

ANESTHESIOLOGY

Discharge Readiness after Propofol with or without Dexmedetomidine for Colonoscopy

A Randomized Controlled Trial

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Approximately 15 million colonoscopy procedures are performed annually in the United States,¹ usually in the ambulatory setting. Propofol is commonly the sole agent for anesthesia due to its rapid onset and the rapid offset that allows for a timely recovery.² However, significant hypotension, tachycardia, and apnea, which may not be well tolerated, can occur when large doses are required to complete a procedure.^{3,4} Decreasing the anesthetic level in such situations may lead to inadequate sedation, resulting in patient body movement disruptive to the procedure.

Enhanced recovery protocols employ one or more approaches to improve a procedure's clinical outcome. For colonoscopies, this might involve combining several agents with different mechanisms of action to achieve the desired level of anesthesia.^{5,6} This approach should theoretically decrease the dose of each drug and minimize individual adverse side effects. Dexmedetomidine is a highly selective, α_2 -adrenoceptor agonist with anxiolytic, analgesic, and sedative properties.^{7,8} It can be safely combined with propofol since it has minimal respiratory depressive effects and has been shown to decrease physiologic stress-response to surgical stimulation.^{9–11} Several studies have also shown that it decreases the amount of other anesthetic agents required for sedation.^{10,12,13}

When used alone for sedation, dexmedetomidine is known to delay both time to recover from anesthesia and discharge readiness.^{14,15} In contrast, several studies have

ABSTRACT

Background: Enhanced recovery protocols employ various approaches to minimize detrimental side effects of anesthetizing agents. The authors tested the hypothesis that adding low-dose dexmedetomidine to propofol for anesthesia in ambulatory colonoscopies, compared with propofol alone, would lower the propofol requirement, improve the intra-procedure hemodynamic state, and not increase time-to-discharge.

Methods: In this noninferiority, double-blind, randomized controlled trial, patients having colonoscopies received total IV anesthesia either with propofol and placebo ($n = 50$), or propofol and a bolus dose of dexmedetomidine, $0.3 \mu\text{g}/\text{kg}$ ($n = 51$). Additional propofol was administered to maintain a Bispectral Index score of 60. Following the procedure, readiness for discharge was assessed regularly using the Modified Post Anesthetic Discharge Scoring System until discharge criteria were met. The primary outcome was the percentage of patients meeting discharge criteria within 30 min from procedure end-time.

Results: Twenty-six of 51 (51%) patients receiving propofol-dexmedetomidine were ready for discharge by 30 min from procedure end time, compared with 44 of 50 (88%) receiving propofol ($P < 0.001$). Propofol consumption was lower in subjects receiving propofol-dexmedetomidine ($140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) compared to those receiving propofol ($180 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) with $P = 0.011$. The lowest mean arterial pressure decreased further from baseline in those receiving propofol-dexmedetomidine (-30% ; mean decrease $-30 \pm 10.5 \text{ mmHg}$) compared to propofol (-21% ; mean decrease, $-22 \pm 14.2 \text{ mmHg}$) with $P = 0.003$. There was no difference in incidence of bradycardia, with sustained bradycardia occurring in 3 of 51 (6%) patients receiving propofol-dexmedetomidine compared to 1 of 50 (2%) patients receiving propofol ($P = 0.62$). No apnea episodes requiring positive-pressure ventilation occurred in either group.

Conclusions: For anesthesia in ambulatory colonoscopy, combining low-dose dexmedetomidine with propofol delayed discharge readiness and provoked hypotension compared to propofol alone.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- It is unknown whether adding low-dose dexmedetomidine to propofol for colonoscopies enhances hemodynamic stability without prolonging recovery

What This Article Tells Us That Is New

- One hundred and one patients were randomly assigned to propofol alone or propofol combined with low-dose dexmedetomidine for outpatient colonoscopies, both groups targeting a Bispectral Index of 60
- Adding dexmedetomidine provoked hypotension and prolonged recovery

This article is featured in "This Month in Anesthesiology," page 1A. This article has a visual abstract available in the online version. Part of the work presented in this article has been presented at the State University of New York Downstate Annual Research Day in Brooklyn, New York, April 11, 2018, and at the Annual Meeting of the American Society of Anesthesiologists in San Francisco, California, October 15, 2018.

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reported that the duration of postoperative recovery was decreased when a low dose of dexmedetomidine was used, as an adjunct with other sedatives and analgesics.^{10,12}

With respect to the setting of outpatient colonoscopy, no reports have applied validated discharge criteria to assess whether combining a low dose of dexmedetomidine with propofol affected discharge readiness. For example, Ji *et al.*¹² compared the effects of dexmedetomidine combined with propofol, *versus* propofol only, in 90 patients having colonoscopies for polyp resection. They reported that the recovery time was shorter in patients receiving propofol–dexmedetomidine. However, recovery was defined as “patient alert and oriented to name, age and time.” This definition does not mean that the patient status is appropriate for discharge to home in the ambulatory setting. A validated criteria for “home-readiness” is defined by a score greater than or equal to 9 on the Modified Post Anesthetic Discharge Scoring System scale.^{16,17}

We tested the hypothesis that for patients having ambulatory colonoscopies, anesthesia with a combination of propofol and low-dose dexmedetomidine, compared with propofol alone, would decrease the propofol requirement and improve intraprocedure hemodynamic response, without delaying the time to attain discharge readiness.

