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Effect of creatine phosphate sodium on bispectral index and recovery quality during the general anaesthesia emergence period in elderly patients: A randomized, double-blind, placebo-controlled trial

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Abstract

Objective: To evaluate the effect of creatine phosphate sodium on bispectral index (BIS) and recovery quality during the general anaesthesia emergence period in elderly patients.

Methods: This randomized, double-blind, placebo-controlled study enrolled patients undergoing transabdominal cholecystectomy under general anaesthesia. Patients were randomly assigned to receive either creatine phosphate sodium (1.0 g/100 ml 0.9% saline; group P) or 100 ml 0.9% saline (group C) over 30 minutes during surgical incision. The BIS values were recorded at anaesthesia induction (T_0), skin incision (T_1), cutting the gallbladder (T_2), suturing the peritoneum (T_3), skin closure (T_4), sputum suction (T_5), extubation (T_6) and 1 min (T_7), 5 min (T_8), 10 min (T_9), and 15 min (T_{10}) after extubation. The anaesthesia duration, operation time, waking time, extubation time, consciousness recovery time, time in the postanaesthesia care unit (PACU), and the Steward recovery scores at T_7, T_8, T_9 and T_{10} were recorded.

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Results: A total of 120 elderly patients were randomized equally to the two groups. Compared with group C, the BIS values were significantly higher in group P at T_5, T_6, T_7 and T_8; and the Steward recovery scores at T_7 and T_8 were significantly higher in group P. The waking time, extubation time, consciousness recovery time and time in the PACU were significantly shorter in group P compared with group C.
Conclusion: Creatine phosphate sodium administered during transabdominal cholecystectomy can improve BIS values and recovery following general anaesthesia in elderly patients.

Keywords
Creatine phosphate sodium, bispectral index, recovery quality

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Introduction

Studies have shown that it is difficult to predict the recovery period following general anaesthesia in elderly patients.[1,2] Decreased serum protein content, blood volume, liver and kidney function and basal metabolism, and increased body fat, result in the prolongation of anaesthesia in elderly patients.[3,4] Bispectral index (BIS) is a comprehensive index used to calculate the effect of sedative drugs on the cerebral cortex and anaesthesia depth.[5,6] The Steward recovery score, a reference standard for patients leaving the anaesthesia recovery room after general anaesthesia, is also used to evaluate the quality of postoperative recovery.[7] Creatine phosphate sodium can reserve energy in the myocardium, skeletal muscle, and brain for the resynthesis of ATP, reduce myocardial ischaemia and reperfusion injury, improve heart function, decrease the incidence of coronary heart disease, and protect the brain in the elderly.[8–10] This study investigated the effects of preadministered creatine phosphate sodium on BIS value and recovery quality of elderly patients undergoing transabdominal cholecystectomy during the general anaesthesia emergence period.

Patients and methods

Ethics and trial registration

The Consolidated Standards of Reporting Trials (CONSORT) recommendations were followed in this study.[11] Ethical approval for this study (no. 2015-3-1) was provided by the Institutional Ethics Committee of the Jiangning Hospital Affiliated to Nanjing Medical University, Nanjing, China and this study was registered with the Chinese Clinical Trial Registry (ID: ChiCTR-IOR-16009169) on 7 September 2016. All patients involved in the study were informed of the proposal and gave their written, informed consent.

Study participants

Patients with American Society of Anesthesiologists (ASA) physical status I or II who were scheduled to undergo general anaesthesia for elective transabdominal cholecystectomy in the Department of Anaesthesiology, Jiangning Hospital Affiliated to Nanjing Medical University, Nanjing, China between March 2015 and December 2016 were eligible for inclusion in the study. Patients with drug allergies, neurological diseases, mental health

diseases, a history of alcohol or narcotics abuse and those who had received alcohol, sedatives, analgesics, or opioids within the previous 24 h were excluded. To exclude patients with cognitive impairment, a mini-mental state examination was undertaken.[12] Patients who underwent surgery with an operation time of < 30 min or > 2 h and patients with intraoperative bleeding of > 400 ml were excluded. Patients with an armpit temperature of < 36.5°C or > 37.4°C were also excluded.

