Original Article
Premedication of atropine benefits sedated screening gastrointestinal endoscopy: a randomized, controlled, double-blinded clinical trial

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Abstract: *Objective:* Propofol is often used as a sedative agent in gastrointestinal endoscopy, but it has adverse effects like hypotension, bradycardia, and respiratory depression. This study aims to evaluate if premedication with atropine could stabilize hemodynamics in patients undergoing screening gastrointestinal endoscopy under sedation with propofol and low dose sufentanil. *Methods:* A total of 115 patients undergoing elective screening gastrointestinal endoscopy (esophagogastroduodenoscopy followed by colonoscopy) with American Society of Anesthesiologists physical status I-II were randomly grouped into the atropine group (n = 55) and the placebo group (n = 50). Atropine (0.01 mg/kg) or equivalent normal saline was administrated to patients, respectively, and then patients in both groups received low dose sufentanil (0.05 ug/kg) and propofol through target controlled infusion (TCI) with effect-site concentration of 4 ug/ml, before and during the procedure. We compared the cardiovascular parameters, duration of endoscopy procedure, satisfaction scores of endoscopist and patients, adverse reactions in patients, and the total consumption of propofol. *Results:* Patients in the atropine group tended to have more stable hemodynamics, characterized by less fluctuation in mean arterial pressure (MAP). The colonoscopic insertion time in the atropine group was shorter than placebo group (3.58 ± 1.13 *vs* 4.64 ± 1.24, *P* < 0.001). Also, the satisfaction scores in the atropine group were higher than placebo group for the endoscopists (4.16 ± 0.81 *vs* 3.64 ± 0.96, *P* = 0.003). Moreover, the consumptions of propofol were less in the atropine group (220 ± 35.5 *vs* 240.2 ± 32.6, *P* = 0.003). However, more patients in the atropine group suffered from xerostomia than the placebo group (81.8% *vs* 64%, *P* = 0.039) after gastrointestinal endoscopy. *Conclusions:* Premedication with atropine could improve hemodynamic stability and endoscopist satisfaction, and reduce the time taken to insert the colonoscope under sedation with propofol and low dose sufentanil in screening gastrointestinal endoscopy. *Trial registration:* Registration number: ChiCTR-INR-16009643; Registration date: 2016-10-27.

Keywords: Atropine, gastrointestinal endoscopy, propofol, target-controlled infusion, sedation, sufentanil

Introduction

Gastrointestinal endoscopy is well-established, commonly performed diagnostic and therapeutic procedure [1]. Both patients and endoscopists prefer this invasive procedure with sedation because [2, 3] (i) it minimizes procedural pain and discomfort for patients; (ii) it improves patients' acceptance of having an endoscopy performed, which can lead to earlier diagnosis and treatment of gastrointestinal diseases; and (iii) it provides better satisfaction for endoscopists, due to improved quality of examination.

Because of its [4] quick onset of action, reliable sedation, short half-life, and rapid recovery and discharge from the endoscopy unit, intravenous propofol is frequently used for sedation during gastrointestinal endoscopy. Moreover, multiple clinical reports have demonstrated that its safety in a variety of patients, including the elderly [1], children [5], and even frail and critically ill patients [6]. However, adverse effects including hypotension, bradycardia, and respiratory depression, were also reported, [7, 8] and often occurred during endoscopy.

As one of the most classic muscarinic cholinergic receptor antagonists, atropine is used for

treatment of severe acute organophosphate insecticide poisoning [9], treatment of bradycardia, and for reducing the secretion of the salivary glands in order to decrease the risk of aspiration before and during general anesthesia. Also, because of it's antispasmodic effect, atropine relieves the colonic stimulation caused by colonoscopy [10]. Hence, we hypothesize preconditioning with atropine may result in more stable hemodynamic and shorten the duration of gastrointestinal endoscopy with propofol sedation.