Materials and Methods

This study was approved by the State University of New York Downstate Medical Center Institutional Review Board (no. 932304) and the protocol registered at ClinicalTrials.gov (NCT03139279; registered May 3, 2017, principal investigator Dr. Dimaculangan). The trial was conducted from May 2017 to March 2018 at State University of New York Downstate Medical Center. The article was prepared in accordance with the Consolidated Standards of Reporting Trials guidelines.

After written, informed consent was obtained from patients, we prospectively randomized, in a noninferiority, double-blind design, American Society of Anesthesiologists (ASA) physical classification status I to III patients (aged 18 to 75 yr) having ambulatory elective colonoscopies at State University of New York Downstate Medical Center. The exclusion criteria were as follows: pregnancy, inability to ambulate without assistance, metabolic equivalents less than four per self-report during preoperative assessment, inability to read or understand English, preexisting clinical diagnosis of cognitive impairment in medical history, body weight greater than 135 kg, allergies to constituents of propofol, soy or glycerol, a previous adverse reaction to dexmedetomidine, preexisting diagnosis of acute or chronic renal function impairment (or glomerular filtration rate less than 60 ml/min if preoperative chemistries were available), significant hepatic impairment causing ascites, cirrhosis, or decreased synthetic function with international normalized ratio greater than 1.5 (as documented in medical records or reported by the patient), and use of benzodiazepine

or opioid medications within 24 h of the colonoscopy procedure.

A computerized randomization table in a block of 126 subjects was generated, in a 1:1 ratio of propofol–dexmedetomidine to propofol–placebo, using an online randomization tool.¹⁸ This table was maintained by the research pharmacist who allocated a group assignment for each recruited subject. The clinical pharmacist dispensed pre-made, numbered syringes containing either saline (placebo) or dexmedetomidine, 4 µg/ml, according to the table. This procedure ensured that the patient, the investigators, the clinical anesthesiologists, and nursing staff were blinded to the actual content of each syringe and to each subject’s group assignment. Only the research and clinical pharmacists knew each subject’s group assignment.

Demographic information, including race, sex, weight, and body mass index, was obtained from the medical records. Baseline blood pressure and heart rate were documented in the preoperative holding area. During the procedure subjects were monitored with standard ASA monitors plus a Bispectral Index (BIS) monitor (BIS VISTA; Aspect Medical Systems, Inc., USA). The propofol–dexmedetomidine group received an initial IV bolus dose of 0.3 µg/kg dexmedetomidine (Precedex; Hospira/Pfizer Inc., USA) followed by propofol, 1 mg/kg, to allow initial passage of the endoscope. While the propofol group received saline (placebo) followed by propofol, 1 mg/kg. The clinical anesthesiologist was instructed not to view the BIS monitor until after the first dose of propofol was administered and the endoscope had been introduced. This ensured that the anesthesiologist was not provided with information regarding which study arm the patient was randomized to. Additional doses of propofol were administered at the discretion of the anesthesiologist to maintain a BIS value of approximately 60, for the purposes of standardizing the sedation/anesthesia in our study.

We chose the BIS target value of 60 in order to target levels of anesthesia depth that could be considered both moderate sedation and general anesthesia.¹⁹ As there is no standardized target sedation level during colonoscopy, many centers use moderate sedation and general anesthesia without a secure airway.²⁰ For purposes of comparison, the total propofol administered to each patient was normalized to the patient’s body weight and the length of time of the procedure ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Bolus dosing rather than an infusion of propofol was chosen so that the study protocol would be similar to how propofol is typically administered for colonoscopy procedures in clinical practice at many centers in the community and at our institution. Episodes of sustained bradycardia (heart rate less than 50 beats/min for 5 min or more), apnea (requiring bag mask ventilation), and the largest decrease in mean arterial pressure (MAP) from baseline to lowest value observed during the procedure for each subject, were documented. The timing of study drugs and propofol administration, and the duration

of the procedure, were recorded. Episodes of sustained bradycardia associated with hypotension (MAP less than 60 mmHg) were treated with ephedrine, 5 to 10mg, or glycopyrrolate, 0.2mg, *via* IV boluses, at the discretion of the anesthesiologist. We used a cutoff of less than 50 bpm to define bradycardia in this study.

