

# Dexmedetomidine for Improved Quality of Emergence From General Anesthesia: A Dose-Finding Study

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**BACKGROUND:** Dexmedetomidine provides smooth and hemodynamically stable emergence at the expense of hypotension, delayed recovery, and sedation. We investigated the optimal dose of dexmedetomidine for prevention of cough, agitation, hypertension, tachycardia, and shivering, with minimal side effects.

**METHODS:** In this prospective, randomized, double-blind trial, 216 adult patients were randomly assigned to dexmedetomidine 1 µg/kg (D 1), 0.5 µg/kg (D 0.5), 0.25 µg/kg (D 0.25), or control (C). During emergence, cough, agitation, hemodynamic parameters, shivering, time to extubation, and sedation scores were recorded.

**RESULTS:** A total of 190 patients were analyzed. The respective incidences for the groups D 1, D 0.5, and D 0.25 versus group C were 48%, 64%, and 64% vs 84% for cough—corrected  $P < .003$  between groups D 1 and C; 33%, 34%, and 33% vs 72% for agitation—corrected  $P < .003$  between group C and each of the study groups; and 4%, 2%, and 7% vs 22% for shivering—corrected  $P = .03$  and corrected  $P = .009$  between groups D 1 and D 0.5 versus group C, respectively. The percent increase from baseline blood pressure on extubation for the 3 treatment groups was significantly lower than group C. Percent increase in heart rate was lower than control in groups D 1 and D 0.5 but not in group D 0.25. Time to extubation and sedation scores were comparable. However, more hypotension was recorded during the emergence phase in the 3 treatment groups versus group C.

**CONCLUSIONS:** D 1 at the end of surgery provides the best quality of emergence from general anesthesia including the control of cough, agitation, hypertension, tachycardia, and shivering. D 0.5 also controls emergence phenomena but is less effective in controlling cough. The 3 doses do not delay extubation. However, they cause dose-dependent hypotension. (Anesth Analg 2019;129:1504–11)

## KEY POINTS

- **Question:** What is the optimal dose of dexmedetomidine that improves the quality of emergence from general anesthesia with minimal side effects?
- **Findings:** Dexmedetomidine 1 µg/kg significantly improves the quality of emergence from general anesthesia including cough, agitation, hypertension, tachycardia, and shivering, with associated hypotension.
- **Meaning:** Dexmedetomidine 1 µg/kg might be used to improve the quality of emergence from general anesthesia in hemodynamically stable patients, especially those at particularly high risk for coughing-induced injury.

Emergence from general anesthesia may be accompanied by cough, agitation, hypertension, tachycardia, and shivering. These changes may be detrimental to patients, in particular those with impaired cardiac and pulmonary reserves. Also, they may prolong postanesthesia care unit (PACU) stay.<sup>1</sup> Although coughing during anesthetic

recovery may not be life threatening, periextubation cough might lead to undesirable postoperative events, especially in patients at risk for complications related to increases in intracranial<sup>2</sup> or intraocular pressure<sup>3</sup> or detrimental hemodynamic changes. Therefore, there may be valid reasons to adopt measures to prevent cough, at least in certain situations. The compression phase of coughing is a forced expiration against a closed glottis that can generate intrathoracic pressures as high as 40 kPa,<sup>4</sup> which can be detrimental in patients at risk for bleeding, such as posttonsillectomy, patients with spontaneous pneumothorax,<sup>5</sup> bullae or severe emphysema, or posttracheal reconstruction. In addition, coughing might be associated with respiratory complications, such as laryngospasm, oxygen desaturation, upper airway obstruction, pulmonary edema,<sup>6</sup> and vocal cord injury.<sup>7,8</sup> In extreme situations, it might favor airway rupture.<sup>9</sup> Various drugs have been investigated for the prevention or treatment of these undesirable effects including opioids, lidocaine, ketamine, tramadol, and dexmedetomidine.<sup>10–12</sup>

Dexmedetomidine is a selective  $\alpha_2$ -receptor agonist that has sympatholytic, analgesic, sedative, anxiolytic, amnesic,

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antishivering, and opioid-sparing properties without respiratory depression.<sup>13</sup> Its intraoperative use decreases opioid consumption and pain intensity.<sup>13</sup> Dexmedetomidine has a favorable side effect profile with significantly less impact on the respiratory drive whether used as a single agent or in combination with opioids.<sup>7</sup>

Previous research has shown that dexmedetomidine given as an intraoperative continuous infusion or a bolus at the end of surgery may improve recovery profiles with a variable impact on extubation times and sedation scores.<sup>14–16</sup> In addition, its efficacy in controlling cough and other emergence phenomena is not consistent across the studies. Therefore, some controversies regarding its efficacy and optimal dose still need to be clarified. Our hypothesis is that dexmedetomidine will prevent the occurrence of cough and other emergence phenomena. The aim of this prospective, multicenter, randomized, double-blind, placebo-controlled study is to investigate the optimal dose of dexmedetomidine for prevention of cough (primary outcome) and for a better quality of emergence from general anesthesia as evidenced by stable systolic blood pressure (SBP), heart rate (HR), and absence of agitation and shivering (secondary outcomes) without hypotension, delayed recovery, and excessive sedation.

