubation, response to verbal commands were recorded. **Results:** The mean consumption of desflurane at the end of one hour was significantly less in group D with $p<0.001$ (Group P 21.04±6.33 ml/hr and Group D 14.44±1.83 ml/hr). Eye opening time was significantly less in group D with $p<0.001$(Group P 297.60± 89.97sec and Group D 169.80±22.48 sec). Time for response to verbal commands was significantly less in group D with $p<0.001$ (Group P 423.60±113.02 sec and Group D 269.80±45.29 sec) **Conclusion:** Intraoperative Dexmedetomidine infusion reduces desflurane consumption, hastens recovery from desflurane during entropy guided general anaesthesia.

Key words: Entropy, Desflurane, Dexmedetomidine, Depth of anaesthesia, Blood gas partition coefficient.

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INTRODUCTION

Desflurane is currently in widespread clinical use for maintenance of anesthesia. Desflurane offers the advantage in long surgical procedures by virtue of decreased tissue saturation[1]. Though desflurane is gaining popularity because of its rapid emergence and recovery characters, its high cost is a hurdle in using it for day to day practices.[2] Dexmedetomidine is a highly selective alpha 2 adrenoceptor agonist, which possesses hypnotic, sedative, anxiolytic, sympatholytic and analgesic properties without producing significant respiratory depression [3, 4]. Sedative and hypnotic drugs have the ability to reduce both the anaesthetic and opioid requirements.[5,6,7] Intraoperative

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infusion of Dexmedetomidine has not only shown to reduce the hemodynamic responses to laryngoscopy and intubation[8] but also reduces consumption of sevoflurane, isoflurane intraoperatively.[9] The analgesic potentiating property of Dexmedetomidine also reduces the requirement of intraoperative and post-operative analgesic consumption[10.] Thus the present clinical study was undertaken to assess the impact of Dexmedetomidine infusion on desflurane consumption and recovery characteristics in entropy guided general anaesthesia.

MATERIALS AND METHODS

In this Prospective, randomized, control trial, double blind study, 50 patients between the age 18-50 years, belonging to ASA Grade I and Grade II undergoing elective surgeries under general anaesthesia intubation expected to last less than 150 min were included. Patients with an allergy to adrenergic agonists, history of uncontrolled hypertension, Heart block greater than first degree, history of alcohol or drug abuse, clinically significant neurologic, cardiovascular, renal, hepatic, gastrointestinal diseases were excluded from the study. After obtaining informed written consent and detailed history and physical examination, patients were randomly divided into 2 groups of 25 each (Group D: Dexmedetomidine group and Group P: Control group) based on computer generated randomization. With a minimum Fasting state of 6-8 hours before anaesthesia, IV access was obtained and standard monitoring applied. The spectral entropy and response entropy were measured using plug in Datex ohmeda entropy S/5 module. All patients were pre-oxygenated with 100% oxygen for 3 minutes and inj.Midazolam 0.03mg/kg IV, Inj glycopyrrolate 0.005mg /kg, inj.Fentanyl 2µg/ kg IV were administered. Dexmedetomedine group (D) patients were given a loading dose of inj.Dexmedetomedine 1µg/kg IV made to 20ml with normal saline, over 10 minutes, whereas Control group(P) patients received similar volume of normal saline over 10 minutes. Anaesthesia was induced in both groups with inj. Propofol in successive 30mg doses every 30 seconds until RE drops to 50, and was confirmed with loss of response to verbal commands. Additional doses of inj.Propofol 20-30 mg bolus were given if response entropy values increased beyond 60 before intubation and the total dose of propofol used was recorded. Intubation was facilitated with inj.Vecuronium 0.1mg/kg IV. Anaesthesia was continued with Desflurane in 60% nitrous oxide in oxygen and ventilated to maintain end tidal CO2 between 35-40mmHg. The inspired concentration of desflurane was initially set at 3% and then titrated subsequently to maintain response entropy values between 40 and 60, also based on haemodynamic parameters, to maintain heart rate and mean arterial pressure within 20% of baseline values. The fresh gas flow was initially set at 6 lts/ min till there was equilibrium between the set dial concentration and inspired concentration of desflurane and then subsequently reduced to 1.5 lts / min. Dexmedetomidine was diluted with normal saline in a 20 ml syringe to attain a concentration of 5 µg/ ml and a maintenance dose of inj. Dexmedetomedine infusion at 0.5µg/kg/hour, was administered till the end of surgery in group D. The patients in group P received similar volume of normal saline. The patient and the monitoring anaesthesiologist were unaware of the group allocation and the drug infusion.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), Mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), end tidal carbon dioxide, response and state entropy values (RE and SE) were recorded at-baseline before induction, after induction, before intubation, 1 minute,2 min,3 min,5 min after intubation and every 5 minutes thereafter, till the end of surgery. Inspired and expired concentrations of oxygen was continuously monitored. Inspired and expired fractions of desflurane, and age adjusted minimum alveolar concentration of desflurane were recorded from the agent gas monitoring module of Datex Ohmeda Avance S/5™ anaesthesia work station at every 5 min intervals till the end of surgery. The amount of desflurane consumed was directly recorded from the agent gas monitoring module of Datex Ohmeda Avance S/5™ anaesthesia work station at the end of first hour after intubation and at the end of surgery.