End-of-procedure recovery in the endoscopy suite was assessed using the Modified Aldrete Score (Aldrete score).²¹ Transport time from the endoscopy suite to the postanesthesia care unit (PACU) was noted. A second Aldrete score was obtained upon arrival in the PACU. Discharge readiness was assessed every 10 min, using the Modified Post Anesthetic Discharge Scoring System scale, from the procedure end time until recovery criteria were met.¹⁷ Discharge readiness was defined by a score greater than or equal to 9 on the Modified Post Anesthetic Discharge Scoring System scale.

The primary outcome was the percentage of patients in each group who were ready for discharge within 30 min of procedure end time (as assessed by the Modified Post Anesthetic Discharge Scoring System scale). Secondary outcomes were: extent of recovery from anesthesia on PACU arrival (assessed by the Aldrete score); total propofol consumption normalized to body weight and time of procedure; largest decrease in MAP from baseline value; incidence of sustained bradycardia; incidence of apnea requiring positive pressure ventilation.

Statistical Analysis

Our hypothesis was that the sedation regimen of combined propofol–dexmedetomidine would be noninferior to propofol–placebo. Based on institutional experience and implications from prior studies,^{15,21–23} we projected that the probability of patients being discharged within 30 min would be 90% in the patients receiving propofol alone. We projected that the same probability would apply to patients receiving propofol–dexmedetomidine, but we asserted that if the latter number were as low as 70%, the extra inconvenience to all concerned would be minimal. In other words, this 20% differential represents a margin of clinical importance, and we aimed to demonstrate with reasonable certainty that the actual differential is smaller. This means that there would be no clinically important difference between both groups in the percentage of patients discharged within 30 min. Noninferiority would be shown by the probability that the percentage of patients discharged within 30 min from the end of the procedure would be within the 20% margin of clinical importance for the two groups. This margin was subjectively selected by the clinical anesthesiologists commonly involved in ambulatory endoscopy procedures at our institution.

Assuming equal numbers of subjects in each study arm, the power of the Pearson chi-square test to detect a differential as small as this is 90% for $n = 37$ per arm, given a two-tailed test and significance level of 0.05. However, that test is not always accurate for low prevalence, so we aimed

instead for $n = 50$ per arm, which should yield an expected frequency of five or more in each cell of the 2×2 table that constitutes the principal analysis.

The primary outcome was evaluated with the Farrington–Manning method to compute a one-sided CI for the 30 min Modified Post Anesthetic Discharge Scoring System risks difference and the Fisher exact test. The method of Turnbull was used to estimate cumulative distribution of time to Modified Post Anesthetic Discharge Scoring System greater than 8 in the presence of both interval- and right-censoring. The secondary outcomes were compared between groups using the Mann–Whitney U test for nonparametric variables. Incidences of bradycardia and apnea were reported as total number of patients affected, n (percentage of total in the group). Statistical analyses were performed with SAS version 9.4 software (SAS Institute Inc., USA). Demographic characteristics were summarized with n (%) or median (quartiles) as appropriate. Results were expressed as median [quartiles], or number of patients, n (%). All analyses were planned prior to the investigation.

Results

One hundred and twenty-two adults, scheduled for colonoscopy, consented to study participation between May 2017 and March 2018; 114 patients were randomized to either propofol–dexmedetomidine ($n = 58$) or propofol only ($n = 56$; fig. 1). Thirteen subjects were excluded from the analysis after randomization, as described in figure 1, such that only 51 subjects receiving propofol–dexmedetomidine and 50 subjects receiving only propofol were included in the final per-protocol analysis for noninferiority trials. There were no clinically important differences between groups in age, sex, race/ethnicity, body mass index, baseline mean arterial pressure, baseline heart rate, duration of procedure, and time of arrival in the PACU (table 1).

Results for the primary outcome are shown in figure 2. Significantly fewer subjects receiving propofol–dexmedetomidine met validated discharge criteria within 30 min from procedure end time: 26 of 51 (51%) subjects receiving propofol–dexmedetomidine, compared with 44 of 50 (88%) subjects receiving propofol, scored greater than or equal to 9 on the Modified Post Anesthetic Discharge Scoring System scale within 30 min from the procedure end time ($P < 0.001$).

For the 30-min discharge outcome, a 90% Farrington–Manning CI was constructed for risk difference between study arms. Given that the margin of inferiority was pre-specified as 20 percentage points, this CI is (0.204 to 0.501). $P < 0.001$ for generalized log-rank test for difference between the two groups.