Study design and randomization

This was a randomized, double-blind, placebo-controlled study conducted in two parallel groups. At the time of surgical incision, patients in group P received 1.0 g creatine phosphate sodium (Haikou Qili Pharmaceutical, Hainan, China) dissolved in 100 ml 0.9% saline administered over 30 min, while the same volume of 0.9% saline was administered to those in group C. Drugs were dissolved with 100 ml 0.9% saline in a soft plastic bottle by an anaesthesiologist not involved in anaesthesia induction. To ensure blinding, the bottles with creatine phosphate sodium or normal saline only were designated with two code letters (A and B) and the code was only broken after the statistical analysis had been fully completed. Randomization was achieved by a computer-generated table of random numbers. Both the patients and the assessors had no knowledge of the group division in the study.

Interventions and outcome measures

To decrease upper airway secretions, 0.3 mg scopolamine was injected intramuscularly 30 min before the patients' arrival at the operating room. Patients were punctured (with 20-gauge needles) intravenously on the dorsum of the right forearm and given 0.9% saline at 300 ml/h before anaesthesia. Standard monitors (BeneView T5; Xuansheng Medical Instrument, Shanghai, China), including electrocardiography, heart rate (HR), noninvasive blood pressure measurement, pulse oximetry, and temperature, were applied. A disposable temperature monitoring probe was placed in the armpit of the patient and after 10 min the patient's temperature was monitored continuously. Alcohol-soaked cotton balls were used to clean and degrease the patients' forehead skin. After drying, the BIS electrodes were placed in the specified positions as instructed and the BIS monitor (BIS VISTA™ Monitoring System; Medtronic, Minneapolis, MN, USA) was connected. The detection of all electrode impedance was completed.

After preoxygenation for 3 min, anaesthesia was induced with 0.3 mg/kg etomidate injected intravenously over a period of 20–30 sec. After that, 3 μg/kg fentanyl was injected intravenously over a period of 20–30 sec; then 1 min later, 0.1 mg/kg cisatracurium was injected intravenously over a period of 10–20 sec and endotracheal intubation was performed after 2 min. Tracheal intubation and mechanical ventilation were completed in 5 min. At the time of surgical incision, patients in group P were administered an intravenous infusion of 1.0 g creatine phosphate sodium dissolved in 100 ml 0.9% saline for approximately 30 min (a drop per sec) while those in group C received the same volume of 0.9% saline at the same rate. To keep the BIS value at 40–60 during the operation, anaesthesia was maintained by target controlled infusion of propofol (plasma target concentration 2.0–3.0 μg/ml) and remifentanil (plasma target concentration 2.0–3.0 ng/ml); and an injection pump of cisatracurium (0.1 mg/kg per h). Haemodynamic stability was guaranteed during the

anaesthesia and recovery periods. Ephedrine (6 mg/time) was administrated when hypotension (systolic blood pressure [SBP] < 90 mmHg) occurred, and urapidil (5 mg/time) was given to treat hypertension (SBP > 140 mmHg). Atropine (0.5 mg/time) was intravenously injected when bradycardia (HR < 50 beats/min) occurred, and esmolol (10 mg/time) was used when tachycardia (HR > 100 beats/min) occurred. Cisatracurium was stopped 30 min before the operation ended, while propofol and remifentanil were stopped by the time of suturing. The doses of propofol, remifentanil and cisatracurium were recorded. An antagonist was not allowed to be used to reverse the action of cisatracurium.