## METHODS

This study was approved by the institutional review board of the American University of Beirut Medical Center (Protocol #ANES.MA.10) and of the Lebanese American University Medical Center-Rizk Hospital (UMCRH.VA2.21/FEB/14). The study was registered at <http://clinicaltrials.gov> (registration number: NCT02141412) under the name of Marie Awad on May 19, 2014. This manuscript adheres to the applicable Enhancing the QUALity and Transparency Of health Research (EQUATOR) guidelines.

After obtaining informed written consent for participation in the study, 216 adult patients 18–75 years of age (American Society of Anesthesiologists class I–III) of both genders undergoing elective surgery under general anesthesia with an estimated time of 1–3 hours were enrolled in this study between September 2010 and September 2015. All patients were assessed preoperatively, and participation in the study as well as existing alternatives were discussed. Patients who were allergic to dexmedetomidine, obese (body mass index >35 kg/m<sup>2</sup>), febrile, pregnant, on antidepressants, or in chronic pain using opioid or nonopioid analgesics were excluded from the study.

Patients were randomly assigned to one of 4 groups according to a computer-generated table of random numbers: group dexmedetomidine 1 µg/kg (D 1) (Precedex; Hospira Inc, Lake Forest, IL), group dexmedetomidine 0.5 µg/kg (D 0.5), group dexmedetomidine 0.25 µg/kg (D 0.25), and group control, same volume of normal saline (C). The results of the randomization were concealed in opaque envelopes and opened sequentially immediately before study drug administration. Dexmedetomidine or normal saline was prepared by study personnel who did not participate in data collection, and the syringe was labeled as “study drug.” A 10-mL syringe containing 10, 5, and 2.5 µg/mL of dexmedetomidine or saline was prepared for patients in groups D1, D 0.5, D 0.25, and C, respectively. Patients

received 0.1 mL/kg of the mixture over 10 minutes. The investigator, attending anesthesiologist, resident, PACU nurses, and patients were blinded to group assignment.

Routine monitors were applied including a blood pressure cuff, electrocardiogram, pulse oximeter, capnogram, esophageal temperature probe, and neuromuscular monitoring using kinemyography (GE Datex Ohmeda, M-NMT Module; Healthcare Finland Oy, Helsinki, Finland). Train of four (TOF) was monitored throughout the surgery. Anesthesia was induced using intravenous (IV) midazolam 1 mg, propofol 1.5–2 mg/kg, lidocaine 1 mg/kg, fentanyl 1–2 µg/kg, and rocuronium 0.6 mg/kg. After orotracheal intubation, anesthesia was maintained using N<sub>2</sub>O in oxygen 2:1, sevoflurane 1%–3%, and incremental doses of fentanyl to keep blood pressure and HR within 20% of baseline and rocuronium as needed. All patients received dexamethasone 8 mg IV. Operating room temperature was kept between 21°C and 22°C. Patients were covered with surgical drapes and were actively warmed by forced air warming blankets.

At the end of the surgery, the anesthesiologist who was blinded to the group allocation stopped sevoflurane and nitrous oxide (defined as time zero or baseline of emergence process), increased the fresh gas flow from 3 to 6 L/min, and delivered 0.1 mL/kg of the study drug over 10 minutes using a syringe pump. Ondansetron 4 mg IV was given, and orogastric suction was performed. From time zero till 5 minutes postextubation, the SBP, diastolic blood pressure, HR, blood oxygen saturation level (SpO<sub>2</sub>), end-tidal carbon dioxide (EtCO<sub>2</sub>), end-tidal sevoflurane, agitation (defined as limb movements requiring restraint), sedation scores, cough scores, and number of coughing episodes were recorded every 2 minutes. Residual neuromuscular blockade defined as TOF ratio <0.9 was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. The trachea was extubated when patients were fully awake and responsive with a TOF ≥0.9. The following data were also recorded: patient’s temperature, total intraoperative fentanyl dose, duration of anesthesia and surgery, total amount of fluids, and time to extubation (from time zero).

In PACU, the nurse who was blinded to the study drug recorded the following parameters every 10 minutes and till discharge: SBP, HR, axillary temperature, shivering score, sedation score, numerical rating scale for pain (0 = no pain and 10 = worst pain imaginable), and postoperative nausea and vomiting (PONV) score. IV meperidine 0.35 mg/kg was the rescue medication for shivering (shivering scale ≥2). In the presence of pain (numerical rating scale score >3), paracetamol 1 g IV, ketoprofen 100 mg IV, and morphine IV at 1–2 mg increments were used. Discharge from PACU was as per the institution’s discharge criteria based on the modified Aldrete score.