Delay in discharge readiness was primarily due to inability to ambulate. Of the subjects receiving propofol–dexmedetomidine, 22 of 25 (88%) who failed to meet discharge criteria within 30 min scored a 0 out of 2 on the ambulation portion of the Modified Post Anesthetic Discharge Scoring

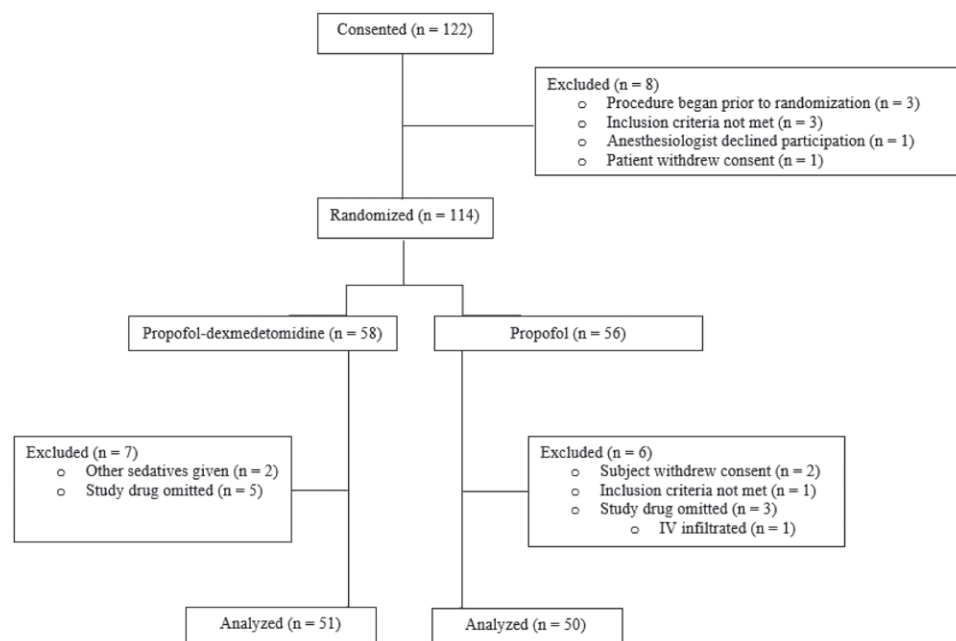


Fig. 1. Consolidated Standards of Reporting Trials flow diagram. IV, intravenous line.

Table 1. Patient and Procedure Characteristics

	Propofol– Dexmedetomidine (n = 51)	Propofol (n = 50)
Age (yr)	57 [52 to 61]	56 [49 to 65]
Body mass index (kg/m ²)	28 [24 to 31]	29 [24 to 33]
Weight (kg)	77 [66 to 88]	84 [69 to 93]
Sex		
Female	31 (61)	33 (66)
Male	20 (39)	17 (34)
Race		
Black	45 (88)	42 (84)
White	4 (8)	6 (12)
Asian	2 (4)	1 (2)
Unknown	0 (0)	1 (2)
ASA physical status classification		
I	7 (14)	1 (2)
II	33 (65)	32 (64)
III	11 (21)	17 (34)
Baseline HR (min ⁻¹)	72 [61 to 78]	71 [62 to 81]
Baseline MAP (mmHg)	99 [94 to 111]	99 [91 to 111]
Procedure duration (min)	19 [15 to 25]	19 [15 to 24]
Time to PACU arrival (min)	10 [9 to 13]	10 [9 to 12]

Data presented as n (%) or median [25th and 75th quartiles].

ASA, American Society of Anesthesiologists; HR, heart rate; MAP, mean arterial pressure; PACU, Postanesthesia Care Unit.

System scale. Similarly, all six (100%) subjects receiving only propofol who failed to meet discharge criteria within 30 min also received a score of 0 out of 2 on the ambulation portion of the Modified Post Anesthetic Discharge Scoring

System scale. Nursing staff reported that those patients who received a 0 on the ambulation portion of the Modified Post Anesthetic Discharge Scoring System scale were too drowsy to safely ambulate at that time point. These residual anesthetic effects had diminished significantly in both groups by 40 min from procedure end time such that an aggregate of 82% of subjects receiving propofol–dexmedetomidine (and 96% of subjects receiving propofol) had met Modified Post Anesthetic Discharge Scoring System criteria for discharge to home (fig. 2). In other words, the difference in discharge-readiness was less clinically important after 40 min, since the difference between both groups fell below our predetermined threshold of a 20% differential margin of clinical importance.

Intraprocedure findings and recovery outcomes are shown in table 2. Propofol consumption was lower in subjects receiving propofol–dexmedetomidine, with a median (quartiles) value of 140 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (120 to 200 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) compared with 180 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (130 to 240 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) in subjects receiving propofol ($P = 0.011$). The median (quartiles) percentage decrease in MAP, from baseline to lowest value during the procedure was -30% (-25% to -38%) in subjects receiving propofol–dexmedetomidine, and -21% (-14% to -29%) in subjects receiving propofol ($P = 0.003$). Sustained bradycardia occurred in 3 of 51 (6%) subjects receiving propofol–dexmedetomidine and in 1 of 50 (2%) subjects receiving propofol ($P = 0.617$). Of the three patients in the propofol–dexmedetomidine group with sustained bradycardia, one patient had a preoperative baseline heart rate of 46 bpm. The other two patients had baseline heart rates in the

