Original Article

Recovery Profiles after General Anesthesia in Patients undergoing Anterior Cervical Discectomy and Fusion (ACDF) Surgery with or without Dexmedetomidine as an Anesthetic Adjuvant: A Double Blinded Randomized Study

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Objective: The purpose of the present study was to evaluate the effect of dexmedetomidine as an anesthetic adjuvant on recovery profiles after general anesthesia for anterior cervical discectomy and fusion [ACDF] surgery.

Materials and Methods: Ninety-eight patients who scheduled for ACDF were randomized into 2 groups by computer-generated random numbers. The dexmedetomidine group (group D, n = 49) received dexmedetomidine 0.5 mcg/kg loading in 30 min then 0.5 mcg/kg/h. The control group (group N, n = 48) received volume-matched 0.9% NaCl or normal saline [NSS]. General anesthesia was maintained with desflurane (bispectral index (BIS) around 40 to 60) and continuous intravenous infusion of neuromuscular blocking agent and intravenous fentanyl. Study drug was started after positioning and stopped 30 minutes prior to the end of surgery. Desflurane was turned off at the time of suturing the last stitch and neuromuscular reversal agent was given. The recovery profiles were evaluated by using Riker sedation agitation score (1 to 7) and respiratory parameters. Riker sedation agitation score was reevaluated at 15 minutes post-extubation at PACU. The analgesic used and pain scores were assessed in 24 hours postoperatively.

Results: The recovery profiles were not different between two groups. The incidences of emergence agitation (Riker score 5 to 7) were 13 (26.5%) in Group D vs. 20 (42.6%) in group N, $p = 0.098$. The intraoperative fentanyl, desflurane consumption significantly decreased in group D. The extubation time was slightly longer in group D (8.3±5.3 min) compared to group N (5.7±2.8 min) with statistical significance ($p = 0.003$). In group D, the incidence of severe pain (Numeric rating score ≥7) at 4 h was also lower. The incidence of intraoperative hypertension was lower in group D but higher incidence of hypotension.

Conclusion: Dexmedetomidine as an anesthetic adjuvant in ACDF surgery failed to demonstrate effect to reduce emergence agitation, and had higher risk of adverse hemodynamic complications.

Keywords: Dexmedetomidine, Cervical spine surgery, Recovery, Riker sedation agitation score

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Emergence agitation [EA] was first described in 1960s, but the underlying etiology is still not fully understood which may lead to serious complications such as self-extubation, bleeding, self-removal of intravenous catheter, episodes of hypertension, aspiration, pain and re-operation. Possible causes include pain, preoperative anxiety, type of surgical procedures, personal characteristics of the patient, and type of anesthetics[1]. EA has been reported a 3% to 20% in adult patients undergoing general surgery[2,3].

In cervical (c) spine surgery, especially anterior cervical discectomy and fusion [ACDF] which

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the surgery field is close to the patient's airway. Avoidance coughing, straining, and providing a smooth emergence without EA are desirable in order to avoid airway and respiratory complications e.g. airway hematoma or edema especially in immediate post-anesthetic period.

There were many techniques and drugs that have been studied to prevent emergence agitation or to improve the recovery profile after surgery. Dexmedetomidine is one of these drugs; it is a selective alpha 2 adrenergic receptor agonist, that produces dose-dependent sedation, anxiolysis, analgesia without respiratory depression[4,5] and ensure hemodynamic-stabilizing properties[6]. Moreover, intraoperative dexmedetomidine infusion decreases the severity of emergence agitation in children[7], decrease incidence of emergence delirium, postoperative pain, antiemetic effect in adult patients[6,8-10]. Dexmedetomidine also decreases postoperative analgesics use in some studies[11]. All of these benefits make dexmedetomidine an attractive adjunct for c-spine surgery. However, the studies comparing the effect of dexmedetomidine focused on recovery profiles (emergence agitation, ventilation such as tidal volume and respiratory rate and patient's co-operation) after general anesthesia in adults are limited.

