Pilot Study

Efficacy and Tolerability of Sufentanil, Dexmedetomidine, or Ketamine Added to Propofol-based Sedation for Gastrointestinal Endoscopy in Elderly Patients: A Prospective, Randomized, Controlled Trial

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ABSTRACT

Purpose: To investigate the optimal agent combined with propofol for sedation in elderly patients undergoing gastrointestinal endoscopy.

Methods: A total of 120 elderly patients scheduled for gastrointestinal endoscopy under propofol-based sedation were randomly allocated to receive propofol + saline (control group), propofol + sufentanil 0.1 μg/kg, propofol + dexmedetomidine 0.4 μg/kg, or propofol + ketamine 0.4 mg/kg. Mean arterial pressure, heart rate, pulse oximetry, pressure of end-tidal carbon dioxide, respiratory rate, and Ramsay sedation scale score were recorded. Induction time, procedure time, recovery time, propofol dose, and adverse events were also recorded.

Findings: During the sedation procedure, the AUC of HR was lowest in the propofol + dexmedetomidine group (all, $P < 0.05$), and the AUC of pulse oximetry was significantly higher in the propofol + dexmedetomidine and propofol + ketamine groups compared to the other 2 groups (both, $P < 0.05$). The propofol + dexmedetomidine group had the highest prevalences of hypotension and bradycardia, and the control group experienced the largest number of hypoxia episodes (all, $P < 0.05$). The control group consumed the highest dose of propofol, while the propofol + ketamine group needed the lowest dose (all, $P < 0.05$).

Implications: The combination of propofol + ketamine 0.4 mg/kg maintained hemodynamic and respiratory stability, as evidenced by less hypotension, bradycardia, and hypoxia events, in elderly patients undergoing gastrointestinal endoscopy. China clinical trial registration (chictr.org.cn) ID: ChiCTR-INR-17013710. (*Clin Ther*. 2019;41:1864−1877) © 2019 Published by Elsevier Inc.

Key words: dexmedetomidine, elderly patients, gastrointestinal endoscopy, ketamine, propofol, sufentanil.

INTRODUCTION

The world's population is aging at an accelerating rate.[1,2] As a result, the number of elderly patients who are scheduled for diagnostic or therapeutic endoscopic procedures will rapidly increase in the coming decades.[3,4] According to a nationwide survey of endoscopic sedation, >98% of routine procedures

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in the United States are performed with the patient under sedation.[5] In elderly patients, appropriate sedation during the procedure could help to alleviate anxiety and stress, reduce the prevalence of complications,[6] promote cooperation with physicians, increase the success rate of endoscopy, and improve patients' satisfaction.[7]

Propofol is widely used for sedation during endoscopy. With the profile of rapid onset and resolve, propofol is quite suitable for outpatient sedation.[8] However, in elderly patients, a higher risk for hypoxia (pulse oximetry [SpO_2] <90%) may occur during propofol-induced sedation.[9] Despite sedation strategies that aim to reduce the consumption of propofol in elderly patients, the prevalence of adverse events, including hypoxemia, hypotension, bradycardia or tachycardia, arrhythmia, myocardial infarction, or and even cardiac and/or respiratory arrest, remains significant (3.4% in patients aged >80 years vs 0.5% in younger patients).[10]

Several studies have investigated propofol for sedation in endoscopic procedures and found that the related complications were in proportion with the propofol dose.[11–13] Opioids, dexmedetomidine, and ketamine have been used in combination with propofol for endoscopic sedation, which may help to maintain stable hemodynamics and minimize the risks for respiratory depression and other adverse events. However, the optimal combination in elderly patients has yet to be determined.

Sufentanil, a potent synthetic opioid agent, has been used in combination with other medications for outpatient sedation.[14,15] In one study of anesthesia induction, a loading dose of sufentanil 0.05 μg/kg combined with propofol 1–2 mg/kg appeared to be a good choice in patients undergoing gastrointestinal endoscopic procedures.[12] Dexmedetomidine is a highly selective α_2-agonist that induces sedation without significant respiratory depression.[16] A study in elderly patients showed that a single dose of dexmedetomidine 0.5 μg/kg before induction effectively inhibited the cardiovascular response by tracheal intubation and did not cause respiratory depression.[17] Ketamine, another commonly used anesthetic agent, induces analgesia and sedation without respiratory depression. It has been reported that a propofol + ketamine combination for sedation led to better hemodynamic stability (less fluctuation in blood pressure [BP] and heart rate [HR] during the procedure) and less need for additional propofol (mean [SD], 32.5 [7.1] vs 44.69 [10.9] mg) than did a propofol + opioid combination.[18] Studies suggest that many adverse effects associated with sedatives are dose dependent, and that use of a combination could help to reduce the prevalence of adverse events.[19,20]

This prospective, randomized, controlled study was designed to compare the efficacy and tolerability of propofol + sufentanil, propofol + dexmedetomidine and propofol + ketamine for sedation in elderly patients undergoing gastrointestinal endoscopy. The primary outcome measure of this study was stability of respiration and hemodynamics (as measured by the prevalences of hypotension/hypertension, bradycardia/tachycardia, and hypoxia). We expected to determine the best choice for a satisfactory level of sedation without significant adverse events.