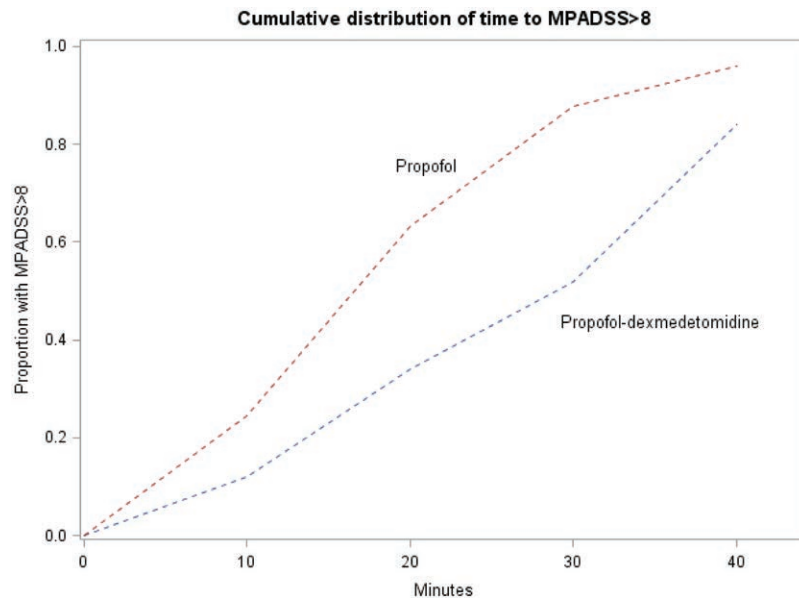


Fig. 2. Cumulative distribution comparing the proportion of subjects in each group who were ready for discharge at various time points from procedure end. Readiness for discharge was assessed every 10 min from procedure end time using the Modified Post Anesthetic Discharge Scoring System (MPADSS). Readiness for discharge is defined as a score of 9 or 10 on the MPADSS scale. $P < 0.001$ for generalized log-rank test for difference between the two groups. The method of Turnbull was used to estimate cumulative distribution of time to MPADSS greater than 8 in the presence of both interval- and right-censoring.

Table 2. Intraoperative Findings and Recovery Outcomes

	Propofol–Dexmedetomidine (n = 51)	Propofol (n = 50)	P Value
Propofol consumption ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	140 [120 to 200]	180 [130 to 240]	0.011
Maximum change in MAP as % of baseline	–30 [–25 to –38]	–21 [–14 to –29]	0.003
Patients with sustained bradycardia	3 (6)	1 (2)	0.617
End of procedure Aldrete score	5 [4 to 6]	5 [4 to 6]	0.112
PACU Aldrete score	8 [7 to 9]	10 [9 to 10]	< 0.001
Patients discharged within 30 min from procedure end	26 (51)	44 (88)	< 0.001

Sustained bradycardia defined as heart rate less than 50 beats/min for greater than or equal to 5 min. Data presented as n (%) or median [25th and 75th quartile]. MAP, mean arterial pressure; PACU, postanesthesia care unit.

mid-70s bpm. The only patient with sustained bradycardia in propofol group had a preoperative baseline heart rate of 70 bpm. No episodes of apnea requiring intervention with positive pressure ventilation occurred in either group.

There was no significant difference between groups in the median Aldrete scores assessed immediately following the procedure: The median (quartiles) Aldrete score was 5 (4 to 6) in subjects receiving propofol–dexmedetomidine and 5 (4 to 6) in subjects receiving propofol ($P = 0.112$). However, two (4%) subjects receiving propofol–dexmedetomidine and four (8%) subjects receiving propofol scored greater than or equal to 9 on the Aldrete scale at this stage (not shown). At the time of PACU arrival, fewer subjects

receiving propofol–dexmedetomidine scored greater than or equal to 9 on the Aldrete scale: the median (quartiles) Aldrete score was 8 (7 to 9) in subjects receiving propofol–dexmedetomidine and 10 (9 to 10) in subjects receiving propofol ($P < 0.001$).

Discussion

The primary finding of this study is that adding a single, low-dose bolus of dexmedetomidine (0.3 $\mu\text{g}/\text{kg}$) to propofol at the beginning of colonoscopy for ambulatory patients delays discharge readiness compared with propofol alone. We did not find any previous publications that used

validated discharge criteria to assess the effects of this anesthesia modification for outpatient colonoscopies. Ji *et al.*¹² compared the effects of a similar regimen on vital signs and anesthetic depth. As a secondary outcome, they reported that recovery time was less in the group of patients who received the combined regimen compared with the group who received only propofol.¹² However, the definition of recovery in that report was not based on validated discharge criteria. Our study implemented the Aldrete scoring system¹⁹ and the Modified Post Anesthetic Discharge Scoring System scale^{16,17} to assess, respectively, recovery from the immediate effects of anesthetics (Phase 1 recovery), and home-readiness (Phase 2 recovery).

