Effect of dexmedetomidine on recovery profile of patients undergoing anterior cervical discectomy and fusion

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Abstract

Background and Aim: Smooth and rapid emergence and extubation, with minimal coughing, is desirable after cervical spine surgery to facilitate early neurological examination. The present study investigated the effect of dexmedetomidine as an intraoperative anesthetic adjuvant on postoperative extubation and recovery profile in patients undergoing anterior cervical discectomy and fusion (ACDF) surgery.

Material and Methods: Sixty-four, American Society of Anesthesiologist I or II adult patients (age 18–60 years) were randomized in this placebo-controlled, double-blind study. In group D, dexmedetomidine was started at 0.2 µg/kg/h after a loading dose of 1 µg/kg before induction and in group P, volume and infusion rate-matched normal saline was used. Perioperative hemodynamics, intraoperative anesthetic consumption, and postoperative recovery profile were observed.

Results: Thirty-one patients in each group successfully completed the study. Time to emergence (6.9 min vs 10 min, P < 0.001), time to extubation (8.5 min vs 12.2 min, P = 0.002), and time to achieve modified Aldrete score ≥9 (5 min vs 10 min, P < 0.001) were earlier in group D compared to group P, respectively. Pain score at extubation was lower (0 vs 20) and time for first analgesic was longer (50 min vs 15 min) in group D compared to group P. Coughing at extubation was comparable in both the groups. One patient in group D had severe postextubation bradycardia.

Conclusions: Intraoperative use of dexmedetomidine at the lowest recommended dosage in adults undergoing ACDF surgery results in a favorable recovery profile with reduced emergence/extubation time and postoperative pain, but similar incidence of coughing.

Keywords: Cervical spine, dexmedetomidine, postoperative recovery

Introduction

Anterior cervical discectomy and fusion (ACDF) of cervical spine for degenerative disease or disc protrusions is one of the most commonly performed spine surgery nowadays. A smooth and rapid emergence from general anesthesia after this surgical procedure is mandatory to permit early neurological examination. Good recovery from anesthesia in these cases requires a patient to be conscious, cooperative, hemodynamically stable, pain-free with preserved airway reflexes, and breathing adequately without straining or coughing, because reintubation if needed after surgery could be technically challenging due to spine fixation and may damage the spinal cord. Attempts have been made to provide “ideal” extubation by the use of many drugs, alone or in combination, but nothing is foolproof.

Dexmedetomidine, a highly selective α₂-receptor agonist that has sedative, analgesic, anxiolytic, and opioid sparing effects without significant respiratory depression, has appeared as a promising adjuvant.
potential anesthetic additive in improving the recovery profile after variety of surgical procedures.\textsuperscript{9,14} We hypothesize that dexmedetomidine could be a particularly useful anesthetic adjuvant for ACDF surgery for providing smooth and rapid emergence and improving the quality of postoperative recovery.

The primary outcome measure of this study was to assess postoperative recovery profile based on time to emergence. Secondary outcome measures included severity of coughing on emergence, time to attain modified Aldrete score (MAS) \( \geq 9\), total intraoperative sevoflurane/fentanyl consumption, postoperative pain score, time to first analgesic requirement in the postoperative period, perioperative hemodynamics, and incidence of postoperative complications.

**Material and Methods**

The study protocol was approved by the Institutional Ethics Committee. After obtaining written informed consent, 64 adults of both sexes with the American Society of Anesthesiologists (ASA) physical status I or II, aged 18–60 years, undergoing elective ACDF surgery were enrolled for this prospective, randomized, double-blind, controlled study. Exclusion criteria included active smokers (history of smoking any time in past 6 months); preexisting bradycardia [heart rate (HR) below 50/min] or hypotension (systolic arterial pressure <100 mmHg); planned elective postoperative ventilation; poor respiratory reserve and poor cough reflex; presence of cardiac, renal, hepatic, and respiratory dysfunction; cognitive impairment; known allergy to \( \alpha_2 \)-agonists; and use of \( \beta \)-blockers, digoxin, or \( \alpha_2 \)-agonists.