Materials and methods

Study design

This single-center, prospective, randomized, controlled, double-blinded study was performed at the Department of Anesthesiology, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China) between October 2016 and December 2016 (registration number ChiCTR-INR-16009643). Approval was given by the Hospital Ethics Committee of the Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, chaired by Professor Xueqiong Zhu (No L-2016-15). Written consent was signed by patients prior to participation.

Patients

Patient inclusion criteria were: (1) American Society of Anesthesiologists (ASA) classification of I-II; (2) Scheduled for elective gastrointestinal endoscopy (esophagogastroduodenoscopy followed by colonoscopy); (3) Aaged 18 to 65 years; and (4) Body Mass Index (BMI) between 18 and 26 kg/m^2. Exclusion criteria were: (1) Allergies to propofol, eggs, beans, or latex; (2) Sinus tachycardia and other arrhythmia; (3) Heart, liver or kidney dysfunction; (4) Scheduled for gastrointestinal endoscopic treatment; (5) Glaucoma or prostatic hypertrophy; (6) Abdominal surgery; (7) Hyperthyroidism, diabetes, or other endocrine disease.

Intervention and processes

The patients were randomly divided into two parallel groups, atropine group and placebo group, with a random number generated by SPSS 23. An independent supervising nurse who was blinded to this study prepared the study medications (atropine or equivalent normal saline) according to the random number sequence.

Oxygen at a rate of 5 L/min was delivered via Venturi mask when patients entered the endoscopy unit. Monitors included blood pressure (NIBP), electrocardiogram (ECG), peripheral oxygen saturation (SpO$_2$) and respiratory rate (the IntelliVue MP50; Philips, Shanghai, China). Vital signs were recorded every three minutes. Vital signs 10-minutes after patients laid down the mobile operating table were defined as the baselines. Sufentanil (0.05 ug/kg, Sufentanil Citrate Injection; Renfu Pharma Co., Ltd, Yichang, Hubei, China) and atropine (0.01 mg/kg, Atropine Sulfate Injection; Tianfang Pharma Co., Ltd, Zhumadian, Henan, China) or equivalent normal saline (0.9% Sodium Chloride Injection; Minsheng Pharma Co., Ltd, Hangzhou, Zhejiang, China) were administered respectively, through peripheral vein access which was established preoperatively with a 20-gauge intravenous cannula by the same supervising nurse. A propofol (Propofol Medium and Long Chain Fat Emulsion Injection; Fresenius Kabi, Graz, Austria) infusion was started by a TCI system (CONCERT-CL, Guangxi Veryark Technology Co.,Ltd, Nanning, Guangxi, China) with Marsh model one minute later, and the effect-site concentration was set as 4 ug/ml, which was proved to be effective in our pilot study and a similar trial [11]. During the procedure, various standard interventions were employed depending on the clinical situation including (i) administration of a 0.5 mg/kg bolus of propofol if the patient moved; (ii) use of a jaw-thrust in order to open the airway and/or mask ventilation if the patient had respiratory depression according to the anesthesiologist; and (iii) administration of a 6mg ephedrine if the NIBP was reduced to lower than 20% of baseline.

After completing the induction, which was confirmed by lost reflex of the eyelid, the same senior endoscopist (20 years of experience, more than 1500 gastrointestinal endoscopies performed annually in recent 10 years) executed the gastrointestinal endoscopy, starting with esophagogastroduodenoscopy, then colonoscopy. When the colonscope reached the ileocecal valve and prepared to exit, the infusion of propofol by TCI system was terminated. Both the endoscopist and the anesthesiologist were blinded in grouping information.