Phase 1 recovery was assessed at the end of the procedure in the endoscopy suite, and again upon arrival in the PACU, by a score of greater than or equal to 9 on the Aldrete scale. Phase 2 recovery was evaluated using the Modified Post Anesthetic Discharge Scoring System every 10 min from the end of the endoscopy procedure through the PACU stay, until home-readiness was attained.

The Modified Post Anesthetic Discharge Scoring System criteria objectively determines that a patient is ready to be discharged to home by incorporating assessments of pain control, nausea and ability to ambulate.¹⁷ We found that recovery from the effects of anesthesia, as well as home-readiness, were delayed in the group of subjects who received dexmedetomidine as an adjunct. The median Aldrete score upon arrival in the PACU was 8 in subjects receiving propofol-dexmedetomidine, compared with 10 in those receiving propofol only (table 2). Similarly, only an aggregate of 51% of subjects receiving propofol-dexmedetomidine were ready for discharge to home after 30 min from the procedure end time, compared with 88% of subjects receiving propofol. The value for those receiving propofol-dexmedetomidine is well outside the probability range of 70 to 90% for discharge to home within 30 min from end of procedure that we defined as indicative of noninferiority.

The total propofol consumption was also considerably lower in subjects receiving propofol-dexmedetomidine ($140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) compared with those receiving propofol ($180 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). These values include the initial bolus dose of 1 mg/kg administered to each subject at the beginning of the procedure to allow passage of the endoscope. This result is consistent with findings by Ji *et al.*¹² and is likely due to the α_2 -adrenoceptor agonist-mediated sedative and analgesic effects of dexmedetomidine⁸ having an additive effect with the hypnotic effects of propofol to achieve the desired level of sedation.

Subjects receiving propofol-dexmedetomidine had a larger decrease in MAP, from their preprocedure baseline to the lowest value observed during the procedure, compared with subjects receiving propofol. In those receiving propofol-dexmedetomidine, the MAP decreased by 30%, from a median baseline value of 99 mmHg, to 70 mmHg during the procedure. In subjects receiving propofol, the decrease

was only 21%, from a median baseline value of 99 mmHg, to 78 mmHg during the procedure. Although the effect on MAP was statistically significant ($P = 0.003$), the clinical implications of this decrease in blood pressure are likely less relevant because recent studies suggest that maintaining a MAP of 65 is equally good as the classic “20%” rule of keeping the blood pressure within 20% of preoperative values. A recent retrospective analysis found no clinically important interaction between preoperative blood pressure and intraoperative blood pressure targets.²⁴

Although dose-dependent bradycardia is a known side effect of dexmedetomidine, and significant bradycardia has been reported with the use of dexmedetomidine alone for sedation,^{15,25} we found no statistically significant difference in the occurrence of either sustained bradycardia or apnea between the two groups. These findings are consistent with our expectations and are similar to the results of other studies that used a low dose of dexmedetomidine as an analgesic adjunct. While some of these studies found a lower heart rate in subjects receiving dexmedetomidine, the values were generally above 50 beats/min and, as such, typically did not require administration of medications to counteract bradycardia.^{9,10,12,13}

If a lower dose of propofol had been used in this study, we would expect similar results because the delay in discharge readiness seems clearly related to the addition of dexmedetomidine to the anesthesia regimen. While it is difficult to speculate if the results would have been different if dexmedetomidine was administered as an infusion rather than a bolus dose, we would expect that similar effects would be observed although the onset of such effects may be delayed with an infusion as the time to peak effect of the drug would be longer.

Our study had several limitations. First, we did not assess variables that may have been advantageous for the subjects receiving dexmedetomidine, such as the incidence of patient movements that could affect the endoscopy procedure. Anecdotally, several anesthesiologists at our institution have reported that adjunctive administration of dexmedetomidine seemed to decrease patient movement and improve the endoscopist's satisfaction with the procedure. Ji *et al.* reported significantly less body activity affecting the colonoscopy procedure in patients who received dexmedetomidine as an adjunct.¹² Similarly, in a randomized trial, Wang *et al.* reported a lower requirement for rescue fentanyl in a group of patients having ambulatory inguinal hernia repairs who were sedated with dexmedetomidine *versus* those sedated with propofol.¹³

A second limitation of this study is that we measured anesthesia depth using BIS monitors instead of standard methods such as the Modified Observer Assessment of Alertness/Sedation, which defines sedation levels according to patient response. However, BIS monitor values have been shown to correlate significantly with the Richmond Agitation Sedation Scale and Observer Assessment of Alertness and Sedation.^{26,27}

Another limitation of this study is our definition of apnea as oxygen desaturation requiring intervention with positive pressure ventilation. This form of apnea is a rare event during anesthesia for endoscopic procedures,²² and did not occur in either of our study groups. Studies that have used less stringent definitions for respiratory issues, such as transient hypoxemia and occurrence of airway obstruction, reported advantages for subjects sedated with propofol plus dexmedetomidine compared with propofol only.^{13,15} Furthermore, we evaluated the effects of only one dose (0.3 µg/kg) of dexmedetomidine. It is possible that a lower dose would yield more favorable hemodynamic results and reduce the effect on the duration of recovery. Future investigations using lower doses of dexmedetomidine may be warranted.