PATIENTS AND METHODS

Ethics and Trial Registration

The protocol of this prospective, randomized, double-blind, controlled study was approved by our Shenzhen Hospital, Southern Medical University (protocol no. NYSZYYEC20170015). The study was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn; ChiCTR-INR-17013710). All participants gave their written informed consent in person.

Patients Selection and Study Medications

Between January 1, 2017, and January 1, 2018, patients with American Society of Anesthesiologists (ASA) physical status class I to III who were aged 60–80 years and scheduled for elective gastrointestinal endoscopy (with an expected procedure time of <40 min) were recruited in this study.

Exclusion criteria were as follows: ASA class IV or more, myocardial infarction within the 6 months prior to screening; uncontrolled hypertension; systolic BP of >160 mm Hg; chronic lung disease; pneumonia; decompensated liver or kidney disease; neuromuscular or neuropsychiatric disorder; epilepsy; anticipated difficult airway; allergy to eggs, seafood, soy or medications used in this study; history of β-

receptor agonist use; or contraindications to the study medications. Those who did not provide written consent were also excluded.

The medications used in this study included propofol,* sufentanil†, dexmedetomidine‡, and ketamine.‡

Provided by:

Grouping and Blinding

An investigator (T.S.) who was not involved in the subsequent study conducted the randomization using a computer-generated sequence. Patients were randomly assigned to 1 of 4 groups: a control group (propofol + saline), propofol + sufentanil, propofol + dexmedetomidine, and or propofol + ketamine. Another independent investigator (J.P.H.) prepared the study medications (saline, sufentanil 50 μg, dexmedetomidine 200 μg, and ketamine 200 mg) and diluted them with saline to a volume of 5 mL as clear solutions in the same bottles with codes according to the randomization order. To ensure allocation concealment, randomization results were sealed until the end of the study. All sedation procedures were conducted by the same attending anesthesiologist (S.Y.). All investigators, health care staff, follow-up observers, and patients were masked to group assignment.

Sedation Procedures

All of the patients were evaluated at the anesthesia clinic 1 day prior to the procedure. Standard monitoring included continuous pulse oximetry (SpO_2), noninvasive BP, and ECG. A 20G IV cannula was inserted via the antecubital vein for fluid infusion. Patients received lactated Ringer's solution at 8 mL/kg/h for 40 min prior to the procedure, followed by 4 mL/kg/h until discharge from the postanesthesia care unit (PACU). Oxygen supplementation of 4 L/min was delivered via a nasopharynx tube throughout the study. The pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) was monitored by using a device connected to the nasopharynx tube. Prior to sedation procedures, patients received local spray anesthesia with 4% lidocaine. The endoscopic procedures were performed using a standard technique by an experienced endoscopist.

Before sedation, the study drugs were diluted with normal saline to 50 mL, with final concentrations of 1 μg/mL for sufentanil, 4 μg/mL for dexmedetomidine, and 4 mg/mL for ketamine. All patients received standard sedation with propofol. First, lidocaine 0.5 mg/kg IV was administered to alleviate pain caused by the propofol injection. Next, sedation was induced using 0.1 mL/kg of study medication infused over 5 min, followed by propofol 1 mg/kg over 30 s. For sedation maintenance, propofol was continuously infused at 3−5 mg/kg/h (50−83 μg/kg/min) until the end of the procedure. The depth of sedation was assessed using the Ramsay sedation scale (RSS), in which a value of 5 or higher indicates an appropriate sedation level. If the RSS score was below 5 or a sudden body movement occurred, a bolus of propofol 0.25 mg/kg could be injected.

After the procedure, patients were monitored in the PACU for at least 1 h. The criteria for PACU discharge was a score of 9 or more on the modified Aldrete scale. Patients went home after PACU discharge and were followed up by telephone at 24 h after discharge.

Primary and Secondary Outcome Measures

The primary outcome measure of this study was the stability of the respiratory system and hemodynamics (hypotension, bradycardia, and hypoxia events). Secondary outcome measures were RSS score, total propofol consumption, recovery time (from discontinuation of sedatives to spontaneous eye opening), prevalence of intraoperative and postoperative sedation-related and procedure-related adverse events, and the use of medications. Intraoperative sedation-related adverse events included hypertension and hypotension (systolic BP changes of >20% of the baseline value), tachycardia (HR > 100 bpm), bradycardia (HR < 50 bpm), hypoxia (SpO_2 <90%), $P_{ET}CO_2$ waveform disappearance of >30 s, bucking or coughing, and body movement. Postoperative sedation-related adverse events included hypertension, hypotension, tachycardia, bradycardia, hypoxia, nausea and vomiting, and delirium. Delirium was assessed using the confusion-assessment method.[21,22] Procedure-related events included bleeding and gastrointestinal perforation. *Use of medication* was

* AstraZeneca SpA (London, UK).

† Yichang Renfu Pharmaceutical Co Ltd (Yichang, China).

‡ Jiangsu Hengrui Pharmaceutical Co Ltd (Jiangsu, China).

defined as the need for atropine, ephedrine, epinephrine, lidocaine, nitroglycerine, and/or phenylephrine.