The main purpose of our study was to evaluate the effect of dexmedetomidine as an anesthetic adjuvant on recovery profiles such as sedation scores (using Riker sedation agitation scores), respiratory pattern, patients' co-operation and the secondary outcomes was anesthetic requirement, amount of analgesic consumption, postoperative pain score, respiratory and other adverse events or complications.

Materials and Methods

After getting approval from Siriraj Institutional Review Board (Si. 018/2559) in May 2016 and we registered at http://clinicaltrials.in.th (registration number TCTR20170607001), a prospective, randomized, double-blinded placebo-controlled study was performed. Randomization was performed by computer-generated numbers (in blocks of 4). The sequence numbers and groups were placed inside concealed envelopes, which were opened before anesthetic induction. The researchers enrolled the participants and preparing the drugs did not take part in patient care and assessment.

The inclusion criteria were (i) the patients who were scheduled for ACDF surgery in neurological surgery and orthopedic department, Siriraj hospital as an elective cases; (ii) American Society of Anesthesiolo gists [ASA] physical status I to III; (iii) age between 18 to 70 years old; and (iv) expected to be immediately extubated after the surgery. The patients with (i) unstable hemodynamics before the surgery; (ii) uncontrolled hypertension (SBP >140 mmHg); (iii) ischemic heart disease or other severe cardiac diseases; (iv) baseline heart rate less than 50 beats/min, patients whose EKG showed heart block or received beta blocker agents; (v) weakness of any extremities or motor power less than grade IV; (vi) abnormal renal or liver function; (vii) allergic to dexmedetomidine and opioids and (viii) BMI >30 kg/m^2 were excluded from the study. The consent was obtained from patients on the day before surgery.

On arrival to the operating room, standard ASA monitoring such as non-invasive blood pressure, pulse oximetry, electrocardiogram and the bispectral index (BIS) were connected to the patients and the baseline values was measured. At least one intravenous line (16 to 20 gauge catheter) was inserted and checked. General anesthesia was induced with fentanyl 1 to 2 mcg/kg and propofol 1.5 to 2 mg/kg and tracheal intubation was facilitated with atracurium 0.5 mg/kg or cisatracurium 0.15 mg/kg. The study drug was started infusion after positioning. General anesthesia was maintained with desflurane (0.5 to 1.5 MAC) in 50% O_2/air, intermittently intravenous fentanyl and continuous infusion of muscle relaxant (atracurium 0.3 to 0.5 mg/kg/h or cisatracurium 0.06 to 0.1 mg/kg/h) until 30 minutes before the end of the surgery.

The Dexmedetomidine group (group D) received dexmedetomidine 0.5 mcg/kg (prepared by researchers) loading in 30 min then 0.5 mcg/kg/h started after positioning and continued until 30 min before the end of the operation. The control group (group N) received volume-matched normal saline. An anesthetic nurse who did not involve in data collection prepared the solution. The anesthesiologist, the surgeon, the patients and the data collectors and recovery profiles assessors were blinded to group allocation.

During the surgery, rising in heart rate or hypertension (systolic blood pressure [SBP] >160 or above 20% from baselines) was treated by (i) increased desflurane concentration to keep BIS 40 to 60 (maximum desflurane 1.5 MAC). (ii) Fentanyl 25 mcg was administered intravenously to the patient every 5 minutes (maximum 2 times). (iii) if hypertension persisted, nicardipine 0.2 to 0.4 mg was given intravenously to the patients. In case of hypotension (SBP <90 mmHg or below 20% from baseline),

intravenous fluid or intravenous vasopressors were administered in discretion of attending anesthesio logist. Any occurrence of bradycardia (heart rate <40 beats/min) was treated by atropine 0.6 mg intravenously. Hemodynamics variables, the numbers and doses of drug administered were recorded.

Thirty minutes prior to the end of surgery (about the time surgeon placed the cervical plate), the study drug and muscle relaxant were discontinued. All patients received dexamethasone (10 mg) and ondansetron (8 mg). Desflurane was turned off at the time of suturing the last stitch. Neuromuscular reversal agent, neostigmine (2.5 mg) and atropine (1.2 mg) were administered after the cervical collar was placed and the TOF count more than 2.