Figure 1. Flow Diagram.
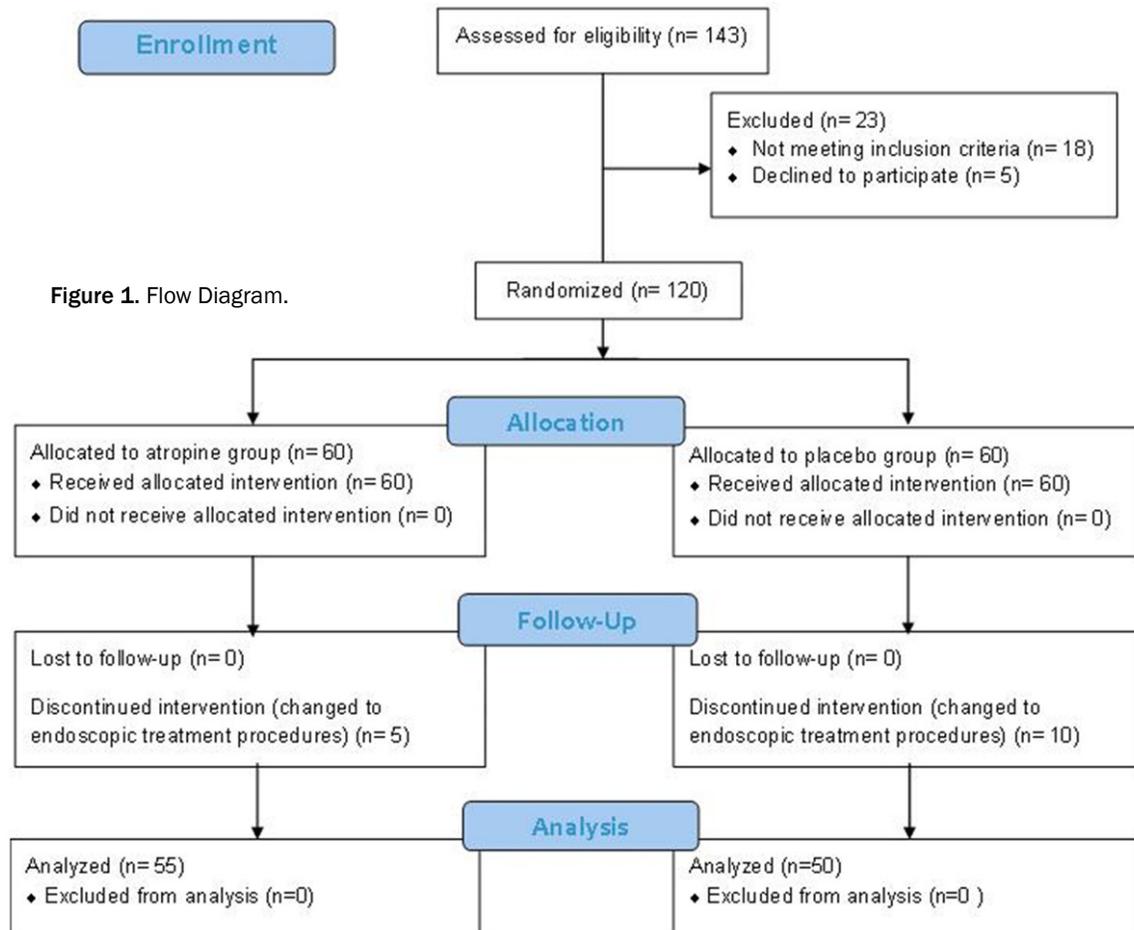
Measurements

The primary outcomes of this research were the stability of hemodynamics characterized as fluctuations of mean arterial pressure (MAP) compared with baseline (presented as *D-value of MAP,* different values of measurement MAP with baseline) at 5 different time-points and the duration of gastrointestinal endoscopy. The five different time-points were, T1, the time-point after induction; T2, the time-point the gastroscope was removed from the mouth; T3, the time-point of the lowest blood pressure during endoscopy; T4, the time-point of colonoscope entry into the anus; and T5, the time-point of the colonoscope reaching the ileocecal valve. The following time consumptions during the endoscopy were respectively recorded and compared, (i) the duration of esophagogastroduodenoscopy: the time from gastroscope entry into mouth to removal from the mouth; and (ii) the duration of colonoscopic insertion time: the time from colonoscope entry into the anus to reaching the ileocecal valve.