The grade of cough was assessed using a 4-point scale (0 = no cough; 1 = mild, single cough; 2 = moderate, >1 cough lasting for <5 seconds; and 3 = severe, sustained for >5 seconds). Shivering score (0 = no shivering; 1 = mild fasciculations of face or neck; 2 = moderate, visible tremor in >1 muscle group; and 3 = severe, gross muscular activity involving the entire body). Sedation score was assessed using a 6-point scale (1 = alert; 2 = alert but drowsy; 3 = responds to voice; 4 = responds to gentle tactile stimulation; 5 = responds to vigorous tactile stimulation; and 6 = unarousable). PONV score was assessed using a 4-point scale (1 = absent; 2 = mild nausea; 3 = severe nausea; and 4 = vomiting).

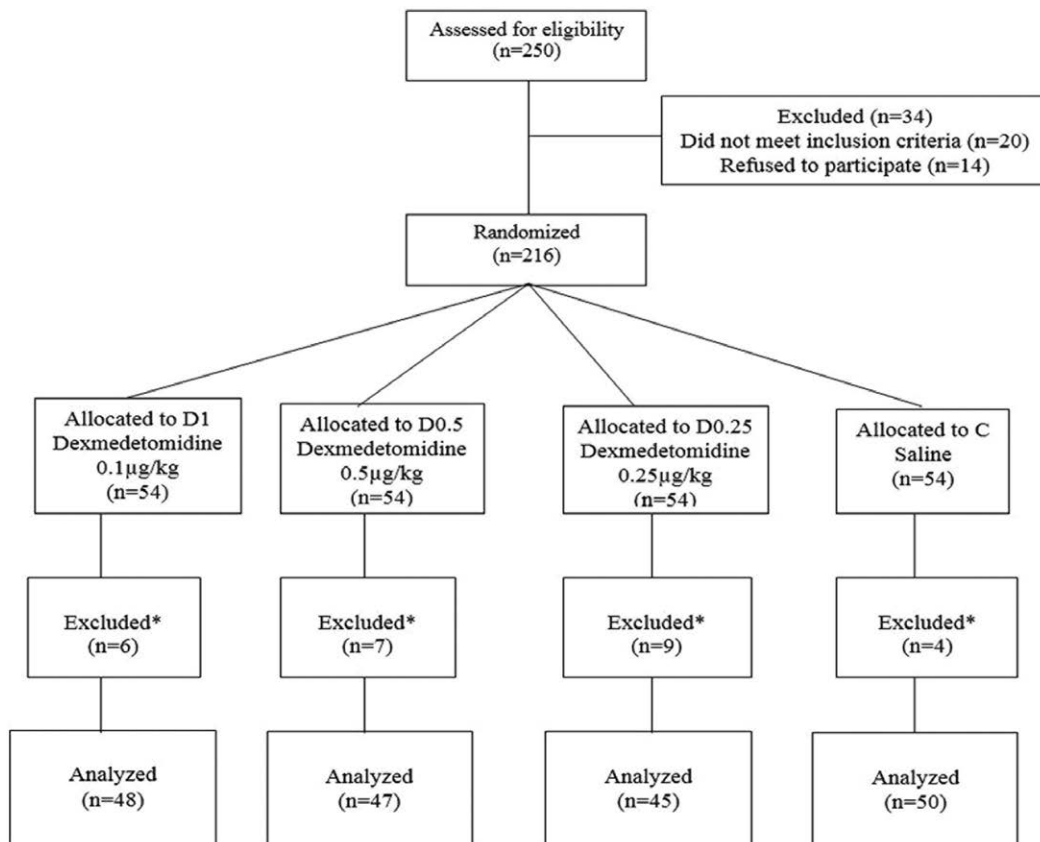
## Statistical Analysis

A previous report showed an incidence of 76% cough during emergence from general anesthesia in the group C.<sup>17</sup> We assumed that a 40% decrease in this incidence (down to 46%) with dexmedetomidine prophylaxis is considered clinically significant. With  $\alpha = .05$  and  $\beta = .2$ , 47 patients would be required in each group. To account for 15% dropout, 54 patients were included in each group. Absolute values and percent changes of SBP and HR from baseline, time to extubation and discharge, and temperature values were expressed as means and standard deviations and analyzed using analysis of variance. Post hoc comparisons were performed using Bonferroni. Shivering, cough, sedation, pain, and nausea scores were expressed as medians and ranges and analyzed using Kruskal-Wallis test. Incidences of shivering, cough, and agitation were expressed as numbers and percentages and analyzed using  $\chi^2$  test or Fisher Freeman-Halton as required. Three pairwise comparisons between each of the treatment groups and the group C were reported. The Bonferroni correction was used to adjust for the multiple comparisons of outcomes by multiplying the unadjusted *P* values by the number of comparisons (ie, 3). Bonferroni-adjusted *P* value was denoted by "corrected *P*."  $P < .05$  and the corrected  $P < .05$  were considered statistically significant. Statistical analysis was performed using statistical package for social sciences (SPSS, version 22; IBM Corp, Armonk, NY).

## RESULTS

A total of 250 patients were assessed for eligibility, and 216 subjects were enrolled in the study. The remaining 34 patients were excluded because either they did not meet the inclusion criteria ( $n = 20$ ) or they refused to participate ( $n = 14$ ). Fifty-four patients were allocated to each group. Due to protocol violation, 6 patients were excluded from group D 1, 7 patients from group D 0.5, 9 patients from group D 0.25, and 4 patients from group C. Therefore, 48 patients in group D 1, 47 patients in group D 0.5, 45 patients in group D 0.25, and 50 patients in group C were analyzed (Figure 1).