In the operation theatre, pulse oximetry (\( \text{SpO}_2 \)), electrocardiogram, noninvasive blood pressure, and bispectral index (BIS) were applied. Intravenous (IV) and radial artery cannulations were performed. A computer-generated randomization chart was used to assign the patient to either the dexmedetomidine group (group D, \( n = 32\)) or placebo/normal saline (NS) group (group P, \( n = 32\)). A 50 ml syringe containing dexmedetomidine (4 \( \mu \)g/ml in NS) or NS was prepared by an anesthesiologist who was part of this study and not involved in the perioperative management. The study drug infusion was started soon after recording the baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure (MBP). IV fentanyl 2 \( \mu \)g/kg was given at this time. Patients in group D received IV infusion of dexmedetomidine (1 \( \mu \)g/kg bolus over 10 min followed by 0.2 \( \mu \)g/kg/h as maintenance) and those in group P received volume-matched saline at similar rate.

Induction was started immediately after the loading volume of study drug or NS, with IV propofol at 1 mg/s by syringe infusion pump till the loss of verbal commands. IV rocuronium (1 mg/kg) was given to facilitate tracheal intubation. Trachea was intubated 90 s after administering rocuronium. Hemodynamics were recorded just prior to tracheal intubation, at intubation and at 1, 3, and 5 min after intubation.

Anesthesia was maintained with 60% nitrous oxide in oxygen and sevoflurane at a fresh gas flow of 1.5 l/min to maintain an end-tidal carbon dioxide (\( \text{EtCO}_2 \)) of 35 ± 2 mmHg and intermittent boluses of IV rocuronium (10 mg). Intraoperatively, HR, SBP, DBP, MBP, minimum alveolar concentration (MAC), and BIS values were recorded every 10 min. BIS values were maintained between 45 and 55 by titrating sevoflurane concentration. Sympathetic response (HR >100/min or SBP >20% above baseline) sustained for 3 min, with the targeted BIS value maintained, was treated with bolus of IV fentanyl (1 \( \mu \)g/kg). Repeat dose, if needed, was administered after 5 min.

Perioperative bradycardia (HR <45/min) was treated with IV atropine 0.5 mg; SBP decrease to >20% from baseline or <100 mmHg (whichever was lower) with targeted BIS values maintained, defined as hypotension, was treated first with fluid bolus, followed by decrease of inhalation anesthetic in steps of 0.5% down to a minimum MAC of 0.7, and/or 5 mg IV mephenetermine. Ringer lactate, NS, and colloids were used for replacement and maintenance.

At completion of surgery, muscle relaxant was antagonized with mixture of glycopyrrolate and neostigmine. After these steps, sevoflurane and drug/NS infusion were discontinued and patients ventilated with 100% oxygen at 8 l/min. The patients were then left undisturbed except for continuous verbal commands for their name to open eyes. Trachea was extubated once patient achieved spontaneous regular respiration and followed simple commands.

Emergence time was defined as time interval between discontinuing of anesthetic agent and eye opening of patient either spontaneously or on gentle verbal commands. Extubation time was the time interval between discontinuing of anesthetic agent and tracheal extubation. Hemodynamic variables were noted at switching-off of sevoflurane; and every minute for first 5 min and then at every 5 min for first half-an-hour posttracheal extubation.

Grade of coughing at emergence was measured using five-point extubation quality score (EQS) as used by Turan et al.\textsuperscript{[15]} I = no cough, easy breathing; II = slight coughing (one or two), easy breathing; III = moderate
coughing (three or four); IV = heavy coughing, breathing hard; and V = laryngospasm, severe coughing, and hardly breathing. Any other immediate postoperative complications such as bradycardia, hypotension, nausea, vomiting, agitation, shivering, desaturation (SpO₂ < 92%) were also noted. After extubation, all patients were transferred to postanesthesia care unit (PACU) and monitored by an observer blinded to the groups.

Postoperative pain (from the iliac bone site, if graft was taken) was rated by verbal rating scale (VRS) score (0 = no pain and 100 = severe unbearable pain; explained preoperatively to patients) in the immediate postextubation period, on arrival to PACU and then every 10 min till the administration of rescue analgesic. Rescue analgesic was IV fentanyl 1 µg/kg given when VRS was >30 or patient demanded analgesia. The time to first analgesic was noted. Discharge readiness from PACU was assessed using MAS. Time for MAS to reach ≥9 was noted and considered optimal for shifting out a patient.