Desflurane administration was cut off at the beginning of skin closure and the fresh gas flow was increased to 6L/minute of 100% oxygen at the end of the skin closure. This would define the beginning of recovery period. Residual neuromuscular blockade was reversed with inj.Neostigmine 0.05mg/kg and inj. Glycopyrrolate 0.01mg/kg and patient was extubated after recovery of adequate respiratory effort and muscle power as guided by TOF ratio of >0.9. Time to extubation was considered as time from discontinuation of desflurane till the patient was extubated. Time for eye opening was considered from the time of discontinuation of desflurane till the time when the patient opened his/ her eyes spontaneously. Time for response to verbal commands was recorded from the time of desflurane cut off till the patient responded to simple verbal commands. If time to extubation exceeded more than 30 minutes from the discontinuation of desflurane, it was considered as delayed recovery and recorded. Age, sex, body weight, duration of surgery (minutes), duration of anaesthesia (minutes) were recorded. Post operatively, recovery of patient was assessed using modified Aldrete scoring system at 5, 10, 15, 30, 45 and 60 min after

extubation. Haemodynamic parameters were also recorded at same intervals and other side effects if any were noted.

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Levenes test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data.

RESULTS

Patients in group D and group P had comparable demographic profile. Duration of surgery and the total dose of propofol required for induction was also comparable between the two groups.

Duration of desflurane used was 74.20±18.01 min in group D and 74.20±18.97 min in group (p – 1.0), was clinically and statistically comparable.

Table 1: Demographic data and duration

Parameters	Group D	Group P	P value
Age, years(mean±SD)	38.20±7.80	38.12±6.27	0.968
Weight, kg (mean+ SD)	51.28±5.92	51.76±6.72	0.772
Duration of surgery ,min	80.60±18.73	82.60±18.26	0.704
Duration of desflurane used	74.20±18.01	74.20±18.957	1

Table 2: desflurane consumption at 1 hour and total desflurane consumption

Parameter	Group D	Group P	P value
Desflurane consumption at 1 hour (Mean±SD)	14.44±1.83	21.04±6.33	<0.001
Total Desflurane consumption (Mean±SD)	19.80±4.92	28.38±11.76	0.014

Consumption of Desflurane at 1 hour was 14.44±1.83 ml in Group D, whereas in Group P Desflurane consumption was 21.04±6.33 ml with P value <0.001 which was clinically and statistically highly significant. Total consumption of Desflurane was 19.80±4.92 ml in Group D and in Group P total desflurane consumption was 28.38±11.76 ml with P value 0.014 and was clinically and statistically highly significant. Baseline Heart rate was comparable in both the groups studied. Heart rate was significantly lower in group D compared to group P from 2nd min of starting infusion and then throughout intraoperative period, except at 5th, 35th, 40th and 50th min after intubation. SBP was significantly lower in group D compared to group P after premedication and at 4th, 6th, 8th, 10th minute during drug infusion. However, the values were comparable during intraoperative period. DBP in group D and group P were comparable except after premedication and at 4th, 10th minute during Dexmedetomidine infusion and 10th and 80th minute after intubation. MAP was significantly lower in group D than in group P after premedication and during infusion of Dexmedetomidine. Response entropy was comparable at baseline in both groups. There was reduction in RE values in group D compared to group P from 2nd min till 10th min during infusion of drug. State entropy was comparable at baseline in both groups. There was reduction in SE values in group D compared to group P from 2nd min till 10th min during infusion of drug. The average MAC of Desflurane in Group D was 0.81±0.1 % whereas in Group P average MAC of Desflurane was 1.08±0.53 which was clinically and statistically significant.(P=0.013).

