WITHDRAWN:
Effect of Nalbuphine Combined With Intravenous Propofol for Anesthesia During Intestinal Endoscopic Submucosal Dissection in the Elderly

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Abstract

Objective: To investigate the effects of different doses of nalbuphine combined with an intravenous propofol pump for anesthesia during intestinal endoscopic submucosal dissection (ESD) in the elderly.

Methods: A total of 85 elderly patients attending the Hanchuan People's Hospital from January 2016 to January 2018 were divided into low, medium, and high dose groups according to the intravenous dosing of nalbuphine given with a continuous propofol pump.

The heart rate (HR), mean arterial pressure (MAP), and blood oxygen saturation (SaO2) were evaluated at five different time points (T1-T2).

The levels of norepinephrine (NE), cortisol and blood glucose were intervals recorded. The occurrence of adverse reactions, hospitalization days, visual analogue scale (VAS) score, Ramsay sedation, and wake score after waking from anesthesia were assessed. Neurocognitive function was assessed at discharge and after surgery using the Montreal Cognitive Assessment (MoCA).

Results: MR, MAP and SaO2 decreased significantly at T0-T4 in tested groups. The levels of NE, Cor, and Glu were significantly increased in three groups at T1-T3 and decreased among the medium-dose group. There was no statistically significant difference between the three groups in the total duration of anesthesia and the operative duration. The medium-dose group was performing significantly better than the low and high dose groups in clinical indicators. The postoperative VAS and Ramsay scores were higher in the low dose group (P 0.05). There was a significant difference in neurocognitive function scores and no significant differences in postoperative anesthesia satisfaction and hospitalization days were observed amongst the three groups (P>0.05).

Conclusions: The use of nalbuphine (0.1 mg/kg) combined with propofol for anesthesia during intestinal ESD in the elderly can shorten recovery times and reduce the incidence of postoperative adverse events and neurocognitive disorders.

1. Introduction

Gastrointestinal (GI) tumors are a worldwide burden and the third-largest cause of morbidity and mortality [1]. The incidence of GI tumors is in the top ten cancer indications in China and the mortality from GI ranks in the leading five causes of cancer death [2]. GI tumors are also more common in middle-aged and elderly patients. The development and implementation of gastroscopy and the continuous promotion of cancer prevention strategies such as physical examinations and early screening have led to an increase in the detection of early-stage GI tumors [3].

Surgical resection is established as a relatively effective treatment for GI tumors and endoscopic submucosal dissection (ESD) has shown promising clinical outcomes [4]. Compared to traditional open or laparoscopic surgery, ESD causes less trauma, can be used for multiple treatments in multiple

locations, has relatively low cost and requires a shorter hospitalization time for patients [5, 6]. However, the operation times for ESD are longer and the operation is more complex, which requires a higher quality of anesthesia [7].

Surgical anesthesia is a major risk factor for elderly patients undergoing surgery [8]. The decline of physiological function in the elderly leads to the weakening of drug metabolism and the attenuation of organ function that can result in more complications [9]. Routine preoperative preparations such as fasting and water deprivation may also affect the circulation of elderly patients [10]. Decreased liver and kidney function in elderly patients may also increase the action time of anesthetics [11].

To avoid the occurrence of postoperative complications, elderly patients have higher requirements for postoperative recovery. In ESD surgery, propofol is an intravenous anesthetic used in clinical practice as it has a fast onset and a rapid recovery time. However, the risk of respiratory depression increases with increasing doses of propofol [12, 13]. Studies have shown that nalbuphine has a major effect on visceral neuralgia. The use of nalbuphine combined with propofol for intravenous anesthesia can reduce the amount of propofol required and the occurrence of early cognitive dysfunction [14, 15].

The present study aimed to assess the effects of different doses of nalbuphine combined with an intravenous propofol pump for anesthesia during intestinal endoscopic submucosal dissection in the elderly to provide a reference point for future clinical applications.