Participants were observed for BIS value from T_0 to T_{10} by an anaesthesiologist (J.L.) without knowledge of the pretreatment drug as follows: at anaesthesia induction (T_0), skin incision (T_1), cutting the gallbladder (T_2), suturing the peritoneum (T_3), skin closure (T_4), sputum suction (T_5), extubation (T_6) and 1 min (T_7), 5 min (T_8), 10 min (T_9), and 15 min (T_{10}) after extubation. The time of anaesthesia, operation duration, recovery time (from drug withdrawal to opening eyes by order), extubation time (from drug withdrawal to extubation), consciousness recovery time (from drug withdrawal to when the Steward score was > 4 points), duration that patients stayed in the postanaesthesia care unit (PACU) and the Steward recovery scores from T_3 to T_6 were also recorded. Extubation indications were as follows: (i) clear consciousness: hearing verbal instructions (e.g. open eyes); (ii) active reflection: obvious swallowing and coughing reflections; (iii) muscle strength recovery: holding strongly, looking up persistently; (iv) respiratory frequency: 16–25 times/min, tidal volume > 5 ml/kg, $Sp0_2 > 95\%$. Steward recovery scores were as follows: (i) level of consciousness (2 points: fully awake; 1 point: response to stimulation; 0 points: no response to stimulation); (ii) degree of airway patency (2 points: coughing according to the order; 1 point: maintaining airway patency without support; 0 points: supported respiration); (iii) physical activity (2 points: conscious activity; 1 point: unconscious activity; 0 points: no limb activity). Patients could leave the anaesthesia recovery room if the Steward recovery score was > 4 points.

Statistical analyses

Based on the results of the first 20 patients in this study (10 patients per group), the BIS value at T_5 and T_6 and the Steward scores at T_7 and T_8 in group P were approximately 15% higher than those in group C. Power analysis indicated that a sample size of at least 54 per group would have a 90% power to detect a 15% increase rate with a type I error of 0.05, using a single-sided test. This study aimed to enrol 60 patients in each group.

All statistical analyses were performed using the SPSS® statistical package, version 16.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Continuous variables are presented as mean ± SD and the differences between groups were analysed by mutual comparison after single factor variance analysis (one-way analysis of variance [ANOVA]). Repeated measures of variance analysis (repeated ANOVA) was used to compare values at different time-points within the same study group. Categorized variables and frequencies are presented as *n* of patients (%) and analysed using Mann–Whitney *U*-test. A *P*-value < 0.05 was considered statistically significant.

Results

A total of 120 eligible patients (age range 65–80 years) who underwent general anaesthesia for elective transabdominal cholecystectomy were enrolled in the study. None of