Statistical analysis was carried out using Stata 11.0 (College Station, TX). Data were presented as number (%), mean ± SD, or median (range) as appropriate. Continuous variables were compared between the groups using the Student’s t-test; for independent variables, the Wilcoxon rank-sum test was used. Categorical variables were compared using the Chi-square test/Fisher’s exact test. Hemodynamic parameters over a period of time between and within the groups were analyzed using generalized estimating equation because the observations were correlated. A P value < 0.05 was considered as significant. A power analysis based on pilot study suggested that a sample size of 29 patients for each group should be adequate to detect a 30% reduction in time to emergence with α = 5% and power = 90%. Assuming few dropout of cases, we decided to enroll 32 patients per group in the study.

**Results**

Thirty-one patients in each group successfully completed the study over a period from June 2012 till May 2014. One patient in each group was excluded because one patient was electively ventilated postoperatively for surgical concern in group P and the surgical plan was changed to laminoplasty for one patient in group D. Both the groups were comparable demographically [Table 1] and regarding duration of surgery [Table 2].

The dose of propofol for induction, intraoperative number of fentanyl boluses, and sevoflurane consumption were significantly lower in group D as compared to group P [Table 2]. The total intraoperative IV fluid administered, mephentermine boluses, blood loss, and urine output were comparable between the two groups.

Mean HR was lower in the group D compared to group P at all time points perioperatively [Figure 1]. Similarly, mean SBP was almost equal or lower in group D compared to group P at all time points perioperatively except during the preintubation period (PreI) when SBP in group D was higher than in group P [Figure 2]. Intraoperatively, two patients in group D had bradycardia and needed IV atropine. Tachycardia (HR >100 bpm) and hypertension (SBP >20% from baseline value) were observed in more number of patients of group P than group D at emergence and immediate postoperative period [P < 0.001, Table 3 and Figures 1 and 2]. MAC values were lower in group D compared to group P intraoperatively at all time points [Figure 3].

Time to emergence from anesthesia and to extubation was earlier in group D than group P. Also, the BIS values were lower in group D than group P at the time of emergence (P < 0.001). VRS scores on emergence and on PACU admission were lesser in group D than group P (P < 0.001); and the mean time interval when patients required first analgesic postoperatively was longer in group D than group P (P < 0.001) [Table 3]. Degree of coughing indicated by EQS was comparable in both the groups [P = 0.227, Figure 4]. Median time to

**Table 1: Demographic data**

|                | Group P (n=31) | Group D (n=31) | P    |
|----------------|---------------|---------------|------|
| Age (year)     | 44.6±10.5     | 42.3±9.3      | 0.360|
| Weight (kg)    | 66.8±13.3     | 66.0±11.6     | 0.801|
| Height (cm)    | 163.8±11.9    | 167.8±11.2    | 0.187|
| Body mass index| 24.9±4.7      | 23.3±2.6      | 0.106|
| Sex (M:F)      | 25:6          | 21:10         | 0.353|
| ASA status (1:2)| 27:4          | 26:5          | 0.681|

*Data are mean±SD or numbers*

**Figure 1:** Perioperative heart rate. * = intergroup difference (P ≤ 0.05), † = intragroup (dexmedetomidine) difference (P ≤ 0.05) from baseline, T = intragroup (placebo) difference (P ≤ 0.05) from baseline, B = baseline, PreI = preintubation, Int = intubation, T (No.) = time in minutes postintubation, PIN = at pin insertion, SI = at skin incision, IT (No.) = intraoperative time in minutes postskin incision, SO = Switch-off of inhalational agent, Ext = at extubation, eT (No.) = time in minutes postextubation
reach MAS ≥ 9 was 5 min earlier in the group D compared to group P (P < 0.001). The length of hospital stay in days was same for both the groups (P = 0.666).