2. Materials And Methods

2.1 Clinical data

A total of 85 elderly patients undergoing intestinal ESD surgery in Hanchuan People's Hospital (Hubei, China) from January 2016 to January 2018 were selected for retrospective analysis. The participated patients were divided into three groups according to the dosage of nalbuphine administered; low (LDG, n = 25), medium (MDG, n = 30) and high (HDG, n = 33) dose groups.

2.2 Inclusion and exclusion criteria

The inclusion criterion was patients aged 65–80 years. In contrast, the exclusion criteria were patients with systemic diseases or impaired organ functions who could not tolerate surgery and anesthesia, patients with mental illnesses, patients with a history of allergy to the study drugs and patients with coagulation dysfunction.

2.3 Ethical statement

Before data collection, the aims of the study were briefly explained to all participated patients. The required information such as age, gender, height, body mass index (BMI), American Society of

Anesthesiologists physical status, hypertension, diabetes, and smoking history was obtained using a pre-tested standard questionnaire. All patients were recruited under written informed consent.

2.4 Methods

All patients enrolled in this study fasted for 6 hours and were water-free for 4 hours before the operation. After entering the operating room, the upper limb venous access was opened. The low dose group was intravenously injected with nalbuphine (2 mL:20 mg) 0.05 mg/kg + propofol (20 mL:200 mg) 1 mg/kg. The medium-dose group was intravenously injected with nalbuphine (2 mL:20mg) 0.1 mg/kg + propofol (20 ml:200mg) 1 mg/kg. The high-dose group was intravenously injected with nalbuphine (2 mL:20 mg) 0.15 mg/kg + propofol (20ml:200mg) 1mg/kg. Surgery was performed when the patient had fallen asleep and the eyelash reflex had disappeared.

2.5 Observational indicators

The hemodynamic changes (heart rate, mean arterial pressure, and oxygen saturation) of patients were recorded at 5 minutes before anesthesia (T1), at the beginning of anesthesia (T2), 5 minutes from the beginning of surgery (T3), 30 minutes from the beginning of surgery (T4) and at the end of surgery (T5). The levels of NE, cortisol and blood glucose were compared at each time point. Venous blood was extracted to determine the blood glucose levels of patients. Serum NE levels were determined using a fluorescence kit method (Jiancheng, Nanjing, China), serum Cor was detected by radioimmunoassay and Glu levels were determined from venous blood analysis.

The duration of anesthesia, the duration of operation, duration of induction, duration of awakening and duration of stay in the recovery room were recorded for each patient. The incidence of adverse events, surgical complications, post-anaesthesia complications, and stay length were recorded in each group. The visual analogue scale (VAS) was used to evaluate the degree of postoperative pain (0–10 points). The Ramsay grading method was used to assess the degree of sedation degree in the patients (1 = quiet and irritable, 2 = quiet and cooperative, 3 = drowsy but able to follow instructions, 4 = arousal sleep, 5 = arousal retarded sleep, 6 = non-arousal deep sleep). The Steward awakening score was used to assess the degree of wakefulness, unblocked degree of the respiratory tract, and limb movement degree, respectively, using scores of 0–2 points for each dimension (the higher the score, the more awake state of the patient). Score > 4 indicated that the patient could leave the Postanesthesia care unit(PACU)room.

Neurocognitive function was evaluated at 6, 12, 24 and 48 hours after surgery using the cognitive assessment scale. The scoring criteria involve eight cognitive domains with a total score of 30 points. Scores ≦ 23 points were defined as cognitive dysfunction. The anesthesia satisfaction of each group was recorded.

2.6 Statistical methods

The obtained results were analyzed by using SPSS (Version 22.0) program. Categorical data were reported as n (%) and expressed as the mean ± standard deviation (x ± s). Analysis of variance and LSD *t-test* were used for comparison between multiple groups. Also, the χ^2 test was used to compare between the groups. A rank-sum test was used for the comparison of ranked data. P values (< 0.05) were defined as statistically significant.