The duration of withdrawal of the colonoscope was not included because withdrawal time was fairly different for individual patients, and was not comparable.

The secondary outcomes included the degree of satisfaction of endoscopists and patients, the total consumption of propofol, and adverse events such as bucking/hiccupping, body movement, and xerostomia. The satisfaction scores of the endoscpist and patients were acquired by a survey (0-5 points, representing *Not Satisfied At All* to *Highly Satisfied*) when the endoscopy was completed and patients were fully oriented as determined by if patient could tell his/her correct birth date.

Power of the study and statistical analysis

The sample size was calculated based on the result of our pilot study with a commercial software, Pass11, in which we found that the average change to baseline in MAP was 14.7 ± 11.5 (n = 12) in the atropine group and 21.3 ±

Table 1. The characteristic of the patients

Variables	Atropine group (n = 55)	Placebo group (n = 50)	P-value
Gender (M/F)	31/24	30/20	0.781
Age (yr)	45.8 ± 9.6	44.2 ± 9.3	0.393
Height (cm)	166.7 ± 5.9	167.1 ± 7.4	0.746
Weight (kg)	61.5 ± 7.4	61.1 ± 7.9	0.833
BMI (kg.m^{-2})	22.1 ± 1.7	21.8 ± 2.1	0.572
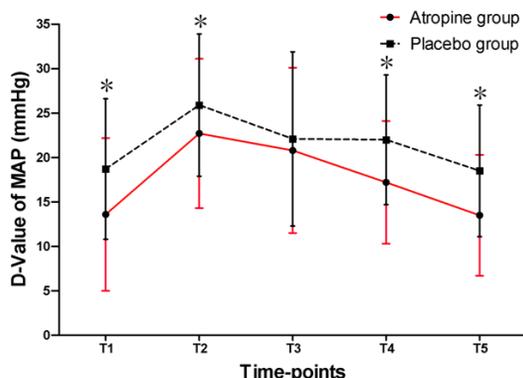
Figure 2. Results of D-values of MAP (difference value of measurement MAP with baseline) at 5 different time-points in two groups. Data is presented as mean ± SD, n = 55 in the atropine group, and n = 50 in the placebo group. *P < 0.05 between groups. T1, the time after induction; T2, the time of gastroscope removal from mouth; T3, the time of the lowest blood pressure; T4, the time of colonoscope entry into anus; and T5, the time of colonoscope reaching the ileocecal valve.
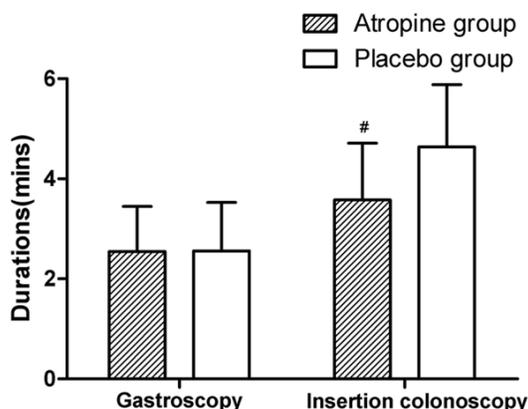
Figure 3. Durations of gastroscopy and insertion time of colonoscopy in two groups. The result is presented as mean ± SD, n = 55 in the atropine group, and n = 50 in the placebo group. #P < 0.01 between the groups.

9.8 (n = 12) in the placebo group. Thus we calculated 42 patients for each group to meet the minimum requirement of α = 0.05 and

power = 0.8. With consideration of dropping-out, we chose to enroll 60 patients per group (120 total).