Data Collection

Patients' demographic characteristics, including age, sex, body mass index, ASA physical status, and comorbidities, were recorded before the procedure. HR, mean arterial pressure (MAP), SpO_2, respiration rate (RR), and $P_{ET}CO_2$ were recorded at baseline (T_0), 40 min after fluid infusion (T_1), immediately after study medication injection (T_2), immediately after propofol injection (T_3), at the beginning of gastroscopy (T_4), 5 min after the beginning of gastroscopy (T_5), at the end of gastroscopy (T_6), at the beginning of colonoscopy (T_7), and at the end of colonoscopy (T_8). In addition, RSS scores were recorded at T_2 to T_8. Procedure time, recovery time, and total propofol consumption were also recorded.

During the procedure, the following adverse events were recorded: hypertension, hypotension, tachycardia, bradycardia, hypoxia, $P_{ET}CO_2$ waveform disappearance, bucking or coughing, and body movement. In the PACU, the following adverse events were recorded: hypertension, hypotension, tachycardia, bradycardia, hypoxia, nausea and vomiting, and delirium. Procedure-related events and the use of medications were also recorded.

Statistical Analysis

Sample-size calculation was performed using PASS software version 11.0.7 (NCSS, Kaysville, Utah). Based on our preliminary data and the effect size (W) of 0.212 in the χ^2 effect-size estimation, the required sample size was calculated to be 25 per group. We included 30 cases in each group to account for possible dropouts.

Statistical analysis was performed using Prism version 7 (GraphPad, San Diego, California). Continuous variables are shown as mean (SD), and categorical variables are reported as number (%) of patients. To determine the overall effect of an intervention during a period of time, the AUCs of RSS, HR, MAP, SpO_2, RR, and $P_{ET}CO_2$ were calculated using the trapezoidal method.[23] Differences were evaluated using 1-way ANOVA followed by the Tukey test, χ^2 test (Fisher exact test), Mann-Whitney *U* test, or Kruskal-Wallis test. A 2-sided *P* value of <0.05 indicated a statistically significant difference.

RESULTS

Patient Flow Diagram and Characteristics

Figure 1 shows the CONSORT study flow diagram of the patients in this study. A total of 189 patients were evaluated. After the exclusion of 69 patients, 120 patients were found to be eligible and were randomly assigned to the study groups. Finally, 30 patients per group completed the study, and their data were analyzed. Patients' characteristics are shown in Table I. There were no significant differences in demographic data, comorbidities, or endoscopic diagnosis among the 4 groups.

Table II presents the procedure-related characteristics of the study groups. The procedure time and total amount of fluid infusion were comparable between the 4 groups. In the propofol + dexmedetomidine group, a significantly longer mean (SD) induction time for adequate sedation (RSS >4; 10.9 [1.8] minutes; $P = 0.01$) and a longer recovery time (17.4 [3.9] minutes; $P < 0.001$) were needed compared with those in the other groups. The total dose of propofol was highest (228.0 [29.0] mg) in the control group and lowest (158.0 [15.8] mg) in the propofol + ketamine group ($P < 0.001$). Overall, sedation was well maintained during the procedure, without significant differences in RSS scores among the groups (Figure 2).

Hemodynamic Outcomes

HR and MAP outcomes are shown in Table II and Figure 2. Compared to the baseline HR values, the control group had a higher HR from T_1 to T_7, the propofol + ketamine group had a higher HR from T_2 to T_8, the propofol + sufentanil group had a higher HR at T_4, and the propofol + dexmedetomidine group had a lower HR from T_2 to T_8 (all, $P < 0.05$). Compared to baseline MAP values, all groups had a lower MAP at different time points. After analyzing the AUC, the propofol + dexmedetomidine group had a significantly lower AUC of HR during the procedure than did the other groups ($P < 0.05$). The AUC of MAP did not differ among the groups. In the propofol + ketamine group, MAP and HR remained stable throughout the study period.

Respiratory Outcomes

SpO_2, RR, and $P_{ET}CO_2$ outcomes are shown in Table II and Figure 3. The AUC values of SpO_2 were