Patient characteristics and intraoperative data were comparable among the 4 groups (Table 1). Operations were a mix of orthopedic, laparoscopic, gynecological, urological, head and neck, and general surgical procedures and were evenly distributed among the 4 groups. At the time of extubation, end-tidal sevoflurane and nitrous oxide were 0 in the 4 groups. The incidence of cough was 48% in group D 1, 64% in D 0.5, and 64% in D 0.25 versus 84% in group C; corrected  $P < .003$  between groups D 1 and C. Also, moderate and severe cough were significantly lower in group D 1 than group C (21% vs 56%; corrected  $P < .003$ ). The incidence of emergence agitation was lower in the 3 treatment groups than in group C (33% in D 1, 34% in D 0.5, and 33% in D 0.25 versus 72% in C; corrected  $P < .003$  between group C and each of the study groups). The incidence of patients experiencing shivering was significantly lower in groups D 1 and



**Figure 1.** Consort flow diagram. \*Exclusion due to protocol violation: patients operated under regional anesthesia only, use of laryngeal mask, did not receive intervention. C indicates control, normal saline; D 1, dexmedetomidine 1 µg/kg; D 0.5, dexmedetomidine 0.5 µg/kg; D 0.25, dexmedetomidine 0.25 µg/kg.

D 0.5 than in group C (4% in D 1 and 2% in D 0.5 versus 22% in C, corrected  $P = .03$  and corrected  $P = .009$ , respectively) (Table 2).

On extubation, the respective percent increase from baseline SBP measured at time zero was 4%, 11%, and 17% for groups D 1, D 0.5, and D 0.25, respectively, versus 35% for the group C ( $P < .001$ ,  $P < .001$ , and  $P = .003$ , respectively) (Table 2). Thirteen patients (27%) developed hypotension  $<90$  mm Hg in the D1 group, as compared to 9 patients (19%) in D 0.5 group and 7 patients (16%) in D 0.25 group, which was statistically significant as compared to group C where no hypotension  $<90$  mm Hg was noted (corrected

$P < .003$ , corrected  $P = .003$ , and corrected  $P = .012$ , respectively) (Table 2). At 10 and 15 minutes from time zero, at extubation, and 5 minutes after extubation, SBP was significantly lower in groups D 1, D 0.5, and D 0.25 than in group C (Figure 2). On extubation, the percent increase from baseline HR measured at time zero was 11%, 12%, and 30% for the groups D1, D 0.5, and D 0.25, respectively, compared to 43% in the group C ( $P < .001$ ,  $P < .001$ , and  $P = .2$ , respectively) (Table 2). In group D 0.25, the percent increase in HR was not different from group C but was statistically significant as compared to groups D 1 and D 0.5 ( $P = .03$  and  $P = .01$ , respectively) (Table 2). The differences in HR at the different

**Table 1. Patients' Characteristics and Intraoperative Data**

	Group D 1 (n = 48)	Group D 0.5 (n = 47)	Group D 0.25 (n = 45)	Group C (n = 50)
Age (y)	46.9 ± 16.6	44.2 ± 16.7	47.2 ± 15.3	46.3 ± 16.1
Weight (kg)	72.9 ± 14.1	76.9 ± 14.2	73.2 ± 13.1	73.6 ± 14.5
Height (cm)	167 ± 7	170 ± 12	165 ± 10	168 ± 10
Gender				
M	14 (29)	23 (49)	16 (36)	20 (40)
F	34 (71)	24 (51)	29 (64)	30 (60)
Daily smoking during past year	20 (42)	16 (34)	15 (33)	21 (42)
ASA				
1	22 (46)	27 (58)	20 (44)	24 (48)
2	21 (44)	18 (38)	20 (44)	17 (34)
3	5 (10)	2 (4)	5 (11)	9 (18)
Fentanyl consumption (µg)	225 ± 78	206 ± 11	219 ± 75	238 ± 82
Fentanyl consumption (µg/kg)	3.2 ± 1.2	2.7 ± 1.1	3.1 ± 1.3	3.3 ± 1.1
Fentanyl consumption (µg/kg/h)	0.04 ± 0.02	0.04 ± 0.01	0.04 ± 0.02	0.04 ± 0.02
Duration of surgery (min)	82 ± 39	77 ± 26	85 ± 41	91 ± 39
Duration of anesthesia (min)	109 ± 43	99 ± 26	111 ± 43	119 ± 43
Intraoperative fluids (mL)	1145 ± 839	1131 ± 493	1266 ± 601	1313 ± 679
Baseline end-tidal sevoflurane	1.3 ± 0.5	1.1 ± 0.5	1.1 ± 0.6	1.3 ± 0.4

Values are mean ± SD or numbers (%).