The data sets with normal distribution were analyzed with independent 2-sample t-test and the data sets with non-normal distribution were analyzed with nonparametric tests. The quantitative data sets were expressed as frequency or rate were compared using a Chi-Square test or Fisher's exact test. The recorded P value was 2-sided, with P < 0.05 considered statistically significant. All of the data was analyzed with SPSS23.
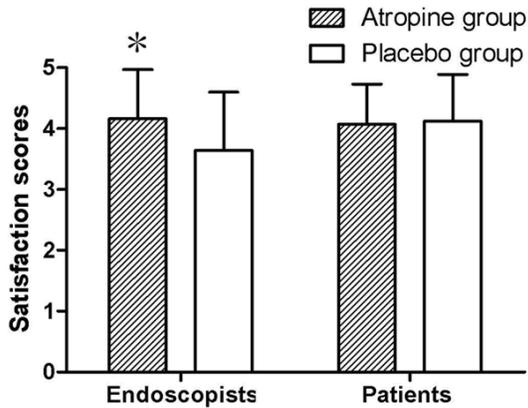
Results

A total of 120 patients were enrolled. With 15 dropouts, 55 patients remained in the atropine group and 50 in the placebo group. The patient flowchart is presented in **Figure 1**. The remaining patients underwent endoscopy only for diagnostic procedures. None of the patients involved had severe complications. The characteristics of the patients are presented in **Table 1**. There were no differences in these parameters including the proportion of genders, the mean age, BMI, weight, and height in the two groups (all P > 0.05).

There was no statistically significant difference for baseline of MAP (92.6 ± 11.4 mmHg in atropine group vs 93.0 ± 10.2 mmHg in placebo group, P = 0.851) between the two groups. However, more fluctuations of MAP (presented as D-value of MAP) were observed in the placebo group compared with the atropine group in the 5 recorded time-points, presented as **Figure 2**. Durations of esophagogastroduodenoscopy in the two groups were nearly the same (2.55 ± 0.9 min in the atropine group vs 2.56 ± 0.97 min in the placebo group, P = 0.937), but the time length of insertion of the colonoscope was shorter in the atropine group (3.58 ± 1.13 min in the atropine group vs 4.64 ± 1.24 min in the placebo group, P < 0.001), presented as **Figure 3**.

The consumption of propofol was less in the atropine group (220 ± 35.5 mg in the atropine group vs 240.2 ± 32.6 mg in the placebo group, P = 0.003). And the endoscopist satisfaction score in the atropine group was higher than the placebo group (4.16 ± 0.81 in atropine group vs 3.64 ± 0.96 in placebo group, P = 0.003). However, there was no significant dif-

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Figure 4. Endoscopist and patient satisfaction scores in the two groups. The result is presented as mean ± SD, n = 55 in the atropine group, and n = 50 in the placebo group. *P < 0.05 between the groups.

ference in patient satisfaction (4.07 ± 0.66 in atropine group vs 4.12 ± 0.77 in placebo group, P = 0.738), presented as **Figure 4**.

The results for adverse events in the two groups are presented in **Table 2**. No statistically significant difference was noted in bucking/hiccupping or body movement, all P > 0.05. More patients in the atropine group suffered xerostomia (81.8% in atropine group vs 64.0% in the placebo group, P = 0.039) after gastrointestinal endoscopy.

Discussion

This study aims to evaluate whether atropine could alleviate the adverse effects of propofol, such as hypotension during the procedure of gastrointestinal endoscopy. Results reveal that compared with placebo, preconditioning with atropine can stabilize hemodynamics and reduce the amount of time taken to insert the colonoscope. Moreover, atropine could also improve satisfaction scores of endoscopists and reduce consumption of propofol.