Table 3: Comparison of end tidal desflurane between two groups

End tidal Desflurane	Group D	Group P	P value
1 min	1.68±0.51	2.26±0.92	0.008**
2 min	2.02±0.55	2.54±0.79	0.009**
3 min	2.13±0.57	2.91±0.73	<0.001**
5 min	2.43±0.46	3.36±0.89	<0.001**
10 min	2.50±0.70	3.49±1.12	<0.001**
15 min	2.60±0.49	3.34±0.84	<0.001**
20 min	2.63±0.65	3.53±0.78	<0.001**
25 min	2.81±0.62	3.48±0.86	0.003**
30 min	2.69±0.56	3.31±0.83	0.003**
35 min	2.42±0.64	2.92±0.87	0.027*
40 min	2.52±0.83	2.72±1.13	0.486

End tidal concentration of desflurane was clinically and statistically low in group D patients compared to group P patients until 35 min of desflurane anesthesia .Thereafter it was similar.

Table 4: Comparison of recovery parameters between two groups

	Group D	Group P	P value
Eye opening (sec)	169.80±22.48	297.60±89.97	<0.001**
Time for extubation (sec)	228.4±37.5	366.4±97.07	<0.001**
Response to verbal commands (sec)	269.80±45.29	423.60±113.02	<0.001**

Time for eye opening in group D was significantly shorter in group D (169.80±22.48 sec) compared to group P (297.60±89.97 sec) (p <0.001). Time to extubation was significantly shorter in group D (228.4±37.5) compared to group P (366.4±97.07) (p <0.001). Response to verbal commands was significantly faster in group D (269.80±45.29) compared to group C (423.60±113.02) (p <0.001). Modified Aldrete score was low in group D compared to group P at first min in post-operative period. This was statistically significant. During the subsequent periods the scores were comparable between the groups.

DISCUSSION

Important factors in the suitability of an anaesthetic are how quickly its effects kick in and how quickly they abate. These factors are determined by the solubility of the anaesthetic agent in blood and in lipids. Those anaesthetics which exhibit a low solubility in blood have a quicker onset and offset than those which are more soluble. Meanwhile, if they have a high lipid solubility, prolonged use can lead to after effects being felt. Desflurane is a widely used major anaesthetic agent with rapid onset of action and rapid dispersal. It is one of the most commonly used volatile anaesthetic agent and has an excellent safety record. Because it can be irritating to the airways, desflurane is typically used to maintain anaesthesia after induction with other agents. When general anaesthesia is provided to an adult patient planned for any surgery, The target is to achieve optimal surgical conditions in terms of anaesthesia, analgesia and proper muscle relaxation, while ensuring a rapid early recovery from the anaesthesia with minimal side effects. Although experience with α2-agonists as sole anaesthetic is limited[11], these drugs reduce anesthetic requirement and provide a more stable cardiovascular course, presumably because of their sympatholytic effect and the need for lower dose of cardioactive anaesthetics.[12, 13] Dexmedetomidine a selective α2-adrenoceptors has a 1600:1 preference for α2 receptors compared to α1 receptors.[14] This drug was introduced into clinical practice as an adjunct to regional, local and general anaesthetics. In healthy volunteers Dexmedetomidine increases sedation, analgesia and amnesia and decreases heart rate, cardiac output and circulating catechalomines in a dose dependent fashion. The purported MAC-reducing sedative and analgesic effects demonstrated in preclinical and voluntary studies have largely been borne out in clinical practice. An EEG or Auditory evoked potential based monitor would enable objective, reproducible and continuous measurement of anaesthetic depth even when the patient is fully paralysed or lost all response to painful external stimuli.[15] There are many studies which reported the influence of Depth of Anaesthesia monitoring on consumption of anaesthetic drugs. A common protocol was used in most of these studies, wherein a standard group was compared with one or two study groups in which titration of the anaesthetic drug depended on the selected Depth of Anaesthesia monitors like BIS, Narcotrend, Auditory evoked potential and Spectral entropy. Khan ZP *et al.*[16], in their study on human volunteers assessed the effect of different plasma concentrations of Dexmedetomidine on isoflurane requirements. They observed that there was dose dependant decrease in isoflurane requirement, with higher plasma concentrations of Dexmedetomidine producing greater decreases in isoflurane requirement. C R patel *et al.*[17], in their study assessing the effect of Dexmedetomidine on sevoflurane consumption, used 1 mcg/ kg of Dexmedetomidine as initial bolus followed by 0.2 to 0.8 mcg/ kg infusion throughout the surgery and observed 21% reduction in sevoflurane consumption.