One patient in group D had severe bradycardia (HR ≈ 20/min) at fifth minute postextubation and became unresponsive. Intravenous atropine 0.5 mg bolus followed by mask ventilation with 100% oxygen and cardiac massage was given for approximately 1 min. Patient was successfully resuscitated without any neurological deficit. In group P, two patients developed breathlessness postoperatively without desaturation: one due to pharyngeal edema and another due to right recurrent laryngeal nerve palsy. There were no episodes of bronchospasm, desaturation, or allergic reaction in either group.

**Discussion**

Studies have not been conducted to demonstrate the safety and efficacy of dexmedetomidine to improve recovery profile in patients undergoing ACDF. We used the lowest recommended maintenance sedation dose of dexmedetomidine (at 0.2 µg/kg/h, after giving the loading dose at 1 µg/kg) in this study, a dose which has been observed to provide better recovery from anesthesia in a previous study by Ozkose et al.[12]

**Time to emergence and extubation**

Patients are most vulnerable during the immediate postoperative period.[21] Also, inadequate recovery from anesthesia can lead to various adverse events such as laryngospasm, aspiration, loss of airway patency, or inadequate ventilatory drive, and culminating hypoxemia. Thus, with a more rapid and complete emergence from general anesthesia, fewer patients would be at risk of airway-related complications.

In our study, we found a significantly earlier time to emergence and time to extubation in the dexmedetomidine group compared to placebo. A recent meta-analysis on perioperative use of α₂-agonist during various surgical procedures showed that time

| Table 2: Intraoperative parameters | Group P (n=31) | Group D (n=31) | P |
|-----------------------------------|---------------|---------------|---|
| Induction dose of propofol (mg)   | 105.3±18.3    | 62.8±19.6     | <0.001|
| No. of fentanyl boluses per patient | 2 (0-4)      | 1 (0-2)       | <0.001|
| No. of mephenesotamine boluses per patient | 0 (0-4)      | 1 (0-3)       | 0.185|
| No. of atropine boluses per patient | 0 (0-0)      | 0 (0-2)       | 0.147|
| Sevoflurane consumed (ml/min)     | 0.1±0.03      | 0.08±0.02     | 0.002|
| Crystallloid transfused (ml)      | 2108.1±600.8  | 2187.1±519.6  | 0.582|
| No. of patients infused with Colloid | 8 (25.8)    | 4 (12.9)      | 0.333|
| Colloid transfused (ml)           | 550±283       | 625±250       | 0.504|
| Blood loss                        | 200 (50-2000) | 150 (50-700)  | 0.279|
| Urine output (ml)                 | 600 (50-2000) | 600 (150-1500)| 0.379|
| Duration of anesthesia (min)      | 222.3±62.5    | 227±56.3      | 0.754|
| Duration of surgery (min)         | 153.6±59.9    | 160.±52.8     | 0.637|
| No. of patients with one: two level discectomy | 19:12        | 20:11         | 0.069|

Values are mean±SD or median (range) or number (%).

| Table 3: Postoperative data of various parameters | Group P (n=31) | Group D (n=31) | P |
|--------------------------------------------------|---------------|---------------|---|
| Time emergence (min)                             | 10±2.9        | 6.9±2.3       | <0.001|
| Time extubation (min)                            | 12.2±3.4      | 8.5±3.1       | 0.002|
| BIS value at emergence                           | 86.3±3.3      | 83.6±3.2      | <0.001|
| BIS value at extubation                          | 91.6±3.2      | 88.9±3        | <0.001|
| VRS score extubation                             | 20 (0-70)     | 0 (0-40)      | <0.001|
| VRS score PACU                                    | 40 (0-80)     | 0 (0-40)      | <0.001|
| Time for MAS ≥ 9 (min)                           | 10 (2-40)     | 5 (1-15)      | <0.001|
| Time to 1st analgesic (min)                      | 15 (0-55)     | 50 (1-90)     | <0.001|
| LOHS (days)                                      | 3 (2-8)       | 3 (2-8)       | 0.666|
| Tachycardia                                      | 25 (80.6)     | 2 (6.4)       | <0.001|
| Hypertension                                     | 23 (74.2)     | 8 (25.8)      | <0.001|
| Nausea/vomiting                                  | 6 (19.4)      | 1 (3.2)       | 0.052|
| Shivering                                        | 2 (6.4)       | 0             | 0.246|
| Agitation                                        | 3 (9.7)       | 0             | 0.119|