3. Results

3.1 General characteristics of participants

Before the surgery, we checked the general characteristics of the patients. shows the general patient characteristics and no significant differences were observed in the general patient characteristics (Table 1).

Table 1
General characteristics of patients who participated in this study

	LDG(n = 25)	MDG(n = 30)	HDG(n = 33)	χ^2/R^2	*P* value
Gender(Male/Female)	12/13	15/15	19/14	0.6170	0.7345
Age(years)	71.2 ± 3.5	70.7 ± 3.3	69.8 ± 3.9	0.02630	0.3222
Height(cm)	163.5 ± 4.7	162.7 ± 5.1	163.1 ± 4.8	0.0043	0.8322
BMI(kg/m^2)	22.8 ± 2.5	23.2 ± 2.8	22.5 ± 2.3	0.01393	0.5510
ASA status				0.8129	0.6660
I	18	22	21		
II	7	8	12		
Hypertension	8	11	16	1.7972	0.4072
Diabetes	7	10	12	0.4533	0.7972
Smoking history	13	14	17	0.3494	0.8397
χ^2 = Chi-square test statistic,					

3.2 Basic information of the operation in the three patient groups

The basic information of the operations in the three groups of patients was compared. The results showed no statistically significant differences in the total duration of the anesthesia and the duration of surgery amongst the three groups (P>0.05). The duration of induction, awakening and stay in the recovery room in the MDG was significantly lower (P<0.05) than in the LDG and HDG (Table 2).

Table 2
Basic information of the operation

	Total duration of anesthesia(min)	The operation time(min)	Duration of induce(min)	The wake-up time(min)	PACU time(min)
LDG(n = 25)	88.6 ± 7.15	73.5 ± 5.84	2.8 ± 0.4	10.3 ± 1.48	14.5 ± 2.64
MDG(n = 30)	87.4 ± 7.33	73.1 ± 5.67	1.9 ± 0.2*#	9.3 ± 1.02*#	12.1 ± 2.39*#
HDG(n = 33)	87.9 ± 7.24	74.5 ± 6.03	2.6 ± 0.5	9.9 ± 1.18	13.8 ± 2.27
*compare to LDG,P < 0.05;#compare to HDG P < 0.05					

3.3 Hemodynamic changes in the patient groups

The hemodynamic changes in the three groups were compared at each time point. The results revealed that the heart rate, mean arterial pressure (MAP) and blood oxygen saturation of patients in all three groups increased and then recovered at T0 - T5 points. These results showed that the MAP of the patients in the MDG was significantly higher than the LDG and HDG at the end of the surgery (P<0.05). Significant differences were observed in HR between the MDG and HDG at 5 minutes from the beginning of the surgery and the end of the surgery (P<0.05).

At the end of the surgery, the heart rate of the MDG was significantly different from the LDG and HDG (P<0.05). The SpO_2 levels in the MDG at the beginning of anesthesia, 5 minutes from the beginning of surgery, 30 min from the beginning of surgery, and at the end of surgery were significantly different from the LDG and HDG (P<0.05). The data are shown in Figure 1.

3.4 Stress responses in three patient groups

The present results were revealed that the adrenaline levels in the MDG were significantly lower (P<0.05) at T2-T5 compared to the low and HDG. At T3 and T4, the NE levels in the HDG were significantly lower than the LDG (P<0.05). The cortisol levels in the MDG were significantly lower (P<0.05) at T2-T5 compared to the low and HDG. At T4, the Cor levels in the HDG were significantly lower (P<0.05) than in the LDG. The blood glucose levels in the MDG at T2-T5 were significantly lower (P<0.05) than in the LDG and HDG, as shown in Figure 2.

3.5 Sedation and analgesia-related scores

The current results showed the postoperative VAS and Ramsay sedation scores were significantly lower in the HDG compared to the LDG. The Steward waking score was significantly increased in the MDG compared to the LDG (*P*<0.05), as shown in Table 3.