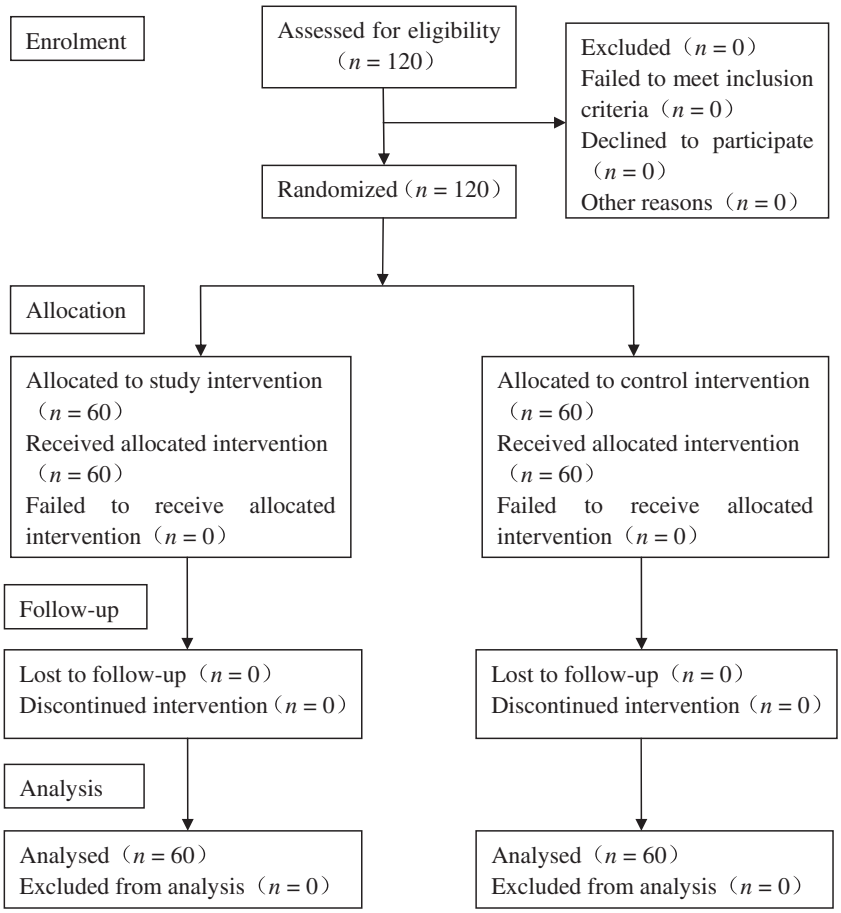

Figure 1. CONSORT flow diagram showing patient screening, enrolment, randomization and withdrawal from a randomized, double-blind, placebo-controlled trial to evaluate the effect of creatine phosphate sodium on bispectral index and recovery quality during the general anaesthesia emergence period in elderly patients.

the patients were excluded from the trial so data from all patients were analysed. Patient disposition is presented in Figure 1. The patients in the two randomized groups shared similar demographic and clinical characteristics (Table 1). Similar doses of propofol, remifentanil and cisatracurium were administered to the patients in the two randomized groups (Table 2).

The BIS values of the patients during the operation (T_1, T_2, T_3 and T_4) were similar in the two randomized groups (Table 3). The BIS value of patients in the two groups at T_5, T_6, T_7 and T_8 were significantly lower than those at T_0, T_9 and T_{10} ($P < 0.05$ for all comparisons; repeated ANOVA) (Table 4). Compared with group C, the BIS values at T_5, T_6, T_7, and T_8 in group P were significantly higher ($P < 0.001$ for all comparisons; one-way ANOVA).

The Steward recovery scores at T_7 and T_8 were significantly higher in group P

Table 1. Demographic and clinical characteristics of elderly patients ($n = 120$) enrolled in a randomized, double-blind, placebo-controlled trial to evaluate the effect of creatine phosphate sodium on bispectral index and recovery quality during the general anaesthesia emergence period.

Characteristic	Group P $n = 60$	Group C $n = 60$
Age, years	71.1 ± 4.3	71.3 ± 4.4
Sex, male/female	32/28	31/29
Weight, kg	65.1 ± 6.0	64.8 ± 6.2
ASA PS, I/II	26/34	24/36
Anaesthesia duration, min	77.4 ± 6.1	75.8 ± 6.5
Operation duration, min	70.9 ± 4.5	71.9 ± 4.5

Data are presented as mean ± SD or *n* of patients.
No significant between-group differences; Mann–Whitney *U*-test was used to compare categorical variables and continuous variables were compared using one-way analysis of variance ($P \geq 0.05$).
ASA PS, American Society of Anesthesiologists physical status.

Table 2. Doses of general anaesthetic drugs used in elderly patients ($n = 120$) enrolled in a randomized, double-blind, placebo-controlled trial to evaluate the effect of creatine phosphate sodium on bispectral index and recovery quality during the general anaesthesia emergence period.

Anaesthetic drug	Group P $n = 60$	Group C $n = 60$
Propofol, mg	475.8 ± 9.1	474.7 ± 9.7
Remifentanil, mg	1.5 ± 0.2	1.4 ± 0.1
Cisatracurium, mg	23.4 ± 2.5	23.8 ± 2.7

Data are presented as mean ± SD.
No significant between-group differences; continuous variables were compared using one-way analysis of variance ($P \geq 0.05$).

than in group C ($P < 0.001$ for both comparisons; one-way ANOVA) (Table 5). The time of waking, extubation, recovery of consciousness and time in the PACU were significantly shorter in group P compared with group C ($P < 0.001$ for all comparisons; one-way ANOVA).