Values are mean±SD or median (range) or number (%). BIS=Bispectral index; VRS=Verbal rating scale; PACU=Postanesthesia care unit; MAS=Modified Aldrete score; LOHS=Length of hospital stay.
to extubation was shortened with the use of dexmedetomidine, although time to emergence (spontaneously or on verbal commands) was not altered.\[13\] However, this meta-analysis included all kinds of surgeries such as abdominal, gynecological, orthopedics, ENT, etc., and there was no study on cervical spine. Only one study by Ozkose et al.\[12\] in this meta-analysis mimicked the dexmedetomidine dosing regimen as in our study, i.e., at 1 µg/kg loading followed by 0.2 µg/kg/h. They also found a significantly shorter time to emergence and extubation, similar to this study. Similarly, Gandhi et al.\[16\] also noted earlier time to respond to verbal commands and time to extubation at dexmedetomidine infusion rate of 0.5 µg/kg/min in cervical spine surgeries but only time to respond to verbal commands was significantly different in their study. It could be possible that at low dose of dexmedetomidine at 0.2 µg/kg/h the anesthetic sparing effect is more prominent than sedative effect and as the dosage is increased its sedative effect also becomes more predominant.

**BIS at emergence and extubation**

An important observation in our study was lower BIS values in group D compared to group P at the time of emergence and extubation (P < 0.001). Kim et al.\[17\] too observed lower BIS values at extubation in their study for dexmedetomidine group compared to control (81.5 vs 83.2, respectively) but values were lower than that observed in our study. Similarly, Gandhi et al.\[16\] found a less time to achieve BIS 80 during emergence in dexmedetomidine group; they, however, not commented on BIS at emergence and extubation. This could be probably because we waited for patients to be more responsive to verbal commands before extubation considering the nature of surgery.

**Severity of coughing on emergence**

Coughing and bucking frequently accompanies tracheal extubation. It can be particularly harmful after cervical spine surgery as it can lead to graft/implant displacement or formation of spinal epidural hematoma.\[18\] Effectiveness of dexmedetomidine to reduce the incidence and severity of coughing at extubation has been shown with variable success by the use of bolus doses in the range from 0.4 to 0.8 µg/kg prior to extubation as compared to placebo\[9,15,19\] or fentanyl\[10\] or remifentanil.\[20\] Reasons for decreased coughing in the dexmedetomidine group have not been clearly defined in any study but have been postulated to the concomitant sedative and analgesic nature of drug. However, continuous infusion of dexmedetomidine has failed to show its superiority over placebo in reducing the incidence of coughing after nasal surgery.\[17\]

In our study, number of patients with no coughing at extubation was comparable in both groups (12 in group P vs 13 in group D; P = 0.067). However, two patients in group P had EQS grade IV coughing compared to none in group D, although this finding was statistically insignificant. Hans et al.\[21\] have shown that inhalational anesthesia and history of smoking are independent risk factors for increased incidence of coughing at extubation in patients operated for cervical spine. Use of low-dose dexmedetomidine and a low-risk population (nonactive smokers) could be the reason for similar incidence of coughing in the two groups in this study. It is possible that higher plasma levels achieved with a bolus dose are more effective in cough suppression compared to an infusion dose (as in our study).

**Intraoperative hemodynamics**

In terms of hemodynamic effects, HR, SBP, and MAP were lower in group D during perioperative period in this study due to sympatholytic effect of dexmedetomidine as observed previously in other studies.\[12-14\] SBP was, however, higher in group D compared to group P prior to intubation, probably due to direct peripheral vasoconstriction by the bolus of drug as well as smaller dose of propofol needed for induction.

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**Figure 3:** Intraoperative MAC values between two groups. PIN = at pin insertion, SI = at skin incision, IT (No.) = intraoperative time in minutes postskin incision, SO = Switch-off of inhalational agent. P value was significant (P < 0.05) at all these time points.