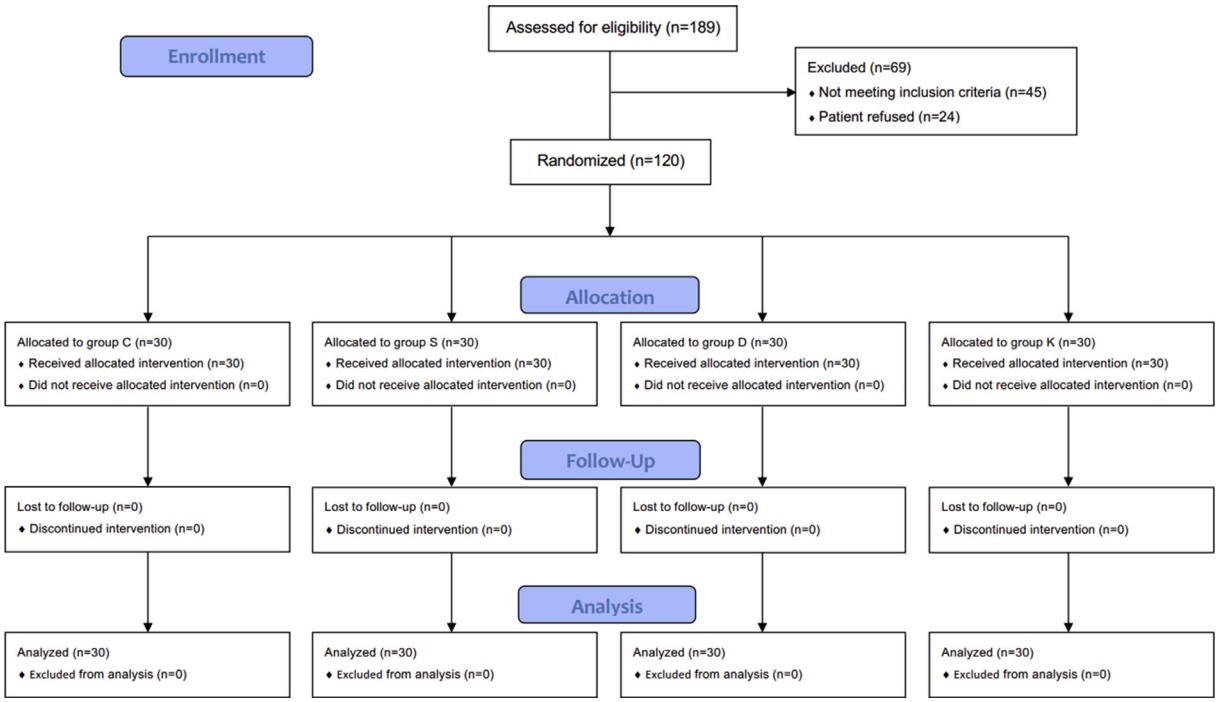

Figure 1. CONSORT flow diagram.

significantly higher in the propofol + dexmedetomidine and propofol + ketamine groups compared to those in the other 2 groups (all, $P < 0.05$). However, there were no significant differences in the AUC of RR or $P_{ET}CO_2$ among the 4 groups.

Adverse Events

Table III shows the adverse events. There were no episodes of hypertension in any of the groups. The prevalences of tachycardia did not differ among the groups. The prevalences of both hypotension and bradycardia were significantly higher in the propofol + dexmedetomidine group compared to the other 3 groups (all, $P < 0.05$). The control group had the highest prevalence of bucking or coughing (all, $P < 0.05$). Hypotension or bradycardia was treated with ephedrine or atropine. The percentage of patients in the propofol + dexmedetomidine group who needed atropine or ephedrine was greater than in the other 3 groups (all, $P < 0.05$). A greater percentage of patients in the control group needed phenylephrine treatment than in the other 3 groups ($P < 0.05$).

The percentages of patients who experienced hypoxia were greater in the control and propofol + sufentanil groups compared to that in the propofol + ketamine group (both, $P < 0.05$), with 7 patients in the control group and 3 in the propofol + sufentanil group requiring mask ventilation and endoscope removal. Similarly, the prevalences of $P_{ET}CO_2$ waveform disappearance of >30 s in the control, propofol + sufentanil, propofol + dexmedetomidine, and propofol + ketamine groups were 50%, 23%, 10%, and 7%, respectively, with the highest prevalence in the control group. There were no significant differences in the prevalences of nausea and vomiting among the 4 groups.

DISCUSSION

Patients who undergo endoscopic procedures could benefit from adequate sedation.[24] Despite that gastrointestinal endoscopy procedures are increasingly performed in elderly patients under sedation, data on outcomes or adverse events

Table I. Patient demographics (n = 30 per group).

Parameter	Propofol (Control)	Propofol + Sufentanil	Propofol + Dexmedetomidine	Propofol + Ketamine	*P*
Sex, male/female, n	12/18	17/13	11/19	13/17	0.456
Age, mean (SD), y	69.8 (4.12)	70.6 (3.33)	70.9 (4.56)	72.5 (3.75)	0.224
Body mass index, mean (SD), kg/m^2	27 (4.14)	28 (3.27)	27 (5.94)	27 (4.85)	0.585
ASA I/II/III, n	12/14/4	9/16/5	13/16/1	14/14/2	0.394
NYHA I/II, n	28/2	27/3	29/1	28/2	0.784
Comorbidities, no. (%)					
Hypertension	11 (37)	11 (37)	14 (47)	8 (27)	0.460
Diabetes	3 (10)	5 (17)	3 (10)	6 (20)	0.604
Ischemic heart disease	2 (7)	1 (3)	0	1 (3)	0.558
Chronic renal insufficiency	1 (3)	2 (7)	1 (3)	1 (3)	0.890
Cerebral vascular insufficiency	1 (3)	0	0	0	0.388
COPD	0	0	0	0	1.000
Endoscopic diagnosis, no. (%)					
Chronic gastritis	20 (67)	19 (63)	21 (70)	20 (67)	0.960
Gastrointestinal polyps	6 (20)	10 (33)	11 (37)	10 (33)	0.511
Peptic ulcer	3 (10)	1 (3)	2 (7)	4 (17)	0.536
Colon cancer	1 (3)	0	0	0	0.388
Esophagus cancer	0	0	1 (3)	0	0.368
Gastric carcinoma	0	0	0	0	1.000