Table 3
Sedation and analgesia-related scores

	VAS score	Ramsay score	Steward score
LDG(n = 25)	3.67 ± 1.18	3.15 ± 0.84	3.97 ± 0.44
MDG(n = 30)	3.05 ± 0.87*#	2.42 ± 0.72*#	5.14 ± 0.68*#
HDG(n = 33)	3.57 ± 1.06	3.01 ± 0.77	4.19 ± 0.54
*compare to LDG,P < 0.05;#compare to HDG P < 0.05			

3.6 Neurocognitive function

These results showed that the neurocognitive function scores of the MDG and HDG were higher at each time point compared to the LDG. Compared to the HDG, the neurocognitive function scores of the MDG were significantly improved at each time point (*P<0.05*), as summarized in Table (4).

Table 4
Neurocognitive function according to time

	after surgery (6 h)	after surgery (12 h)	after surgery (24 h)	after surgery (48 h)
LDG(n = 25)	23.12 ± 1.57	24.51 ± 1.34	26.15 ± 1.45	27.58 ± 1.44
MDG(n = 30)	25.59 ± 1.34*#	26.84 ± 1.06*#	27.91 ± 1.37*#	28.09 ± 1.27
HDG(n = 33)	24.37 ± 1.23*	25.69 ± 1.15*	26.81 ± 1.28	27.79 ± 1.30
*compare to LDG,P < 0.05;#compare to HDG P < 0.05				

3.7 The incidence of adverse reactions in the three groups of patients

In the present result, according to the total incidence of adverse reactions, it was found that the LDG had a (20%) higher rate than the MDG (16.5%) and there was not a statistically significant difference (*P*>0.05). Similarly, the higher rate of adverse reactions was (45.6%) noticed among HDG when compared to LDG and MDG (*P*<0.05), as shown in Table (5).

Table 5
The incidence of adverse reactions between studied groups

Variables	LDG(n = 25)	MDG(n = 30)	HD (n = 33)
Respiratory depression	0(0.0)	0(0.0)	2(6.1)
Arrhythmia	0(0.0)	1(3.3)	2(6.1)
Motor responses	1(4.0)	0(0.0)	3(9.1)
Nausea	1(4.0)	2(6.6)	3(9.1)
Hypersomnia	1(4.0)	1(3.3)	3(9.1)
Pruritus	2(8.0)	1(3.3)	2(6.1)
Occurrence rate	5(20.0)	5(16.5)	15(45.6)*#
*compare to LDG, $P < 0.05$;#compare to HDG $P < 0.05$			

3.8 Satisfaction of anesthesia in the three groups of patients

Our results showed that there was no statistically significant difference ($P>0.05$) observed between the three groups in the days of hospitalization and the satisfaction of anesthesia.

Table 6
Satisfaction of anesthesia

	Length of stay(d)	Anesthesia Satisfaction			
		Great satisfaction	Quite satisfaction	Dissatisfaction	Total satisfaction rate
LDG(n = 25)	3.06 ± 1.08	12(48.0)	6(24.0)	7(28.0)	18(72.0)
MDG(n = 30)	2.84 ± 1.13	17(56.7)	7(23.3)	6(20)	24(80.0)
HDG(n = 33)	3.01 ± 1.16	16(48.4)	9(27.3)	8(24.3)	25(75.7)
d = days					

4. Discussion

ESD is a novel, minimally invasive endoscopic technique that was developed for endoscopic mucosal resection. ESD is highly safe and causes minimal trauma to patients who recover quickly following the surgery. The ESD operation is relatively complex and requires anesthesia drugs that stimulate the

sympathetic nervous system and change hemodynamic stability [16]. Therefore, it is necessary to choose a safe and effective anesthesia plan to avoid intraoperative adverse events and postoperative complications and ensure the operation's success.