Abbreviations: ASA, American Society of Anesthesiologists; C, control, normal saline; D 1, dexmedetomidine 1 µg/kg; D 0.5, dexmedetomidine 0.5 µg/kg; D 0.25, dexmedetomidine 0.25 µg/kg; F, female; M, male.

**Table 2. Data During Emergence Phase**

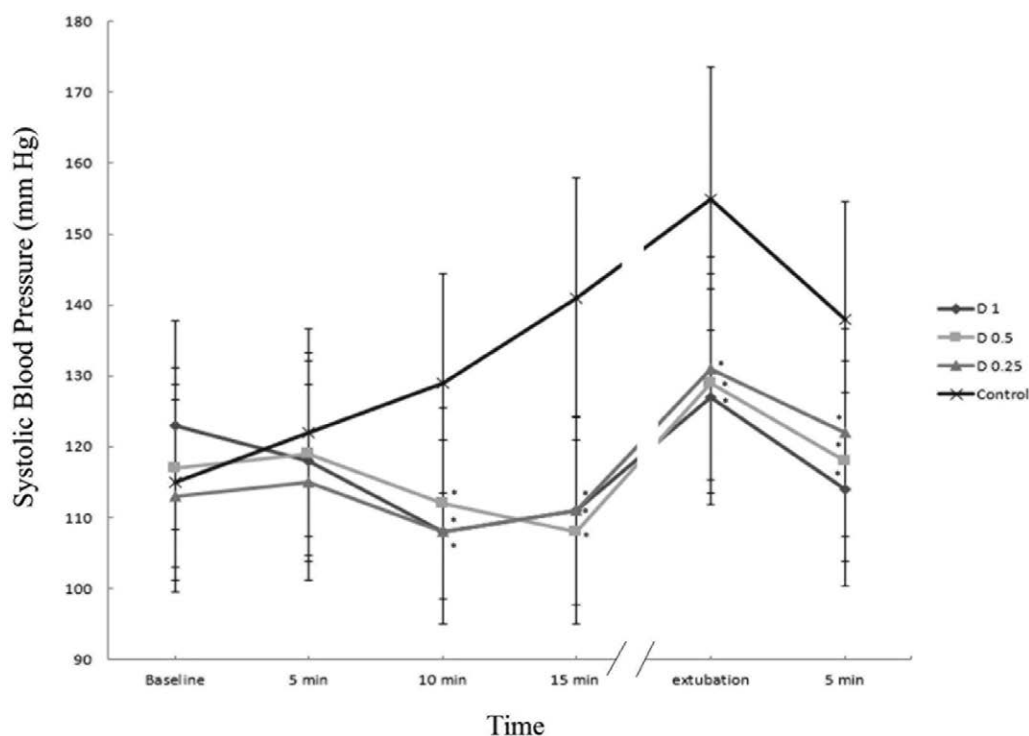
	Group D 1 (n = 48)	Group D 0.5 (n = 47)	Group D 0.25 (n = 45)	Group C (n = 50)	P
Incidence cough	23 (48)	30 (64)	29 (64)	42 (84)	.003 <sup>a</sup>
Corrected $P < .003$					
Incidence moderate and severe cough	10 (21)	16 (34)	18 (40)	28 (56)	.004 <sup>a</sup>
Corrected $P < .003$					
Cough grade	1 (0–2)	1 (0–3)	1 (0–3)	2 (0–3)	.02
$P < .01$		$P < .01$			
Incidence agitation	16 (33)	16 (34)	15 (33)	36 (72)	$<.001^a$
Corrected $P < .003$		Corrected $P < .003$	Corrected $P < .003$		
SBP increase from baseline on extubation (%)	3.80 ± 13.55	11.28 ± 13.96	17.09 ± 20.43	34.96 ± 23.34	$<.001$
$P < .001$		$P < .001$	$P = .003$		
Incidence hypotension (SBP $<90$ mm Hg)	13 (27)	9 (19)	7 (16)	0 (0)	.002 <sup>a</sup>
Corrected $P < .003$		Corrected $P = .003$	Corrected $P = .012$		
HR increase from baseline on extubation (%)	11.01 ± 14.02	11.72 ± 17.62	29.64 ± 29.25	42.73 ± 25.98	$<.001$
$P < .001$		$P < .001$			
Incidence shivering (till discharge from PACU)	2 (4)	1 (2)	3 (7)	11 (22)	.004 <sup>b</sup>
Corrected $P < .03$		Corrected $P = .009$			
Incidence moderate and severe shivering	0 (0)	0 (0)	1 (2)	5 (10)	.01 <sup>b</sup>
Shivering grade	0 (0–1)	0 (0–1)	0 (0–2)	0 (0–3)	.04
$P < .01$		$P < .01$			
Time to extubation (min)	16.69 ± 4.32	18.15 ± 4.19	19.81 ± 5.52	18.00 ± 6.36	.16
Sedation score at extubation	3.35 ± 0.98	3.38 ± 0.84	3.14 ± 0.64	3.39 ± 0.83	.69
Temperature at extubation (°C)	36.20 ± 0.48	36.23 ± 0.38	36.09 ± 0.52	36.27 ± 0.43	.39

Values are mean ± SD, numbers (%), or medians and ranges.