ASA = American Society of Anesthesiologists classification; NYHA = New York Heart Association classification; COPD = chronic obstructive pulmonary disease.

associated with sedation have been limited.[25] Age-related pharmacokinetic changes and patients' comorbidities are of great concern during the sedation process. In China, few studies have focused on the tolerability of propofol use during diagnostic and therapeutic endoscopy in elderly patients.[26] Several factors regarding endoscopic sedation should be taken into consideration, including the type and duration of the procedure and the patient's age, ASA classification, and comorbidities.[24]

In the present study, the primary concern was the safety profiles of the study medications. We evaluated several parameters, including hemodynamic stability; spontaneous respiration; and the prevalences hypertension/hypotension, bradycardia/tachycardia, and other adverse events. Stable hemodynamics without significant respiration depression or other adverse events were found with the propofol + ketamine combination. Ketamine has sympathomimetic activity with minimal respiratory-related adverse effects, which help to maintain stable HR and BP.[27,28] Consistently, studies have indicated that the use of propofol combined with ketamine reduced the prevalences of dose-dependent cardiovascular and respiratory adverse effects associated with each agent.[29,30] A study by Celik et al[47] reported that the prevalence of respiratory depression with ketamine + midazolam (17.5%) was much lower than with propofol + fentanyl (45%) in geriatric patients undergoing endoscopy. Other studies have supported the use of a propofol + ketamine combination in endoscopic procedures.[25,31]

Regarding hemodynamics during sedation, MAP and HR remained stable in the propofol + ketamine group, but not in the control or propofol + dexmedetomidine group. In addition, the highest prevalences of hypotension and bradycardia occurred in the propofol + dexmedetomidine group (57% and 60%,

Table II. Procedure-related characteristics (n = 30 per group).

Parameter	Propofol (Control)	Propofol + Sufentanil	Propofol + Dexmedetomidine	Propofol + Ketamine	*P*
Procedure time, min	27.9 (10.7)	29.3 (7.9)	30.1 (7.2)	28.3 (8.4)	0.782
Induction time, min	7.3 (1.2)	7.4 (1.3)	10.9 (1.8)*†	7.9 (2.1)	0.010
Recovery time, min	11.7 (3.4)	11.3 (4.1)	17.4 (3.9)*†	10.1 (4.0)*	<0.001
Propofol dose, mg	228.0 (29.0)	176.0 (20.0)*	169.0 (19.6)*	158.0 (15.8)*†	<0.001
Total amount of Ringer's lactate, mL	349.8 (15.4)	355.6 (16.7)	370.9 (11.9)	364.5 (10.3)	0.677
AUCs, mean (95% CI)					
$AUC_{(T2\text{-}T8)}$ of RSS	22.15 (20.36–23.94)	23.9 (21.88–25.92)	25.1 (23.42–26.78)	25.2 (23.73–26.67)	0.061
$AUC_{(T0\text{-}T8)}$ of HR	617.2 (592.9–641.5)	627.4 (590.2–664.6)	514.3 (476.7–551.8)†	624.2 (593.7–654.7)	0.001
$AUC_{(T0\text{-}T8)}$ of MAP	617.4 (575.5–659.3)	655.7 (619.2–692.1)	593.1 (554.5–631.6)	661.8 (620.4–703.1)	0.056
$AUC_{(T0\text{-}T8)}$ of SpO_2	775.7 (772.1–779.2)	768.7 (761.8–775.5)	785.1 (779.9–790.3)‡	781.9 (777.1–786.7)‡	0.001
$AUC_{(T0\text{-}T8)}$ of RR	122.7 (113.5–131.9)	118.6 (111.1–126)	123.5 (116–131)	127.4 (117.1–137.6)	0.576
$AUC_{(T0\text{-}T8)}$ of $P_{ET}CO_2$	301.9 (292.6–311.2)	301.5 (292.6–310.4)	287.5 (279.9–295.1)	287.2 (279.3–295.1)	0.087

HR = heart rate; MAP = mean arterial pressure; $P_{ET}CO_2$ = pressure of end-tidal carbon dioxide; RR = respiratory rate; RSS = Ramsay sedation scores; SpO_2 = pulse oximetry; T_0 = baseline; T_2 = immediately after study medication injection; T_8 = end of colonoscopy.
$P < 0.05$ versus *control, †all other groups, ‡propofol + sufentanil.