Table 3. The bispectral index value at different time-points during the operation in elderly patients ($n = 120$) enrolled in a randomized, double-blind, placebo-controlled trial to evaluate the effect of creatine phosphate sodium on bispectral index and recovery quality during the general anaesthesia emergence period.

Operation time-point	Group P $n = 60$	Group C $n = 60$
T_1	47.3 ± 3.6	48.1 ± 3.4
T_2	46.8 ± 3.2	47.4 ± 3.2
T_3	46.1 ± 3.2	46.8 ± 3.0
T_4	48.0 ± 3.2	47.4 ± 2.9

Data are presented as mean ± SD.
No significant between-group differences; continuous variables were compared using one-way analysis of variance ($P \geq 0.05$).
T_1, at skin incision; T_2, at cutting the gallbladder; T_3, at suturing the peritoneum; T_4, at skin closure.

Table 4. The bispectral index value at different time-points before and after the operation in elderly patients ($n = 120$) enrolled in a randomized, double-blind, placebo-controlled trial to evaluate the effect of creatine phosphate sodium on bispectral index and recovery quality during the general anaesthesia emergence period.

Operation time-point	Group P $n = 60$	Group C $n = 60$	Statistical significance[a]
T_0	97.4 ± 1.3	97.7 ± 1.5	NS
T_5	72.3 ± 4.6[b]	63.6 ± 4.2[b]	$P < 0.001$
T_6	84.3 ± 2.5[b]	77.1 ± 2.8[b]	$P < 0.001$
T_7	90.5 ± 2.0[b]	82.0 ± 2.6[b]	$P < 0.001$
T_8	93.3 ± 1.8[b]	88.0 ± 1.9[b]	$P < 0.001$
T_9	96.6 ± 1.4	96.2 ± 1.5	NS
T_{10}	97.1 ± 1.6	96.9 ± 1.7	NS

Data are presented as mean ± SD.
[a]One-way analysis of variance compared with group C.
[b]$P < 0.05$; repeated analysis of variance compared with T_0, T_9 and T_{10}, respectively.
T_0, at anaesthesia induction; T_5, at sputum suction; T_6, at extubation; T_7, 1 min after extubation; T_8, 5 min after extubation; T_9, 10 min after extubation; T_{10}, 15 min after extubation; NS, no significant between-group difference ($P \geq 0.05$).

Table 5. Recovery time and the Steward recovery scores in in elderly patients ($n = 120$) enrolled in a randomized, double-blind, placebo-controlled trial to evaluate the effect of creatine phosphate sodium on bispectral index and recovery quality during the general anaesthesia emergence period.

	Group P $n = 60$	Group C $n = 60$	Statistical significance[a]
Time of waking, min	12.3 ± 1.6	17.9 ± 1.9	$P < 0.001$
Time of extubation, min	16.5 ± 1.5	21.0 ± 1.6	$P < 0.001$
Time of consciousness recovery, min	23.9 ± 2.3	30.5 ± 2.4	$P < 0.001$
Time in PACU, min	40.2 ± 2.9	48.9 ± 3.4	$P < 0.001$
The Steward scores after extubation (time-point)			
T_7	4.0 ± 0.3	3.0 ± 0.6	$P < 0.001$
T_8	4.8 ± 0.7	3.5 ± 0.6	$P < 0.001$
T_9	5.5 ± 0.5	5.6 ± 0.5	NS
T_{10}	5.6 ± 0.5	5.6 ± 0.5	NS

Data are presented as mean ± SD.

[a]One-way analysis of variance compared with group C.

PACU, postanaesthesia care unit; T_7, 1 min after extubation; T_8, 5 min after extubation; T_9, 10 min after extubation; T_{10}, 15 min after extubation; NS, no significant between-group difference ($P \geq 0.05$).

All study participants showed stable cardiovascular profiles during the anaesthesia and recovery periods. No patients experienced bradycardia or hypotension throughout the study. Ephedrine, urapidil, atropine and esmolol were not used.