Abbreviations: C, control, normal saline; D 1, dexmedetomidine 1 µg/kg; D 0.5, dexmedetomidine 0.5 µg/kg; D 0.25, dexmedetomidine 0.25 µg/kg; HR, heart rate; PACU, postanesthesia care unit; SBP, systolic blood pressure.

<sup>a</sup>Analyzed using  $\chi^2$ .

<sup>b</sup>Analyzed using Fisher Freeman–Halton.



**Figure 2.** Systolic blood pressure changes during the emergence phase reported as mean  $\pm$  SD. \* $P < .001$  between treatment groups and group C at 10 min, 15 min, extubation, and 5 min after extubation. C indicates control, normal saline; D 1, dexmedetomidine 1  $\mu\text{g}/\text{kg}$ ; D 0.5, dexmedetomidine 0.5  $\mu\text{g}/\text{kg}$ ; D 0.25, dexmedetomidine 0.25  $\mu\text{g}/\text{kg}$ ; SD, standard deviation.

time points are depicted in Figure 3. Of note, no statistically significant difference for HR was reported between group D 0.25 and group C at any time point (Figure 3). There was no statistical difference in the time needed from sevoflurane discontinuation to extubation among all groups ( $P = .16$ ). Also, sedation scores on extubation were comparable among groups ( $P = .69$ ).

Data on arrival to PACU are provided in Table 3. Sedation scores were similar among the 4 groups. SBP was significantly lower in groups D 1, D 0.5, and D 0.25 than in group C ( $P = .01$ ,  $P < .001$ , and  $P = .002$ , respectively). HR was significantly lower in group D 0.5 as compared to group C ( $P = .003$ ). Pain scores on arrival as well as the highest pain score recorded were significantly lower in group D 0.5 than in group C ( $P = .02$ ). There was no statistical difference among all groups regarding PONV and the highest PONV score. Also, there was no statistical difference among all groups regarding PACU length of stay.

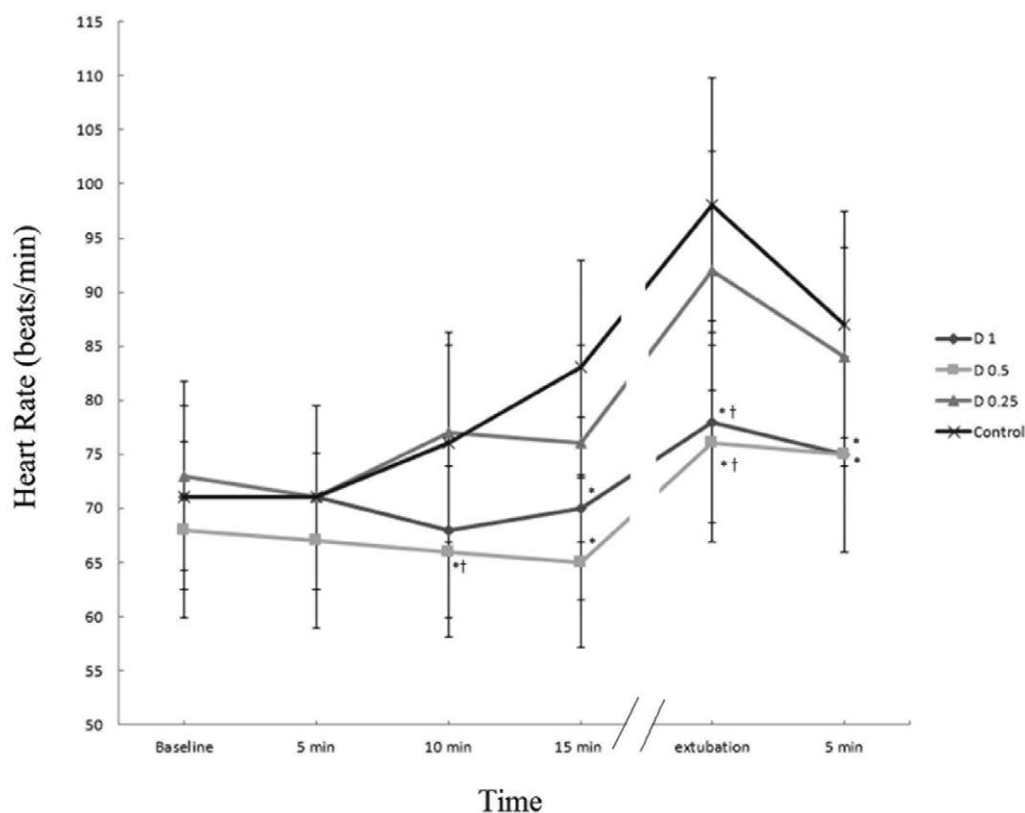
## DISCUSSION

Our results suggest that a single dose of D 1 at the end of surgery significantly reduces the overall incidence of cough, agitation, hypertension, tachycardia, and shivering compared with saline. D 0.5 was also effective in controlling agitation, hypertension, tachycardia, and shivering but not coughing. The 3 doses of dexmedetomidine did not delay extubation and PACU discharge, but caused a dose-dependent hypotension during emergence.