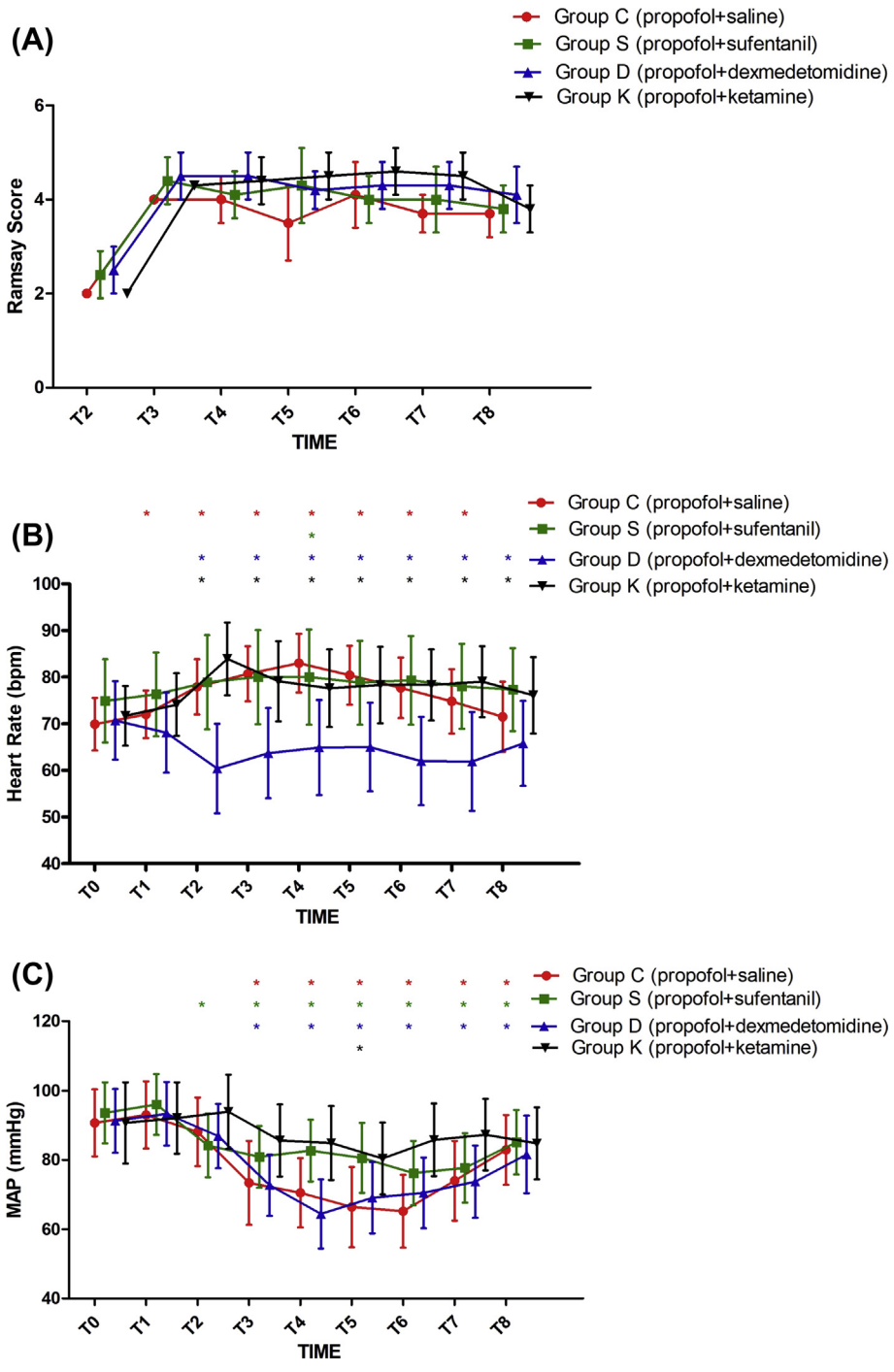

Figure 2. Mean (SD) Ramsay score (A), heart rate (B), and mean arterial pressure (MAP) (C) in elderly patients treated with propofol alone or in combination for sedation during gastrointestinal endoscopy.