From a statistical perspective, this study is also limited by our use of a per protocol analysis without performing an intention to treat analysis. An intention to treat approach was not used because this study was designed as a non-inferiority trial, thus we did not collect outcome data for the excluded cases. Recommendations vary on whether to use an intention to treat or per-protocol approach for noninferiority trials. Some authors recommend using the intention to treat approach for all randomized controlled trials including noninferiority trials.²⁸ Others have showed that there is potentially no benefit to using the intention to treat approach for noninferiority trials.^{29,30}

This study may also be limited by the subjective use of 20% as the noninferiority margin of clinical importance, based on our institutional experience. However, these results are strengthened by the finding that discharge was significantly delayed (convincingly outside our selected noninferiority margin) in subjects receiving propofol–dexmedetomidine (51% ready for discharge within 30 min) compared to subjects receiving propofol (88% ready for discharge within 30 min).

Finally, while our results might be generalizable to adults of all races and ethnicities undergoing ambulatory colonoscopy, it is important to note that our medical center serves a predominantly black population. While minorities were not specifically targeted for recruitment, over 80% of subjects included in this study identified as black. We are not aware of any overall consensus regarding a variable response to anesthesia based on race. However, variability with race in response to sedation has been reported by some investigators.^{31,32}

In conclusion, combining a low dose of dexmedetomidine with propofol for anesthesia decreased propofol consumption in adults having ambulatory colonoscopy, with no effect on the incidence of sustained bradycardia. However, using only propofol for colonoscopy provided more stable hemodynamics, allowed for faster recovery from anesthesia, and faster attainment of discharge readiness, compared with using propofol–dexmedetomidine.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: Leonard.Edokpolo@gmail.com. Raw data available at: Leonard.Edokpolo@gmail.com.

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References

- Centers for Disease Control and Prevention (CDC): Cancer prevention and control. Colorectal cancer screening capacity in the United States. 2016; https://www.cdc.gov/cancer/dcpc/research/articles/crc_screening_model.htm. Accessed March 7, 2018
- Faigel DO, Baron TH, Goldstein JL, Hirota WK, Jacobson BC, Johanson JF, Leighton JA, Mallery JS, Peterson KA, Waring JP, Fanelli RD, Wheeler-Harbaugh J; Standards Practice Committee; American Society for Gastrointestinal Endoscopy: Guidelines for the use of deep sedation and anesthesia for GI endoscopy. *Gastrointest Endosc* 2002;56:613–7
- Horn E, Nesbit SA: Pharmacology and pharmacokinetics of sedatives and analgesics. *Gastrointest Endosc Clin N Am* 2004; 14:247–68