This study showed no significant differences in the total duration of anesthesia and the operative duration amongst the three patient groups (P>0.05). Other clinical indicators were significantly different in the three groups, with the MDG performing significantly better than the low and high groups. The heart rate, mean arterial pressure and blood oxygen saturation measurements in the three groups decreased significantly preoperatively to 30 minutes from the beginning of the operation and then levelled off. The MDG had the best indicators at the end of the operation.

The VAS and Ramsay scores of the MDG and HGD were significantly lower than the LDG (P<0.05). The incidence of postoperative adverse events in the LDG and MDG was significantly lower than in the high-dose group (P< 0.05).

Propofol is used to induce and maintain general anesthesia as it is rapidly distributed around the whole body following intravenous injection [17]. However, the analgesic effect of propofol is weak. When used as a single agent, the dose of propofol is required to be continuously increased to achieve continuous inhibition of the body motor response [18]. With increasing doses, the respiratory and circulatory systems are inhibited and can lead to respiratory depression and reduced blood pressure in patients during the operation [19, 20]. Compound analgesics are required to reduce the dose of propofol and the occurrence of adverse reactions following anesthesia.

A previous study reported that the low dose of dexmedetomidine combined with propofol has minimal effects on the respiratory and circulatory systems with no impact on recovery times [21]. However, most studies have been documented that the combination of opioid analgesics with propofol will prevent the pain resulting from propofol injection [22, 23]. Nalbuphine is an agonist-antagonistic mixed analgesic agent of the opioid receptor. It can stimulate the κ-receptor to play a central analgesic role and antagonize respiratory inhibition, nausea, vomiting, pruritus, and other adverse reactions caused by the μ-receptor [24].

Some reports have demonstrated that nalbuphine's analgesic and sedative effects are positive with few adverse effects, such as cardiovascular diseases. The current results further validate these previous findings and suggest that medium-dose nalbuphine combined with propofol can reduce the stress response indices in patients. This effect is mainly because opioids can act on the precursors of stress hormones or inhibit the secretion of adrenocortical hormones from the pituitary gland to reduce the massive secretion of adrenaline and cortisol [25]. The current work found that the MDG had higher neurocognitive scores at 6, 12, 24 and 48 hours after surgery compared to the HDG. Also, after intravenous injection of middle dose nalbuphine combined with propofol, the effect was quicker and the analgesia lasted longer. These effects delayed the incoming visceral nociceptive stimulus and central sensitization and weakened agitation and the occurrence of delirium to reduce neurocognitive disorders.

Conclusion

In conclusion, the use of nalbuphine (0.1 mg/kg) combined with propofol from ESD in the elderly can shorten recovery times and reduce the incidence of postoperative adverse events and neurocognitive disorders. This approach is most suitable for anesthesia during intestinal endoscopic submucosal dissection in elderly patients.

Abbreviations

The heart rate (HR), mean arterial pressure (MAP), blood oxygen saturation (SaO2), submucosal dissection (ESD), Montreal Cognitive Assessment (MoCA), norepinephrine (NE), Gastrointestinal (GI), Postanesthesia care unit (PACU), visual analogue scale (VAS), nalbuphine administered; low (LDG), medium (MDG) and high (HDG).

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Hanchuan People's Hospital, Hubei Province. Consents were taken from all the patients who participated in this study.

Consent for publication

All authors have agreed to publish this manuscript in BMC anesthiology

Authors' contributions

Jingjing Liu designed and performed the experiments. Biwei Zhan provided support for data analysis and writing the manuscript and Yongjun Zeng provided the supervision, resourses, discussion, design and peer review process. All the authors have seen and approved the manuscript.

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Competing interests

The authors declared no conflict of interest.