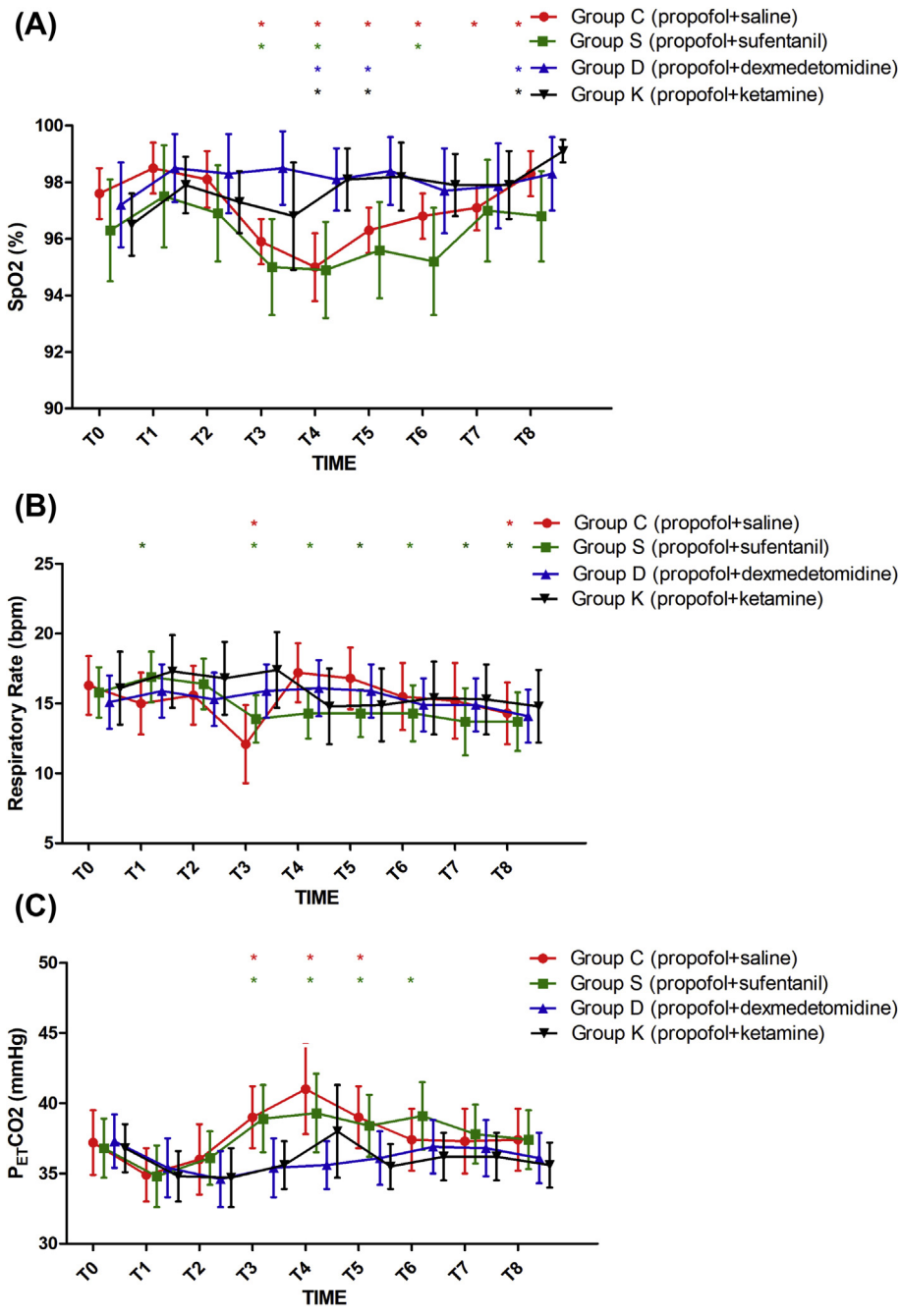

Figure 3. Mean (SD) pulse oximetry (SpO_2) (A), respiratory rate (B), and pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) (C) in elderly patients treated with propofol alone or in combination for sedation during gastrointestinal endoscopy.

Table III. Adverse events and use of other medications (n = 30 per group). Data are expressed as no, (%) of patients.

Parameter	Propofol (Control)	Propofol + Sufentanil	Propofol + Dexmedetomidine	Propofol + Ketamine	*P*
Sedation related, intraoperative					
$P_{ET}CO_2$ waveform disappearance	15 (50)	7 (23)*	3 (10)*	2 (7)*	<0.001
Hypoxia	12 (40)†	7 (23)†	2 (7)*	1 (3)*	0.001
Bucking or coughing	12 (40)	5 (17)*	1 (3)*	1 (3)*	<0.001
Body movement	10 (33)†	6 (20)†	5 (17)	1 (3)*	0.028
Hypotension	9 (30)	5 (17)*	17 (57)*‡	1 (3)*	<0.001
Bradycardia	6 (20)	1 (3)*	18 (60)*‡	0*	<0.001
Tachycardia	3 (10)	3 (10)	0	2 (7)	0.360
Hypertension	0	0	0	0	1.000
Sedation related, postoperative					
Hypoxia	1 (3)	2 (7)	0	0	0.298
Bradycardia	0	0	7 (23)*‡	0	<0.001
Delirium	0	0	0	0	1.000
Hypertension/hypotension	0	0	0	0	1.000
Nausea and vomiting	0	0	0	0	1.000
Tachycardia	0	0	0	0	1.000
Procedure related	0	0	0	0	1.000
Use of other medications					
Phenylephrine	5 (17)	1 (3)*	0*	0*	0.008
Atropine	2 (7)	3 (10)	7 (23)†	0	0.022
Ephedrine	1 (3)	2 (7)	8 (27)*‡	0	0.001
Epinephrine	0	0	0	0	1.000
Lidocaine	0	0	0	0	1.000
Nitroglycerine	0	0	0	0	1.000

$P_{ET}CO_2$ = pressure of end-tidal carbon dioxide.
$P < 0.05$ versus *control, †propofol + ketamine, ‡all other groups.

respectively), while the propofol + ketamine group did not have any hypotension or bradycardia episodes. In addition, patients in the control group also had high prevalences of hypotension and bradycardia (30% and 20% respectively). These findings may have been due to the large and repeated doses of propofol that are used for endoscopic sedation, which increase the risks for dose-related adverse events. Despite the widespread use of propofol for sedation in upper gastrointestinal endoscopy, caution is still needed in high-risk patients.[32] On the other hand, the combination of propofol and dexmedetomidine is reported to be used in endoscopic sedation. However, the use of propofol + dexmedetomidine may cause adverse cardiovascular reactions such as hypertension, hypotension, bradycardia, or even sinus arrest. This risk is further increased in patients undergoing treatment with β-adrenergic antagonists or digoxin and in patients who are in a hypovolemic state.[33]