**Figure 4:** Extubation quality score. Extubation quality score (EQS): I = no cough, easy breathing; II = slight coughing (one or two), easy breathing; III = moderate coughing (three or four); IV = heavy coughing, breathing hard; and V = laryngospasm, severe coughing and hardly breathing.
One episode of significant bradycardia after extubation in group D (requiring CPCR) needs to be interpreted with caution. Blaudszun et al.[13] have mentioned in their meta-analysis that dexmedetomidine increased the risk of postoperative bradycardia. As our study was not powered to assess the effect of dexmedetomidine to cause bradycardia/asystole, we cannot comment whether this episode of bradycardia was due to dexmedetomidine or an incidental happening. Therefore, studies with larger sample size should be conducted to compare the incidence of side-effects with the use of dexmedetomidine in such surgeries.

**Inhalational and opioid consumption**

The analgesic and anesthetic-sparing effect of dexmedetomidine has been demonstrated in several studies.[13,16,22,23] It has been demonstrated that the administration of dexmedetomidine before the completion of major inpatient surgical procedures significantly reduced morphone requirement in the early postoperative period by about 66%.[24] In our study, intraoperative requirement of number of fentanyl boluses was reduced in group D compared to group P (1 vs 2, respectively; \( P < 0.001 \)). Also, pain scores on emergence and at PACU admission were significantly lower and requirement of first dose of analgesic was significantly prolonged in group D than group P.

In adults, targeted plasma dexmedetomidine concentration of 0.7 ng/ml has been shown to reduce MAC of sevoflurane by up to 17%.[25] Harsoor et al.[26] have shown a 28% reduction in the sevoflurane requirement when entropy was targeted to 40–60 with intraoperative dexmedetomidine infusion of 0.5 \( \mu \text{g/kg/h} \). In our study too, the actual consumption of sevoflurane was found to be significantly lower in group D.

**Complications**

The development of operative site hematoma has been reported to be the second most common and potentially catastrophic complication after ACDF surgery (as high as 5.6% of patients) in one case series.[11] It presents mainly as a neck mass associated with dysphagia and occasionally as acute respiratory distress. Providing a stable perioperative hemodynamics but does not have significant effect on cough suppression. It decreases the intraoperative consumption of sevoflurane and fentanyl, and also increases the time to demand of first analgesic in the postoperative period. Finally, further studies must be conducted to establish the safety of dexmedetomidine before it can be labeled as a safe adjuvant for doing statistical analysis of this study.

Postoperatively, nausea/vomiting was seen in six patients in group P compared to only one patient in group D. Similarly, shivering was present only in group P in two patients. Agitation was also observed only in group P in three patients. Dexmedetomidine has been shown to decrease the incidence of nausea/vomiting and agitation in adults.[13,17] Although this study was not powered to show difference in these side-effects, a trend toward lower incidence of nausea/vomiting, and agitation was observed in group D.

**Limitations**

This study, however, had few limitations. First, we included only nonsmokers, between 18 and 60 years of age, undergoing elective ACDF surgery. So, findings of the study need to be extrapolated with caution in patients undergoing emergency surgery for traumatic cervical spine and in elderly (age >60 years) with increased incidence of cervical spondylosis. Second, we only used BIS monitoring as an objective parameter to guide us about the depth of sedation during emergence and did not use any formal sedation scales to assess the responsiveness of our patients. Finally, the use of EQS to grade coughing has not been validated but this pattern of grading is the one commonly used.

**Conclusion**

In conclusion, the findings of our study suggest that intraoperative use of dexmedetomidine at maintenance dosage of 0.2 \( \mu \text{g/kg/h} \) (after a loading dose with 1 \( \mu \text{g/kg} \)), as an anesthetic adjuvant in sevoflurane/nitrous oxide-based anesthesia technique for anterior cervical spine surgery, results in smoother and faster recovery with stable perioperative hemodynamics but does not have significant effect on cough suppression. It decreases the intraoperative consumption of sevoflurane and fentanyl, and also increases the time to demand of first analgesic in the postoperative period. Finally, further studies must be conducted to establish the safety of dexmedetomidine in anterior cervical spine surgeries.

**Acknowledgements**

The authors would like to thank all the study participants for their participation in this study. The authors also thank Dr Mani Kalaivani (Scientist II, Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India) for doing statistical analysis of this study.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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