4. Huang R, Eisen GM: Efficacy, safety, and limitations in current practice of sedation and analgesia. *Gastrointest Endosc Clin N Am* 2004; 14:269–88
5. Kehlet H, Wilmore DW: Multimodal strategies to improve surgical outcome. *Am J Surg* 2002; 183:630–41
6. Lau CS, Chamberlain RS: Enhanced recovery after surgery programs improve patient outcomes and recovery: A meta-analysis. *World J Surg* 2017; 41:899–913
7. Kamibayashi T, Maze M: Clinical uses of alpha 2-adrenergic agonists. *ANESTHESIOLOGY* 2000; 93:1345–9
8. Aantaa R, Scheinin M: Alpha 2-adrenergic agents in anaesthesia. *Acta Anaesthesiol Scand* 1993; 37:433–48
9. Ding L, Zhang H, Mi W, Wang T, He Y, Zhang X, Ma X, Li H: Effects of dexmedetomidine on anesthesia recovery period and postoperative cognitive function of patients after robot-assisted laparoscopic radical cystectomy. *Int J Clin Exp Med* 2015; 8:11388–95
10. Akarsu Ayazoğlu T, Polat E, Bolat C, Yasar NF, Duman U, Akbulut S, Yol S: Comparison of propofol-based sedation regimens administered during colonoscopy. *Rev Med Chil* 2013; 141:477–85
11. Candiotti KA, Bergese SD, Bokesch PM, Feldman MA, Wisemandle W, Bekker AY; MAC Study Group: Monitored anesthesia care with dexmedetomidine: A prospective, randomized, double-blind, multicenter trial. *Anesth Analg* 2010; 110:47–56
12. Ji J, Wang G, Sun K, Zhou G, Wang Z, Wang Y: Application of dexmedetomidine combined with propofol in patients undergoing painless colonoscopy for colonic polyps resection under Narcotrend monitoring [Article in Chinese]. *Nan Fang Yi Ke Da Xue Bao* 2015; 35:264–7
13. Wang HM, Shi XY, Qin XR, Zhou JL, Xia YF: Comparison of dexmedetomidine and propofol for conscious sedation in inguinal hernia repair: A prospective, randomized, controlled trial. *J Int Med Res* 2017; 45:533–9
14. Zhou Q, Shen L, Zhang X, Li J, Tang Y: Dexmedetomidine *versus* propofol on the sedation of pediatric patients during magnetic resonance imaging (MRI) scanning: A meta-analysis of current studies. *Oncotarget* 2017; 8:102468–73
15. Jalowiecki P, Rudner R, Gonciarz M, Kawecki P, Petelenz M, Dziurdzik P: Sole use of dexmedetomidine has limited utility for conscious sedation during outpatient colonoscopy. *ANESTHESIOLOGY* 2005; 103:269–73
16. Phillips NM, Street M, Kent B, Haesler E, Cadeddu M: Post-anaesthetic discharge scoring criteria: Key findings from a systematic review. *Int J Evid Based Healthc* 2013; 11:275–84
17. Chung F: Discharge criteria—a new trend. *Can J Anaesth* 1995; 42:1056–8
18. Randomness and Integrity Services Ltd: List randomizer. <https://www.random.org/lists>. Accessed March 8, 2017
19. Kelly SD: Using the Bispectral Index during anesthesia, Monitoring Consciousness, a pocket guide for clinicians, 2nd edition. Aspect Medical Systems, Inc, 2007, pp 5–10
20. Ramsay MA, Newman KB, Jacobson RM, Richardson CT, Rogers L, Brown BJ, Hein HA, De Vol EB, Daoud YA: Sedation levels during propofol administration for outpatient colonoscopies. *Proc (Bayl Univ Med Cent)* 2014; 27:12–5
21. Aldrete JA: The post-anesthesia recovery score revisited. *J Clin Anesth* 1995; 7:89–91
22. Cohen LB, Hightower CD, Wood DA, Miller KM, Aisenberg J: Moderate level sedation during endoscopy: A prospective study using low-dose propofol, meperidine/fentanyl, and midazolam. *Gastrointest Endosc* 2004; 59:795–803
23. Sipe BW, Rex DK, Latinovich D, Overley C, Kinser K, Bratcher L, Kareken D: Propofol *versus* midazolam/meperidine for outpatient colonoscopy: Administration by nurses supervised by endoscopists. *Gastrointest Endosc* 2002; 55:815–25
24. Salmasi V, Maheshwari K, Yang D, Mascha EJ, Singh A, Sessler DI, Kurz A: Relationship between intraoperative hypotension, defined by either reduction from baseline or absolute thresholds, and acute kidney and myocardial injury after noncardiac surgery: A retrospective cohort analysis. *ANESTHESIOLOGY* 2017; 126:47–65
25. Carollo DS, Nossaman BD, Ramadhyani U: Dexmedetomidine: A review of clinical applications. *Curr Opin Anaesthesiol* 2008; 21:457–61
26. Turkmen A, Altan A, Turgut N, Vatansever S, Gokkaya S: The correlation between the Richmond agitation-sedation scale and bispectral index during dexmedetomidine sedation. *Eur J Anaesthesiol* 2006; 23:300–4
27. Kasuya Y, Govinda R, Rauch S, Mascha EJ, Sessler DI, Turan A: The correlation between bispectral index and observational sedation scale in volunteers sedated with dexmedetomidine and propofol. *Anesth Analg* 2009; 109:1811–5
28. Snapinn SM: Noninferiority trials. *Curr Control Trials Cardiovasc Med* 2000; 1:19–21
29. Brittain E, Lin D: A comparison of intent-to-treat and per-protocol results in antibiotic non-inferiority trials. *Stat Med* 2005; 24:1–10
30. Schumi J, Wittes JT: Through the looking glass: Understanding non-inferiority. *Trials* 2011; 12:106
31. Natarajan A, Strandvik GF, Pattanayak R, Chakithandy S, Passalacqua AM, Lewis CM, Morley AP: Effect of ethnicity on the hypnotic and cardiovascular characteristics of propofol induction. *Anaesthesia* 2011; 66:15–9
32. Dahaba AA, Zhong T, Lu HS, Bornemann H, Liebmann M, Wilfinger G, Reibnegger G, Metzler H: Geographic differences in the target-controlled infusion estimated concentration of propofol: Bispectral index response curves. *Can J Anaesth* 2011; 58:364–70