The awakening time was defined as the time interval between administration of neuromuscular reversal agent and the time of opening eyes spontaneously and following verbal commands. The extubation time was determined as the time interval between administration of neuromuscular reversal agent and the time of extubation.

The Riker sedation agitation score (1 to 7), respiration pattern including respiratory rate, tidal volume (mL), vital capacity (mL) were observed prior to extubation by 3 data collectors and assessors who were blinded to the group allocation. We used 3 data collectors and assessors because one might not be available at the extubation time. The authors chose Riker sedation agitation score because it is widely used for sedation and agitation assessment and the value of 5 or above is considered agitation[9] (Appendix 1).

All patients were shifted to post-anesthesia care unit [PACU]. The Riker sedation agitation score (1 to 7) was reevaluated at 15 minutes post-extubation at PACU. Patients were assessed for cooperation by simple verbal command (such as hands and feet movement) at the time before extubation, 10 minutes and 20 minutes after extubation. Fully cooperated defined as patients can follow command quickly and can move all extremities. After the surgery, all patients were assessed for pain by using numeric rating score for pain [NRS] every 4 hours for 24 hours postoperatively and the analgesic uses were recorded. The event of postoperative nausea vomiting [PONV] and other early postoperative complications were also recorded.

Statistical analysis

From the study by Polat R et al[9], compared EA by using Riker sedation agitation score equal or greater than 5, the incidence was 20% in dexmedeto midine group, comparing to 47% in control group. By using the values of 2-sided type I error = 0.05, 80% power, the sample size was 47 patients for each groups (using nQuery Advisor 6.0 program). The authors enrolled 49 patients for each group for possible drop out during the study.

Statistical package for social sciences [SPSS] for Windows, version 18 (SPSS INc., Chicago, IL, USA) was used for statistical analysis. The distribution of data was analyzed with Kolmogorov-Smirnov test. Normally distributed data such as patient characteristics were analyzed with independent t-test and data were expressed as mean $\pm$ standard deviation. Abnormal distributed data such as bleeding, vital capacity were analyzed using Mann-Whitney U test and expressed as median and interquartile ranges (percentile 25, percentile 75). Incidence of emergence agitation, severe pain and complications were compared with Chi-square test. A p-value <0.05 was considered statistically significant.

Results

During May 2016 to February 2018, one hundred forty-six patients were assessed for eligibility. A total of 98 patients were enrolled in the present study. Forty-nine patients in group D and 47 patients in group N were analyzed. Two patients of group N were excluded from analysis due to early discontinue the study drug and remain intubated (Figure 1). Patient characteristics and operative procedures of each group are shown in Table 1. There were no significant differences between the two groups regarding age, gender, ASA physical status, BMI and the number of fused cervical spine level. Intraoperative values such as the amount of blood loss and BIS were also not different. However, the anesthetic requirement, desflurane and fentanyl were lower in group D compare to group N with statistically significant.

As shown in Table 2, the incidence of emergence agitation which classified as Riker sedation agitation score more than 5 although was higher (42.6%) in group N as compared to 26.5% in group D but had no statistical significance (p = 0.098). No one had dangerously agitation (self extubation, pulling intravenous catheters or self injury). All agitated patients had got physical restraints, verbal reminding of limits and no pharmacological treatment required. Respiratory patterns including respiratory rate, tidal volume and vital capacity prior to extubation were similar between the two groups. The extubation time was

slightly longer in group D (8.3±5.3 min) compared to group N (5.7±2.8 min) with statistical significance (p = 0.003).

The number and percentage of patients in each Riker score prior to extubation was shown in Figure 2 and at 15 min after extubation in Figure 3.