Discussion

Previous studies have shown that the recovery time following general anaesthesia in the elderly is two-to-three times longer than that of the young with ASA physical status I–II.[5,13] In young patients with ASA physical status I–II, the BIS value can be restored to the preanaesthesia level within 5 min after extubation.[5,6] Therefore, this study was designed to record the BIS values and Steward recovery scores in elderly patients for up to 15 min after extubation. The BIS value during surgery can have an impact on the quality of the recovery in elderly patients under general anaesthesia; and fluctuations in BIS values might be obvious at the point of the initial skin incision, when cutting the gallbladder, suturing the peritoneum, and during final skin closure in patients undergoing transabdominal cholecystectomy.[14,15] Thus, this present study recorded and compared the BIS values of patients in the two groups at these time-points during the surgical procedure.

Creatine phosphate sodium, used for the synthesis of adenosine triphosphate (ATP), can reserve energy for cardiac muscles, skeletal muscles and the brain; and the hydrolysis of ATP provides energy for actomyosin contraction.[8,16,17] Studies have reported that an intravenous injection of creatine phosphate sodium (0.5–1.0 g) can rapidly supply energy to compensate for ATP deficiency caused by surgical trauma and hypoxia, improve the energy metabolism of cells under ischaemic hypoxia, increase glucose utilization, enhance myocardial contractility and improve tissue (especially myocardial) tolerance to hypoxia.[18,19] Due to the fact that the elderly's ability to reserve myocardial energy is poorer than that of the young,[19] an intravenous infusion of 1.0 g creatine phosphate

sodium was used in this study. In addition, the 1.0 g of creatine phosphate sodium was dissolved in 100 ml 0.9% saline and intravenously administered over 30 min at a rate of one drop per sec.

In this present study, propofol, fentanyl and cisatracurium might influence the recovery of elderly patients. Propofol and fentanyl are mainly metabolized in the liver.[20,21] Although mainly eliminated by the Hoffman mode, approximately 20% of cisatracurium is hydrolysed by esterase in the liver.[22] ATP is required for the metabolism of these drugs in the liver. As a synthetic component of ATP, creatine phosphate sodium can increase the level of ATP *in vivo*, and thereby promote the metabolism of these drugs in the liver.[23–25] Experiments have shown that creatine phosphate sodium also buffers energy supplies and improves mitochondrial efficiency in the brain.[26,27] As an antioxidant, creatine phosphate sodium can protect brain and nerves.[25] A previous report demonstrated that creatine phosphate sodium can increase the brain excitability by increasing the activity of Na^+-K^+-ATP enzymes in the cerebral cortex and reticular activating system through the N-methyl-D-aspartate-calcineurin pathway.[27] In group P, the BIS values from T_5 to T_8, and the Steward recovery scores at T_7 and T_8, were significantly increased compared with group C; while the waking time, extubation time, consciousness recovery time and time in the PACU were significantly shorter compared with group C. These findings might be the result of the combined effects of creatine phosphate sodium on promoting the metabolism of the three drugs in the liver and increasing the brain excitability. In addition, compared with the T_0 preinduction BIS data, the BIS values at T_9 and T_{10} and the corresponding Steward recovery scores between the two groups showed no significant difference, which was consistent with the results of a previous study.[6]

There was one key limitation to this present clinical trial, which was that the main determinations of physiological outcome (i.e. BIS values and Steward recovery scores) were subjective measures. However, it was not possible to find alternative convenient and accurate indicators based on previous studies.

In conclusion, the findings of this current study demonstrated that administration of creatine phosphate sodium had a positive impact on BIS values, time taken to awaken, time to extubation, time taken to recover consciousness and the Steward recovery scores, suggesting that intraoperative creatine phosphate sodium can promote recovery during the general anaesthesia emergence period in elderly patients.

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Wei Wang, Wan-You Yu and Jie Lv designed the study; Zhong Li supervised the practical carrying out of the clinical trial; Wei Wang and Lian-Hua Chen analysed the data; Wei Wang and Zhong Li wrote the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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