Coughing during emergence from general anesthesia may increase the risk of serious complications. Various modalities have been studied to suppress its occurrence,

such as lidocaine and remifentanyl.<sup>11,12</sup> Intraoperative infusions of dexmedetomidine have been shown to allow for a smooth emergence from anesthesia by attenuating agitation, cough, and hemodynamic changes in children and adults.<sup>15,18</sup> Nevertheless, there has been conflicting results regarding the efficacy of dexmedetomidine as a cough suppressant. In adult patients undergoing nasal surgery, some studies showed that intraoperative dexmedetomidine infusion at a rate of 0.4  $\mu\text{g}/\text{kg}/\text{h}$  from induction of anesthesia until extubation did not reduce cough as compared to saline.<sup>15,19</sup> Whereas, Guler et al<sup>20</sup> found that D 0.5 before extubation attenuate airway reflexes during extubation in patients undergoing ocular surgery. When compared to a remifentanyl target-controlled infusion, a single dose of D 0.5 given 10 minutes before the end of surgery was shown to be less efficient than remifentanyl in reducing cough during emergence from general anesthesia in patients undergoing elective thyroidectomy.<sup>21</sup> Conversely, the same bolus dose of dexmedetomidine seems to be superior to fentanyl 1  $\mu\text{g}/\text{kg}$  for cough suppression during extubation in patients undergoing rhinoplasty.<sup>22</sup> In our study, D 1 attenuated best cough during extubation as compared to control.

Agitation on emergence from general anesthesia is a common occurrence. Risk factors include male gender, type of surgery, inhalation anesthetics, presence of tracheal tube, and preoperative benzodiazepine.<sup>23</sup> We demonstrated a reduction of emergence agitation after the 3 bolus doses of dexmedetomidine, similar to the findings of Kim et al<sup>15</sup> who used a continuous infusion of 0.4  $\mu\text{g}/\text{kg}/\text{h}$  dexmedetomidine throughout the surgery. Our study included a mix of surgical patients that might be a confounding factor



**Figure 3.** Heart rate changes during the emergence phase reported as mean  $\pm$  SD. \* $P < .05$  between treatment groups and group C as follows: at 10 min,  $P = .02$  between group D 0.5 and group C; at 15 min and at extubation,  $P \leq .001$  between groups D 1 and D 0.5 and group C; and at 5 min after extubation,  $P = .01$  and  $P = .002$  between groups D 1 and D 0.5 and group C, respectively. † $P < .05$  between group D 0.25 and group D 1 or D 0.5 as follows: at 10 min,  $P = .02$  between group D 0.25 and group C; at extubation,  $P = .005$  and  $P < .001$  between groups D 1 and D 0.5 and group D 0.25, respectively. C indicates control, normal saline; D 1, dexmedetomidine 1  $\mu\text{g}/\text{kg}$ ; D 0.5, dexmedetomidine 0.5  $\mu\text{g}/\text{kg}$ ; D 0.25, dexmedetomidine 0.25  $\mu\text{g}/\text{kg}$ ; SD, standard deviation.

**Table 3. Data in the PACU**

	Group D 1 (n = 48)	Group D 0.5 (n = 47)	Group D 0.25 (n = 45)	Group C (n = 50)	P
Sedation score on arrival	2 (1–4)	2 (1–4)	2 (1–4)	2 (1–3)	.29
SBP on arrival (mm Hg)	120.57 $\pm$ 22.57 $P = .01$	116.02 $\pm$ 11.81 $P < .001$	118.77 $\pm$ 14.13 $P = .002$	133.67 $\pm$ 17.52	<.001
HR on arrival (bpm)	72.61 $\pm$ 16.68	70.11 $\pm$ 11.05 $P = .003$	78.57 $\pm$ 15.44	80.56 $\pm$ 10.99	.002
Pain score on arrival	0 (0–9)	2 (0–7) $P = .02$	1 (0–10)	4.5 (0–10)	.02
Highest pain score	5 (0–9)	4 (0–8)	5 (0–10)	5 (0–10)	.02
Temperature on arrival ( $^{\circ}\text{C}$ )	36.12 $\pm$ 0.43	36.15 $\pm$ 0.34	36.00 $\pm$ 0.58	36.21 $\pm$ 0.41	.21
Incidence PONV	13 (27)	9 (19)	13 (29)	7 (14)	.26
Highest PONV score	1 (1–3)	1 (0–4)	1 (1–4)	1 (1–3)	.48
Time to discharge from PACU (min)	58.04 $\pm$ 10.30	58.33 $\pm$ 12.03	62.59 $\pm$ 17.20	63.71 $\pm$ 10.60	.16

Values are mean  $\pm$  SD or numbers (%).

Abbreviations: C, control, normal saline; D 1, dexmedetomidine 1  $\mu\text{g}/\text{kg}$ ; D 0.5, dexmedetomidine 0.5  $\mu\text{g}/\text{kg}$ ; D 0.25, dexmedetomidine 0.25  $\mu\text{g}/\text{kg}$ ; HR, heart rate; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; SBP, systolic blood pressure.

regarding the incidence of agitation. Ham et al<sup>24</sup> studied adults undergoing orthognathic surgery. In this high-risk group, a single dose of D 1 failed to prevent emergence agitation.