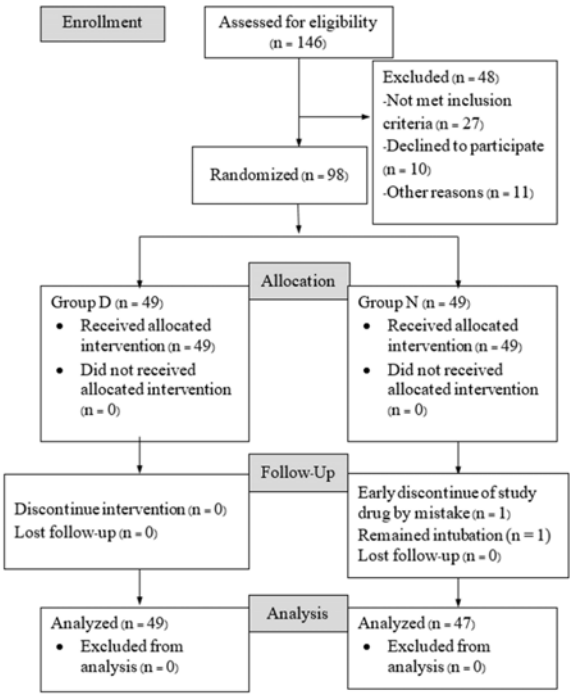


Figure 1. Consort diagram.

However, this differences had no statistically significant (p = 0.098 and 0.533 respectively).

Intraoperative hypertension was frequently observed in control group (p = 0.004). In contrast, the number of hypotensive episodes and amount of ephedrine use was significantly higher in group D than control group (p<0.001). Bradycardia and PONV were lower in control group but has no statistically significant (Table 3).

Multimodal analgesia was used for controlling acute postoperative pain.

Various groups of medications were prescribed by surgeons. But there were no significant differences between the two groups regarding the number of patients receiving tramadol, paracetamol, gabapentin, and NSAIDs. Opioids were used as rescue medication. Postoperative morphine use was higher in group N (median 4 mg, ranges 1.5 to 9.0) compare to group D (median 3 mg, ranges 0 to 6.0) without statistically significant (p = 0.085). The incidence of severe pain at 4 hours which defined as NRS ≥7 after operation was significantly lower in group D (p = 0.006) (Figure 4). There were no early airway and respiratory complications.

Discussion

From the present study, there were no differences in the incidences of emergence agitation which classified as Riker sedation agitation score more than 5. The efficacy of dexmedetomidine in prevention of EA in adults was proven previously

Table 1. Patient characteristics and intraoperative data

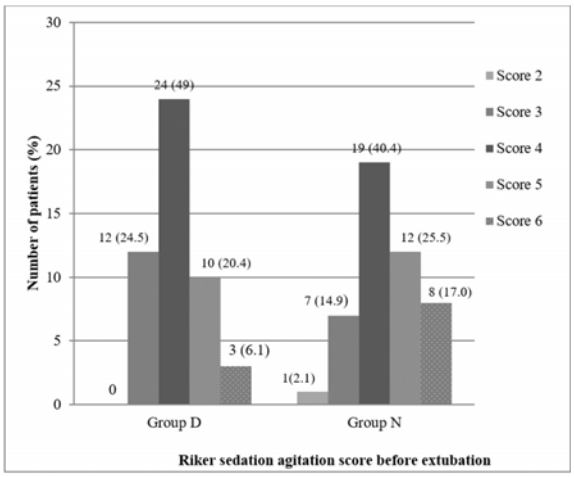
	Group Dex [D] (n = 49)	Group NSS [N] (n = 47)	p-value
Age (year)	56.6±12.7	56.2±13.0	0.867
Gender: female	21 (42.9)	16 (34.0)	0.375
Body mass index (kg/m^2)	24.6±3.7	24.2±3.4	0.576
ASA physical status I/II/III	11/30/8	10/28/9	0.935
Surgical time (min)	141.2±37.3	153.0±44.1	0.161
Number of spine level	1 (1, 2)	1 (1, 2)	0.562
Bleeding (mL)	30 (20, 60)	40 (20, 70)	0.287
Bispectral index	44.6±5.5	43.2±4.9	0.204
Desflurane (% end tidal)	4.2±0.6	4.7±0.8	<0.001*
Fentanyl (mcg)	102±32	133±43	<0.001*
Fentanyl (mcg/kg/h)	0.5±0.2	0.6±0.2	0.020*
Fluid (mL)	1,149±442	1,003±426	0.103