Dr. Neha Garg and co workers[18] compared two different doses of Dexmedetomidine infusion (0.2 mcg/ Kg/ Hr versus 0.4 mcg/ kg/ hr infusion) as an anaesthetic adjuvant for maintenance of anaesthesia in patients undergoing major surgeries They observed that group which received Dexmedetomidine 0.4 µg/kg/hr (Group B) showed a maximum reduction of 41.3% in the mean Isoflurane concentration requirement compared to the group which received Dexmedetomidine0.2mcg/kg/hr (31.4%). They concluded Dexmedetomidine 0.4 mcg/kg/hr appears to be better than Dexmedetomidine 0.2mcg/kg/hr and provides greater reduction in requirement of anaesthetic agents, better haemodynamic stability, sedation and analgesia.

Wu S C *et al.*[19] studied the utility of spectral entropy monitoring in reducing the consumption of sevoflurane as sole inhalational anesthetic and in decreasing the need for antihypertensive drugs in total knee replacement surgery. The sevoflurane consumption was significantly lower in the entropy group than in the conventional group (27.79 +/- 7.4 mL vs. 31.42 +/- 6.9 mL; p < 0.05) and also entropy-guided anesthesia was associated with significantly less frequent need for antihypertensive drugs (0.94 vs. 1.48 times; p = 0.043 (p = 0.012).

S S Harsoor *et al.*[20] studied the effect of intraoperative Dexmedetomidine infusion on Sevoflurane requirement and blood glucose levels during entropy-guided general anesthesia in patients undergoing upper abdominal surgeries. Mean Sevoflurane requirement during first hour was reduced by 28%, in patients receiving Dexmedetomidine. There was 30.2% and 18.6% reduction in average amount of desflurane consumed during first hour and average end tidal concentrations of desflurane respectively in our study and is in agreement with the observations of the above studies.

In the present study, there was decrease in heart rate in patients receiving Dexmedetomidine infusion during infusion and intraoperative period, compared to placebo group. The systolic and mean arterial pressures showed significant decrease only during the period of Dexmedetomidine infusion but was comparable to placebo group during intraoperative period. This is consistent with the observations of Harsoor S S *et al.*, who also observed decrease in heart rate but no significant decrease in systolic, diastolic or mean arterial pressures between Dexmedetomidine and placebo groups intraoperatively

Kaymak C *et al.*[21], in their study comparing two different doses of Dexmedetomidine on haemodynamic parameters during desflurane based BIS guided general anaesthesia, found that there was increase in heart rate compared to baseline during intubation in both groups. There was no significant change in mean arterial pressures between two groups. However, there was no significant increase in heart rate noted in present study during intubation in Dexmedetomidine group, which may be attributed to administration of initial bolus, in addition to infusion, in contrast to only infusion of Dexmedetomidine by Kaymac *et al.* Intravenous Dexmedetomidine infusion at 2 mcg/ kg was associated with decrease in heart rate in human volunteers in a study conducted by Pentilla *et al.*, which was attributed to augmentation of vagal activity[22]. Scheinin H *et al.* in their study noted increased incidence of bradycardia when Dexmedetomidine 2 mcg/ kg was administered intramuscularly as premedicant, 60 min before induction of anaesthesia in patients undergoing surgeries under general anaesthesia[23]. However, there was no incidence of bradycardia in our study, which may be because of lower dose of Dexmedetomidine used and premedication with vagolytic (glycopyrrolate).

Gonul. T. Keles *et al.*[24] conducted a double-blind study in which one hundred ASA I-II patients aged 18–65 were randomly assigned to receive either desflurane with Dexmedetomidine or sevoflurane with Dexmedetomidine in 60 % N2 O for anesthesia management. Extubation time in patients receiving desflurane with Dexmedetomidine was 5.9 ± 2.4 min and is similar to observations in our study. The mean Fast track scores at 5th, 15th, and 25th min post operatively were 12.7 ±0.9, 13. 7±0.5 and 13.9±0.2 respectively in patients receiving desflurane with Dexmedetomidine. This concurs with the observations of our study. The modified Aldrete scores were comparable between Dexmedetomidine and placebo group in post-operative period in the present study. This is due to lower blood gas solubility of desflurane which resulted in faster emergence. The infusion of paracetamol by virtue of decreasing post-operative pain in placebo group may also have contributed for comparable recovery scores in both groups. No significant side effects were observed in both the groups studied. The present study has limitations. Recovery of cognitive functions, assessed using tests such as digit substitution test were not done in this study. Further studies may be done to assess the effect of Dexmedetomidine infusion on cognitive recovery in addition to recovery from anaesthesia during desflurane based anaesthesia and also dose response relationship between the Dexmedetomidine infusion and desflurane consumption may be studied.

CONCLUSION

Our study concludes that Dexmedetomidine infusion reduces desflurane consumption, and hastens recovery from anaesthesia without causing significant haemodynamic disturbances during desflurane based entropy guided general anaesthesia.

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