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Efficacy and safety of ciprofol for general anaesthesia induction in elderly patients undergoing major noncardiac surgery

A randomised controlled pilot trial

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Editor,

With the ageing population, the era of geriatric surgery has arrived. Older patients are frail and have medical conditions, with increased risks for postoperative morbidity and mortality.¹ Hypotension after general anaesthesia induction is common and is associated with adverse outcomes.² Its independent predictors are older age, ASA physical status III–V, pre-operative hypertension, type II diabetes mellitus and use of propofol for induction.^{3,4} Propofol 2 to 2.5 mg kg⁻¹ is most commonly used for inducing anaesthesia in adults. Hypotension, respiratory depression and injection pain are common adverse effects. Elderly patients have increased susceptibility,

even when a reduced propofol of 1 to 1.5 mg kg⁻¹ was used.²

Ciprofol (HSK3486) is a novel sedative/anaesthetic and an analogue of propofol.⁵ Ciprofol has properties of fast onset of action, rapid recovery, reduced injection pain and stable cardiorespiratory function, making it a promising alternative to propofol.^{5,6} Ciprofol 0.4 to 0.5 mg kg⁻¹ provided effective and well tolerated sedation for colonoscopy in nonelderly adults.⁶ A recent study of 24 volunteers suggested that ciprofol 0.3 mg kg⁻¹ may be clinically used in elderly patients.⁷ A multicentre phase III trial investigating ciprofol for anaesthesia induction in adult surgical patients is underway in the United States (NCT04711837). In our randomised, double-blind pilot study, we assessed the efficacy and safety profiles of ciprofol for anaesthesia induction in elderly patients undergoing major noncardiac surgery.

Ethical approval was provided by the Ethics Committee of the First Affiliated Hospital of Soochow University, Suzhou, China (N° 2021-021) on 4 February 2021. This study was registered at the Chinese Clinical Trial Registry (ChiCTR2100044450) and followed the Declaration of Helsinki and the Consolidated Standards of Reporting Trials guidelines.

Between April and October 2021, elderly patients (65 to 80 years old, ASA status I–II and BMI 18 to 30 kg m⁻²) undergoing major noncardiac surgery were screened. All patients provided written informed consent.

An independent biostatistician performed the randomisation (1:1:1) to allocate patients into three ciprofol dose groups (0.2, 0.3 and 0.4 mg kg⁻¹). The randomisation list was sealed in opaque envelopes. An independent investigational nurse reconstituted ciprofol in identical syringes. Patients, anaesthesiologists and observers responsible for data collection were blinded to group assignment.

In the operating room, an intra-arterial cannula was placed in the radial artery for continuous mean arterial pressure (MAP) measurement. FloTrac/Vigileo system (Edwards Lifesciences, Irvine, California, USA) was applied to monitor cardiac index (CI) and stroke volume variation (SVV). Peripheral oxygen saturation (SpO₂), heart rate (HR) and bispectral index (BIS) were monitored. After 3 min of pre-oxygenation, patients received intravenous midazolam 0.2 mg kg⁻¹ and sufentanil 0.3 µg kg⁻¹. We administered midazolam to avoid awareness during induction, especially for patients in the ciprofol 0.2 mg kg⁻¹ group.

Two minutes later, patients received ciprofol over 30 s. Loss of consciousness (LOC) was defined as loss of eyelash reflex and Modified Observer's Alertness/Sedation score of 1 or less. Upon successful induction (defined as LOC and BIS value ≤60), rocuronium 0.9 mg kg⁻¹ was administered. If successful induction was not achieved

after 3 min of the initial ciprofol, 50% of initial dose was given. This additional dose could be repeated once 1 min later. If successful induction of anaesthesia was not achieved after 5 min of the initial ciprofol, propofol could be given as rescue sedation. Anaesthesia was maintained with sevoflurane inhalation.

For this pilot study, sample size calculation was not performed. There is no report on anaesthesia induction with ciprofol in elderly patients undergoing surgery. This pilot study provided data for effect size estimates in future studies. We assumed that 90 patients would be needed to show the efficacy and safety of ciprofol. Data are presented as mean $\pm$ standard deviation (SD), median [interquartile range, IQR] or number of patients (%). Data were compared using analysis of variance, Kruskal–Wallis test or χ^2 test, as appropriate. A two-sided P value less than 0.05 denoted a statistically significant difference.

Ninety patients were randomised and received the scheduled anaesthesia induction (Fig. 1). Table 1 summarises patient and surgical characteristics. The 11-factor modified frailty index score was 1.27 ± 1.1 , 1.10 ± 1.0 and 1.13 ± 1.0 in the 0.2, 0.3 and 0.4 mg kg⁻¹ groups, respectively.