The data are presented as mean ± standard deviation, n (%) and median (P25, P75)
* p-value <0.05 indicates statistical significance
ASA = American Society of Anesthesiologists, BMI = Body Mass Index

Table 2. Recovery profiles after general anesthesia

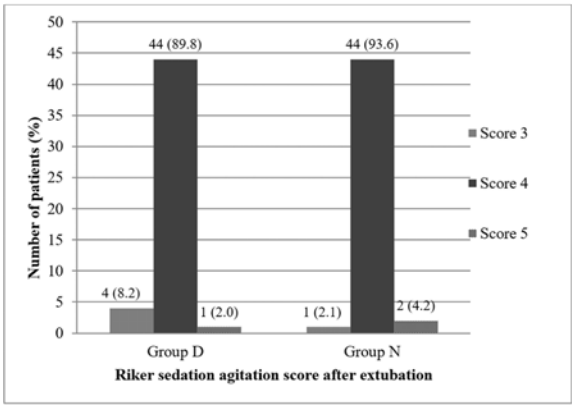
	Group Dex (D) (n = 49)	Group NSS (N) (n = 47)	*p*-value
Emergence agitation (Riker sedation agitation score ≥5)			
Before extubated	13 (26.5)	20 (42.6)	0.098
After extubated 15 min	1 (2.0)	2 (4.3)	0.533
Emergence sedation (score ≤3)	12 (24.5)	8 (17.0)	0.368
Tidal volume (mL/kg)	6.3±2.0	6.5±2.3	0.730
Vital capacity (mL/kg)	11.1 (8.7, 14.3)	11.5 (9.2, 18.5)	0.328
Respiratory rate (min^{-1})	18.5±5.6	18.2±5.0	0.813
Awakening time (min)	5.8±4.3	3.9±2.7	0.010*
Extubation time (min)	8.3±5.3	5.7±2.8	0.003*
Number co-operated patients at different time points			0.691
Before extubated	34 (69.4)	36 (76.6)	
After extubated 10 min	13 (26.5)	10 (21.3)	
After extubated 20 min	2 (4.1)	1 (2.1)	

The data are presented as mean ± standard deviation, n (%) and median (P_{25}, P_{75})
* *p*-value <0.05 indicates statistical significance



Group D = Group Dexmedetomidine (n = 49), Group N = Group Normal Saline (NSS) (n = 47)

Figure 2. Riker sedation agitation score before extubation.



Group D = Group Dexmedetomidine (n = 49), Group N = Group Normal Saline (NSS) (n = 47)

Figure 3. Riker sedation agitation score 15 min after extubation.

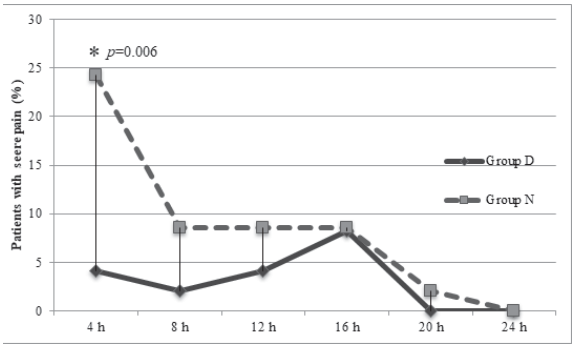
in nasal surgeries, transurethral resection of prostate [TURP], and video assisted thoracoscopic surgery [VATS][9,12,13]. Polat et al had shown that dexmedetomidine was effective in reducing the incidence of EA after nasal surgeries by 57.4% as compared to placebo (20% in the dexmedetomidine group, 47% in control group)[9]. Rim et al had shown that spine surgery was a risk factor of EA[1]. We assume that there was a tendency toward the statistically significance when providing a larger sample size. We calculated the sample size from sinus surgery[9] not from our own pilot study in ACDF surgery. The assumption had been made that both surgeries were related to airway surgery and could cause EA in the same manners.