With the change of dietary structure of Chinese residents in last 30 years, from the original plant-based food, gradually into increased intake of high-protein and high-fat foods, more and more residents are suffering from gastrointestinal diseases [12]. Therefore, gastrointestinal endoscopy, especially with sedation, has been carried out in some hospitals as a routine procedure for gastrointestinal evalua-

tion. Compared with traditional sedative agents, numerous studies [5, 6, 13-15] demonstrate that propofol is a better candidate for safety and efficiency, and has been used extensively for sedation of gastrointestinal endoscopy [6]. However, the main limitation of propofol as sedative agent in endoscopy is its adverse effect on the cardiovascular and respiratory systems [16]. The target-controlled infusion (TCI) system is used in anesthetic practice as an automatically adjusted system to achieve and maintain a target anesthetic blood concentration based on a pharmacokinetics model [17]. The TCI system can effectively avoid the adverse effects caused by fluctuations of anesthetic blood concentration, and TCI of propofol was demonstrated to be safe and effective for sedation during endoscopy [16-19].

Propofol combined with different opioids (e.g., alfentanil, fentanyl, and remifentanil) [19-21] has also been widely adopted in previous studies in gastrointestinal endoscopy. For adult gastrointestinal endoscopy, the combination of propofol and fentanyl was the most common sedative regimen reported in a large study in Australia [20]. Chiang and colleagues' [19] studies suggest that in gastrointestinal endoscopy, combined with alfentanil, TCI of propofol was a better choice than MCI (manually controlled infusion), for recovery time, hemodynamics, and respiratory stability. In the present study, low dose sufentanil (0.05 ug/kg) was selected primarily because (i) sufentanil is the most commonly used analgesic drug during induction of general anesthesia for adults in our clinical practice; (ii) the combination of remifentanil and propofol causes more nausea and respiratory depression [19]; and (iii) alfentanil is not yet available in our hospital. Although there was a low occurrence of minor adverse events, we found TCI of propofol with effect-site concentration 4 ug/ml combined with sufentanil (0.05 ug/kg) was safe and effective in gastrointestinal endoscopy.

Atropine is widely used as an anti-bradycardia agent in clinical anesthesia. It can also increase cardiac output and blood pressure. Lim and colleagues' [22] study suggests that premedication of atropine in spinal anesthesia could accelerate the heart rate, and decrease the incidence of significant hypo-

Table 2. The adverse events of the patients

Adverse event	Atropine group (n = 55)	Placebo group (n = 50)	P-value
Xerostomia	45	32	0.039
Bucking and singultus	8	10	0.459
Body movement	11	8	0.595

tension. Maruyama and colleagues [23] pretreated patients with atropine in a total intravenous anesthesia induction with propofol (target blood concentration of 3 ug/ml) and remifentanil (0.4 ug/kg/min), found that atropine could prevent a decline in heart rate on induction, but not a fall in blood pressure. This is not is consistent with our study. The main reason for this may be the different types and doses of opioids. In their study [23], a relatively large dose of remifentanil was administered to achieve a level of analgesia to complete tracheal intubation. Hypotension secondary to severe vasodilation and low heart rates could be more likely caused by a large dose of remifentanil combined with propofol [24], which would be more challenging to reverse with atropine.

In the present study, we also found that premedication with atropine can reduce insertion time of the colonoscope, improve the satisfaction score of endoscopists, and reduce the consumption of propofol. This may be due to its antispasmodic effects in the gastrointestinal tract [25], and is consistent with similar studies in the literature [10, 26, 27]. However, xerostomia is one of the major adverse effects of atropine. In our study, more patients in the atropine group suffered from xerostomia after gastrointestinal endoscopy.

Several limitations exist in this study. Firstly, our data was obtained merely from a single center and the sample size was relatively small. Secondly, the adverse effects of atropine, such as xerostomia, could cause patient discomfort. Whether or not premedication with other anticholinergic drugs like anisodamine or scopolamine could minimize those adverse effects requires further research. Finally, atropine maintains blood pressure mainly via increased cardiac output due to an increased heart rate. However, this increases myocardial oxygen consumption. Therefore, atropine premedication should be administered cautiously in elderly patients, especially with potential coronary heart disease.

In conclusion, premedication with atropine may offer more benefits in gastrointestinal endoscopy with TCI propofol sedation and low dose of sufentanil.

Disclosure of conflict of interest

None.

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