The primary efficacy outcome was the time to successful induction (Table 2). The overall median [IQR] time to successful induction was 83.5 [69.5 to 108.5] s (92, 88 and

74.5 s in the 0.2, 0.3 and 0.4 mg kg⁻¹ groups, respectively). The three groups had similar time to LOC. Ten patients needed additional ciprofol to achieve successful induction. One patient in the 0.2 mg kg⁻¹ group and two patients in the 0.3 mg kg⁻¹ group needed two additional doses. Rescue sedation with propofol was not used.

The primary safety outcome was the incidence of hypotension (a decrease in MAP $\geq 30\%$ of baseline). Hypotension occurred in 26 out of 90 (28.9%) patients, without significant differences among groups. Hypotension was treated in 17 patients using intravenous ephedrine with or without fluids. Bradycardia (HR ≤ 50 beats min⁻¹) was uncommon, and intervention was not needed. Following tracheal intubation, 27.8% of patients had hypertension (an increase in MAP $\geq 30\%$ of baseline), and 21.1% had tachycardia (HR ≥ 100 beats min⁻¹). Seven patients experienced desaturation (SpO₂ $< 90\%$). Two patients (2.2%) reported mild injection pain.

Compared with baseline, the overall MAP decreased at several timepoints, and the overall HR increased after intubation, without significant changes in overall CI and SVV (Table S1, <http://links.lww.com/EJA/A770> and Fig. S1, <http://links.lww.com/EJA/A769>). Generally, the haemodynamic profiles were similar among the three dosage groups, except that the MAP and CI values were higher

Fig. 1 CONSORT flow diagram.