At high doses or after rapid administration, dexmedetomidine stimulates the  $\alpha_2$  receptors in vascular smooth muscle, causing a transient increase in blood pressure and a reflex drop in HR.<sup>25</sup> The initial transient increase, presumably mediated by peripheral vasoconstriction, is followed by a longer

lasting reduction due to both centrally and peripherally mediated sympatholytic actions. Lower doses in the range of 0.25–0.5  $\mu\text{g}/\text{kg}$ , given as IV infusion in healthy volunteers, result in a monophasic reduction in mean arterial blood pressure. In a dose-finding study of dexmedetomidine for attenuating the hemodynamic response during emergence from anesthesia in patients undergoing total laparoscopic hysterectomy, Seo et al<sup>26</sup> found that an IV infusion of D 0.5 30 minutes before the end of surgery is the optimal dose to be used without

prolonging the extubation time. In our study, dexmedetomidine was infused over 10 minutes, and no biphasic blood pressure responses were seen, even with a dose of 1 µg/kg. The percent increase in blood pressure and HR on extubation for the 3 treatment groups was inversely proportional to the dose. The dose of 0.25 µg/kg was not effective in controlling tachycardia associated with extubation.

Dexmedetomidine at different doses have been suggested to be a useful antishivering agent.<sup>27,28</sup> However, results are conflicting regarding the optimal dose and the quality of evidence. Elvan et al<sup>29</sup> compared a loading dose of 1 µg/kg and continuous infusion of 0.4 µg/kg/h of dexmedetomidine with placebo and found 18% incidence of shivering with dexmedetomidine and 53% with placebo. In a dose-finding study, Kim et al<sup>30</sup> compared 0.5, 0.75, and 1.0 µg/kg infusions of dexmedetomidine for postoperative shivering and pain prophylaxis. Dexmedetomidine 0.75 µg/kg or D 1 significantly reduced the incidence and severity of postoperative shivering compared with saline or D 0.5. A meta-analysis that included 2478 patients indicated that the administration of dexmedetomidine might decrease the incidence of postoperative shivering similar to other antishivering drugs, such as fentanyl, meperidine, tramadol, and clonidine, and the effective dose was 0.5 µg/kg.<sup>31</sup> Also, a Cochrane meta-analysis concluded that dexmedetomidine can reduce postoperative shivering, but the quality of the evidence was very low.<sup>32</sup> Our study seems to confirm the antishivering efficacy of 1 and D 0.5. Of note, the overall incidence of shivering in our study was low with only 22% in the group C, which might be due to the routine use of active warming devices.

Other secondary outcomes such as pain and PONV in the PACU did not show any consistent and clinically significant differences among the 4 groups.

The effect of dexmedetomidine on delaying extubation is controversial. Kim et al<sup>30</sup> showed that extubation time was significantly prolonged in patients receiving 0.75-µg/kg dexmedetomidine or D 1. Similarly, in a study on elderly patients undergoing orthopedic surgery, the time to extubation was significantly longer in the group receiving 0.4 µg/kg/h dexmedetomidine than in the group C.<sup>16</sup> Conversely, dexmedetomidine at the same rate of 0.4 µg/kg/h did not prolong extubation time in patients undergoing nasal surgery.<sup>15</sup> We studied different doses of dexmedetomidine and found that extubation times, sedation scores, and time to discharge from PACU were comparable with the group C. Of note, our study population was relatively young with a mean age of approximately 45 years.

Limitations to our study are 3-fold. First, surgeries were not standardized and their durations variable that may cause some inconsistencies on emergence; also despite an end-tidal sevoflurane of 0 at extubation in all groups, different brain concentrations might have influenced some outcome measures. Second, even though double blindness was maintained, dexmedetomidine-induced hemodynamic changes may have introduced some bias. Last, despite the potential benefits, dexmedetomidine price is prohibitive and might limit its routine use in many institutions.<sup>33</sup> However, its use might still be cost-effective in patients at particularly high risk for coughing-induced injury.

Our study used bolus administration at the end of surgery obviating the need for continuous infusion throughout the surgery, especially during phases of potential hemodynamic instability such as bleeding. Our approach was comprehensive regarding the quality of emergence, as we focused on all its components. We identified D 1 at the end of surgery as the most effective dose in controlling the overall incidence of cough, agitation, SBP, and shivering. D 0.5 was also effective for the control of emergence phenomena such as agitation, hypertension, tachycardia, and shivering, but less effective as cough suppressant. The 3 doses of dexmedetomidine did not delay extubation and PACU discharge. However, they resulted in a dose-dependent hypotension during the emergence phase. Based on our results, D 1 at the end of surgery is associated with a better quality of emergence from general anesthesia. Despite the associated hypotension, it might be used for that purpose in hemodynamically stable patients, especially those at particularly high risk for coughing-induced injury. ■

#### DISCLOSURES

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