Hypoxia is the most common complication during sedation and is often due to the overuse of sedative agents and a subsequent lack of ventilation.[34] The control and propofol + sufentanil groups had lower SpO_2 compared to the other 2 groups, indicating

that propofol alone or combined with sufentanil may lead to respiratory depression, especially in elderly patients. After the procedure, the percentage of patients with SpO_2 <90% in the control group was 17%, which was highest among the groups. Due to the prolonged half-life of sedatives in elderly patients, recovery from sedation may be delayed.[35,36]

One study reported that propofol combined with sufentanil 0.2 μg/kg provided a deep sedation for endoscopy but that respiratory function was compromised.[12] Therefore, we applied sufentanil 0.1 μg/kg in elderly patients in the present study. By adding a small dose of sufentanil, we expected that a reduced use of propofol would achieve adequate sedation with a reduced risk for dose-related adverse events. However, this combination still was associated with in a higher prevalence of hypoxia compared to those with propofol + dexmedetomidine or propofol + ketamine. Moreover, Park et al[37] showed that sedation with propofol and opioids was associated with a high prevalence of pneumonia, especially in elderly patients. Regarding the use of ketamine, we applied a relatively small dose of 0.4 mg/kg, which helped to maintain a stable respiratory system and hemodynamics.

In terms of the efficacy of the combinations investigated in the present study, we considered several factors, including time to sedation, sedation depth, total amount of propofol, and time to recovery. According to the recommendation of Dawes et al[38] on dexmedetomidine use, a loading dose of dexmedetomidine should be administered over 10 min to avoid cardiovascular side effects.[48] Therefore, it is not surprising to have found that patients in the propofol + dexmedetomidine group needed a significantly longer time to achieve sedation compared to the patients in the other 3 groups.

During the procedure, all groups had adequate and comparable RSS scores. The prevalence of bucking or coughing was found to be highest in the control group and the lowest in the propofol + dexmedetomidine and propofol + ketamine groups. The highest prevalence of body movement was found in the control group, and the lowest, in the propofol + ketamine group. Finkelmeier et al[10] had a similar result where they maintained sedation mainly by propofol. In their study, the prevalence of adverse events was still higher in elderly patients than in those who were younger, even when a much lower dose of propofol was used. Saric et al[39] also showed that the amount of propofol used in the propofol + ketamine group was significantly less compared to that in the control group. The findings from a study by Aydogan et al[40] supported the outcome that the total amount of propofol is reduced with propofol + ketamine compared with propofol only, for sedation in endoscopy. In our study, the control group required the highest amount of propofol, while the propofol + ketamine group needed the smallest dose. To some extent, sufentanil, dexmedetomidine, and ketamine all reduced the total dose of propofol needed. Of these, propofol + ketamine turned out to be the optimal combination.

In the present study, recovery time was significantly longer in the propofol + dexmedetomidine group, with no significant differences in the other 3 groups. Similarly, a study by Demiraran et al[41] showed a prolonged recovery time with dexmedetomidine (42 [12.5] minutes), which was even longer than our result (10.1 [4.0] minutes). In another study by Hasanein and El-Sayed,[42] the recovery time (11.19 [19] minutes) was similar to that in the present study after sedation using the propofol + ketamine combination. On the other hand, Sethi et al[43] showed a shorter postprocedural recovery time in the propofol + dexmedetomidine combination group (>90% of patients' modified Aldrete scale scores achieved in a 9−10 score within 5 min in the present study). The difference in the findings between the studies might be explained by the different procedure durations. In the study by Sethi et al,[43] the procedure was endoscopic retrograde cholangiopancreatography, which is a more complex, painful, and prolonged procedure than was that in our study.

There were several limitations of this study. First, we did not use the bispectral index or Narcotrend to monitor the depth of sedation during endoscopy. Instead, we used RSS scores and examinations of reflection to estimate the sedation depth. In addition, the bispectral index and Narcotrend monitor were reported as being sometimes inaccurate during surgery.[44–46] Second, our study included only low-risk elderly patients; thus, these sedative combinations need to be reevaluated in high-risk patients. Third, we assessed only a certain dose regimen rather than include various doses for sedation. Fourth, we did not adjust analyses for potential baseline differences. Adjustment approaches

such as propensity score analysis are used for minimizing potential biases caused by a nonrandom assignment of participants. In this randomized, controlled trial, we conducted the randomization of our patients and ensured the process of allocation concealment. As a result, there were no significant differences in the demographic data, comorbidities, or endoscopic diagnosis among the 4 groups. Finally, the present study was conducted at a single center and had a relatively small sample size. Multicenter studies with larger sample size are needed to confirm our findings.

CONCLUSION

Propofol combined with ketamine 0.4 mg/kg provided stable hemodynamic and respiratory statuses, as evidenced by less hypotension, bradycardia, and hypoxia events, during gastrointestinal endoscopy in elderly patients.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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