Data availability statement

The datasets used to support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

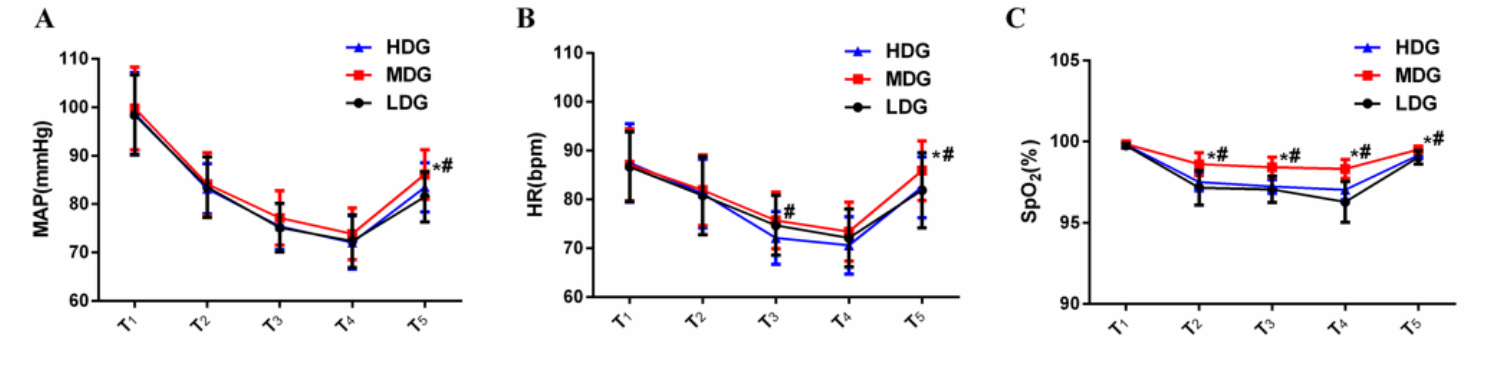

Figure 1

Hemodynamic changes in the three groups of patients. A: Change in MAP change; B: Change in HR; C: Change in SpO2 ; * P<0.05 compared with LDG; # P<0.05 compared with HDG

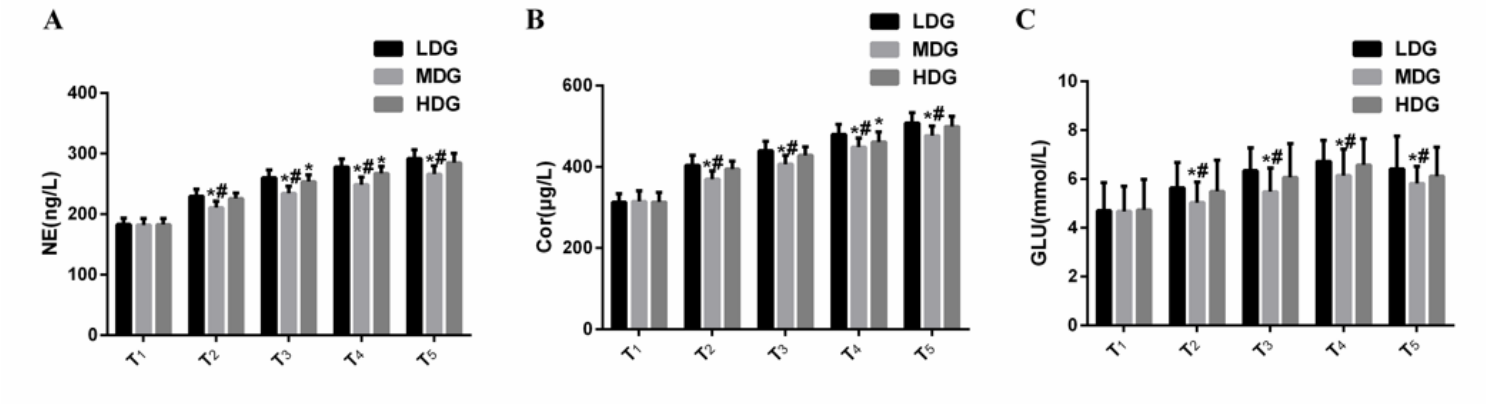

Figure 2

Changes in the levels of stress response indicators in the three groups. A: NE level; B: Cor level; C: GLU level; * P<0.05 compared with LDG; # P<0.05 compared with HDG.