The anesthetic requirement, desflurane and fentanyl were lower in group D compare to group N with statistically significant. Which is concordant to the previous studies that dexmedetomidine was reduced anesthetic requirement and opioids

Table 3. Perioperative complications and treatment

	Group Dex (D) (n = 49)	Group NSS (N) (n = 47)	*p*-value
Hypertension	13 (26.5)	26 (55.3)	0.004
Bradycardia	9 (18.4)	5 (10.6)	0.283
Hypotension	38 (77.6)	19 (40.4)	<0.001*
Ephedrine (mg)	6 (0, 12)	0 (0, 6)	<0.001*
PONV	7 (14.3)	3 (6.4)	0.205

The data are presented as n (%) and median (P25, P75)
* *p*-value <0.05 indicates statistical significance
Hypertension is defined as systolic blood pressure (SBP) >160 or >20% from baselines. Hypotension is defined as SBP <90 mmHg or below 20% from baseline. Bradycardia is defined as heart rate <40 beats/min
PONV = Postoperative nausea and vomiting



* *p*<0.05 indicates statistical significance
The data are presented as percentage.
NRS = Numeric rating score.

Figure 4. Patients with postoperative severe pain (NRS ≥7).

consumption[6,9-11]. As known that dexmedetomidine provides dose-related sedation and analgesia[4,5]. However, the reduction of anesthetic agent (from 4.7% to 4.2%) and intraoperative fentanyl consumption (from 0.6 to 0.5 mcg/kg/min) were too small for clinically significant.

Regarding sedative effect of dexmedeto midine, the awakening time and time to extubation in this study was shown to be prolonged in group of dexmedetomidine ($p = 0.010$, 0.003 in orderly) which was shown in the same manner of most of the previous studies[9,12,14]. Though, the different duration only two to three minutes had no clinical significance.

Dexmedetomidine decreased postoperative opioids consumption in 24 h and postoperative pain score in 24h in colectomy and surgery[11,14]. Likewise, in the present study, the percentage of patients with severe pain (NRS≥7) at 4 h postoperatively was significantly declined ($p = 0.006$). However, after 4 h, the incidences of severe pain were not different. This may account to the effect of dexmedetomidine weared off at that time point. There was no significant reduction in total opioid consumption in 24 h ($p = 0.085$).

In the present study, the patients in dexmedetomidine group had more hypotension and bradycardia. All of the patients were treated by intravenous fluid and drugs as shown in protocol and had no serious further complications. From some studies, dexmedetomine provided more stable hemodynamics compared to control group[6,9]. In other studies, hypotension and bradycardia due to sympatholytic effect occurred more frequently in dexmedetomidine group with no statistically significant[12,14]. There were no differences in the incidences of PONV ($p = 0.205$), although PONV is an adverse effects of dexmedetomine[15].

Limitation

The present study had several exclusions and selected only un-complicated cases of ACDF surgery with relatively short procedures so the incidence of emergence agitation might be lower than other ACDF surgery. The authors followed the cases only 24 hours and no details for late complications and final outcome.

Conclusion

The present study failed to demonstrate the protective effect of dexmedetomidine in EA after general anesthesia in ACDF surgery and the larger sample size may be required. Dexmedetomidine had higher risk of adverse hemodynamic complications.

What is already known on this topic?

Dexmedetomidine reduces intraoperative anesthetic requirement and some analgesia but it can cause sedative effect and delay awakening time.

What this study adds?

Dexmedetomidine did not reduce incidence of emergence agitation after ACDF surgery.

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Trial registration

Clinicaltrials.in.th as TCTR20170607001.

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Potential conflicts of interest

The authors declare no conflict of interest.

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Appendix 1. Riker sedation agitation score

Score	Category	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, trashing side to side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requiring physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calm down on verbal instruction
4	Calm	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli, or gentle shaking
2	Very sedated	Arouse to physical stimuli but does not follow commands
1	Unarousable	Minimal or no response to noxious stimuli