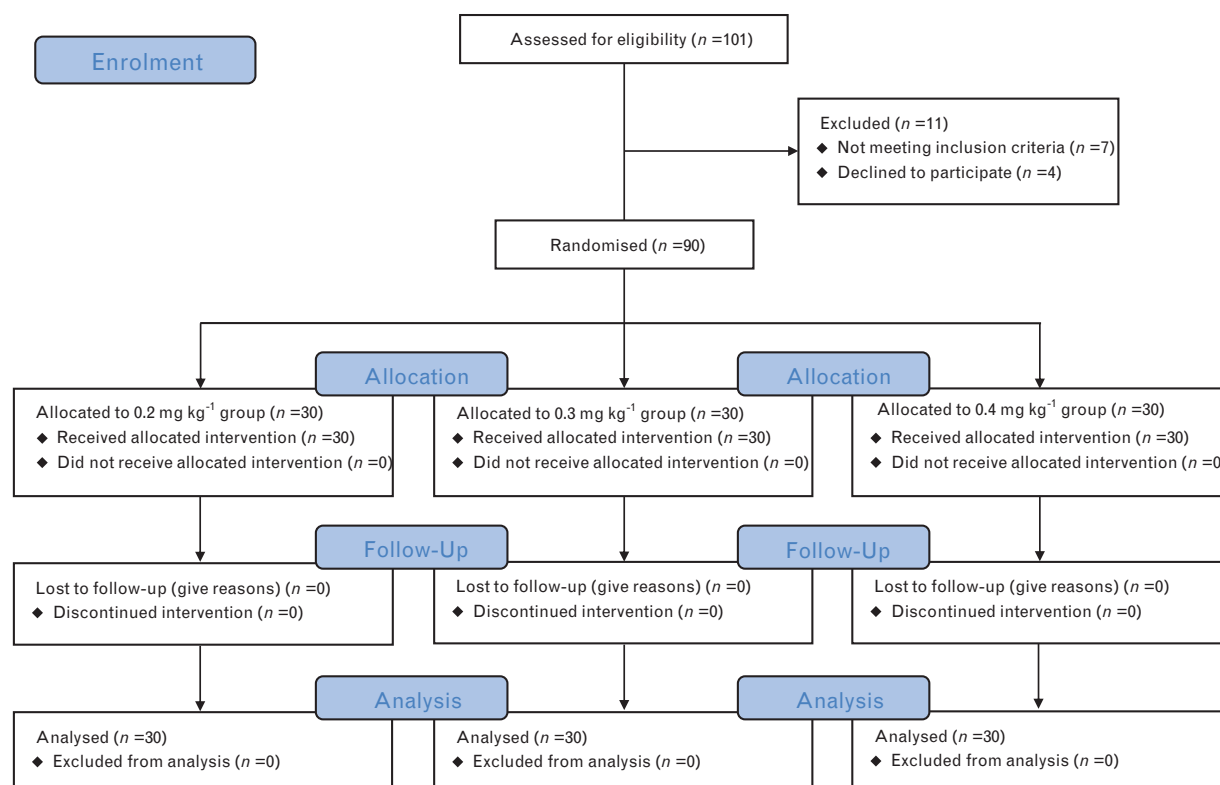


Table 1 Patients' and surgical characteristics

	Overall (n = 90)	0.2 mg kg ⁻¹ (n = 30)	0.3 mg kg ⁻¹ (n = 30)	0.4 mg kg ⁻¹ (n = 30)	P
Age (years)	70 [67 to 75]	68 [65.8 to 73.3]	70.5 [67 to 75.5]	72 [67 to 76]	0.103
Sex					
Male	52 (58%)	16 (53.3%)	21 (70%)	15 (50%)	0.244
Female	38 (42%)	14 (46.7%)	9 (30%)	15 (50%)	0.244
Weight (kg)	61.8 ± 9.1	61.3 ± 8.7	63 ± 8.7	61.2 ± 9.9	0.700
Height (cm)	163.6 ± 8.0	164.1 ± 8.2	165.3 ± 8.6	161.5 ± 6.9	0.180
BMI (kg m ⁻²)	23.1 ± 2.8	22.8 ± 2.8	23.1 ± 2.8	23.4 ± 2.8	0.706
ASA status					
I	18 (20%)	7 (23.3%)	6 (20%)	5 (16.7%)	0.812
II	72 (80%)	23 (76.7%)	24 (80%)	25 (83.3%)	0.812
mFI-11 score	1.17 ± 1.0	1.27 ± 1.1	1.10 ± 1.0	1.13 ± 1.0	0.803
Comorbidities					
Hypertension	56 (62.2%)	15 (50%)	20 (66.7%)	21 (70%)	0.231
Diabetes	20 (22.2%)	8 (26.7%)	8 (26.7%)	4 (13.3%)	0.358
Cerebrovascular disease	10 (11.1%)	5 (16.7%)	2 (6.7%)	3 (10%)	0.455
Cardiovascular disease	9 (10%)	3 (10%)	2 (6.7%)	4 (13.3%)	0.691
Respiratory disease	5 (5.6%)	3 (10%)	1 (3.3%)	1 (3.3%)	0.429
Anaemia	16 (17.8%)	7 (23.3%)	4 (13.3%)	5 (16.7%)	0.587
Malignancy	36 (40%)	10 (33.3%)	14 (46.7%)	12 (40%)	0.574
Antihypertensive treatment					
β-blocker	5 (5.6%)	1 (3.3%)	2 (6.7%)	2 (6.7%)	0.809
ACEI or ARB	17 (18.9%)	6 (20%)	7 (23.3%)	4 (13.3%)	0.602
CCB	16 (17.8%)	3 (10%)	6 (20%)	7 (23.3%)	0.372
Diuretics	3 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	>0.999
Others or unclear	15 (16.7%)	6 (20%)	1 (3.3%)	8 (26.7%)	0.044
Any medication	49 (54.4%)	15 (50%)	14 (46.7%)	20 (66.7%)	0.249
Type of surgery					
Abdominal	34 (37.8%)	11 (36.7%)	12 (40%)	11 (36.7%)	0.954
Urological	11 (12.2%)	6 (20%)	2 (6.7%)	3 (10%)	0.260
Orthopaedic	25 (27.8%)	9 (30%)	7 (23.3%)	9 (30%)	0.801
Thoracic	14 (15.6%)	3 (10%)	6 (20%)	5 (16.7%)	0.553
Neurosurgical	6 (6.7%)	1 (3.3%)	3 (10%)	2 (6.7%)	0.585

Data are mean ± standard deviation, median [interquartile range] or number of patients (%). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor inhibitor; ASA, American Society of Anesthesiologists; CCB, calcium channel blocker; mFI-11, 11-factor modified frailty index.

Table 2 Study outcomes

	Overall (n = 90)	0.2 mg kg ⁻¹ (n = 30)	0.3 mg kg ⁻¹ (n = 30)	0.4 mg kg ⁻¹ (n = 30)	P
Primary efficacy outcome					
Time to successful induction (s)	83.5 [69.5 to 108.5]	92 [69.5 to 132.5]	88 [73.5 to 129.8]	74.5 [60.8 to 88.5]	0.051
Secondary efficacy outcomes					
Time to LOC (s)	56.7 ± 23.9	55.9 ± 22.3	57.9 ± 31	56.3 ± 16.9	0.941
Patients with additional ciprofol	10 (11.1%)	5 (16.7%)	4 (13.3%)	1 (3.3%)	0.232
One additional dose	7 (7.8%)	4 (13.3%)	2 (6.7%)	1 (3.3%)	0.338
Two additional doses	3 (3.3%)	1 (3.3%)	2 (6.7%)	0 (0%)	0.355
Rescue sedation with propofol	0 (0%)	0 (0%)	0 (0%)	0 (0%)	>0.999
Primary safety outcome					
Hypotension	26 (28.9%)	11 (36.7%)	8 (26.7%)	7 (23.3%)	0.495
Secondary safety outcomes					
Hypotension with intervention	17 (18.9%)	7 (23.3%)	6 (20%)	4 (13.3%)	0.602
Bradycardia	3 (3.3%)	1 (3.3%)	1 (3.3%)	1 (3.3%)	>0.999
Bradycardia with intervention	0 (0%)	0 (0%)	0 (0%)	0 (0%)	>0.999
Hypertension	25 (27.8%)	7 (23.3%)	12 (40%)	6 (20%)	0.180
Hypertension with intervention	12 (13.3%)	5 (16.7%)	4 (13.3%)	3 (10%)	0.749
Tachycardia	19 (21.1%)	3 (10%)	9 (30%)	7 (23.3%)	0.154
Tachycardia with intervention	1 (1.1%)	0 (0%)	1 (3.3%)	0 (0%)	0.364
Desaturation	7 (7.8%)	3 (10%)	1 (3.3%)	3 (10%)	0.538
Other outcomes					
Injection pain	2 (2.2%)	1 (3.3%)	0 (0%)	1 (3.3%)	0.600
Unplanned ICU admission	1 (1.1%)	0 (0%)	1 (3.3%)	0 (0%)	0.364
In-hospital mortality	0 (0%)	0 (0%)	0 (0%)	0 (0%)	>0.999

Data are mean ± standard deviation, median [interquartile range] or number of patients (%). LOC, loss of consciousness.

at successful induction in the 0.3 and 0.4 mg kg⁻¹ groups than that in the 0.2 mg kg⁻¹ group.

Following induction and intubation, the mean BIS values were 45 to 52 in the 0.2 mg kg⁻¹ group, 33 to 40 in the 0.3 mg kg⁻¹ group, and 28 to 37 in the 0.4 mg kg⁻¹ group. During surgery, the BIS values were maintained within 45 to 60 for all patients. The duration of low BIS was relatively short, which did not increase haemodynamic or respiratory depression.

This pilot study suggests that general anaesthesia was successfully induced using ciprofol 0.2 to 0.4 mg kg⁻¹ in our elderly patients undergoing major noncardiac surgery, without any serious adverse events. The overall median time to successful induction was 83.5 s. The overall incidence of postinduction hypotension was 28.9%. A recent phase IIa and IIb trial showed that, for patients undergoing colonoscopy, the incidence of sedation/anaesthesia-related adverse events (hypotension, bradycardia, hypoxaemia and apnoea) was 25.8% in the propofol 2.0 mg kg⁻¹ group, followed by 21.9% in the ciprofol 0.5 mg kg⁻¹ group and 16.1% in the ciprofol 0.4 mg kg⁻¹ group.⁶ A recent multicentre study reported that the incidence of hypotension after propofol induction was 36.5% in patients undergoing noncardiac surgery (median age = 55 years).² Hence, the relatively lower incidence of hypotension in elderly patients is an advantage of ciprofol over propofol. The injection pain of ciprofol was uncommon, which can be attributable to the medium and long chain of triglycerides solvent and a low free drug concentration in the aqueous phase.⁵

To our knowledge, this is the first study on ciprofol use for anaesthesia induction in elderly surgical patients. Our results are limited by a small sample size, relatively young age (around 70 years old) and a lack of postoperative outcomes. Apart from that, it lacks a propofol bolus group and another in target-controlled infusion mode. The effects of ciprofol in this study should be interpreted with a fairly large dose of midazolam (0.2 mg kg⁻¹) and a relatively high dose of sufentanil (0.3 µg kg⁻¹). These two medications have additive effects with ciprofol, thus overestimating its efficacy in terms of time to successful induction. Our findings justify further investigations to ascertain the effects of ciprofol on postoperative recovery and long-term outcomes in elderly patients undergoing surgery.

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Yun-ying Ding and Yu-qin Long contributed equally to this study.

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Disadvantages of high fluid infusion rate in cardiac surgery

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Editor,

Cardiac surgery patients are at a high risk of extensive postoperative fluid overload, which is associated with poor outcome.^{1,2} Restrictive peri-operative fluid therapy is related to reduced postoperative complications in different types of major surgery.³ Hence, we sought to investigate the prevalence and magnitude of postoperative fluid administration in cardiac surgery patients. In