

# A Randomised Trial: BIS-Guided Anesthesia Decreases The Incidence of Delayed Neurocognitive Recovery And Postoperative Neurocognitive Disorder But Not Postoperative Delirium

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## Research Article

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# Abstract

**Background.** Postoperative cognitive dysfunction (POCD) renamed of delayed neurocognitive recovery (up to 30 days) and postoperative neurocognitive disorder (up to 12 months), is a frequent complication of the neurological system associated with poor outcome. This randomised controlled trial was aimed to determine whether bispectral (BIS) monitoring has a correlation with delayed neurocognitive recovery, postoperative neurocognitive disorder, or postoperative delirium (POD).

**Methods.** 100 patients were assigned to the BIS group and 97 patients were assigned to the control group in the study. The BIS index was kept in 40-60 in the BIS group, and the depth of anesthesia in the control group was maintained according to anesthetists' clinical experiences. The cognitive function was evaluated from the first day to the seventh day after the operation and the time of discharge, 1 month, 6<sup>th</sup> month and 1 year after the operation.

**Results.** The incidence of delayed neurocognitive recovery (3% vs 21.6%,  $P=0.001$ , at 7<sup>th</sup> day) (1% vs 21.1%,  $P=0.001$ , at 1 month) and postoperative neurocognitive disorder (6.2% vs 21.3%,  $P=0.002$ , at 6<sup>th</sup> month) (4.4% vs 16.3%,  $P=0.009$ , at 1 year) are lower in BIS group. While there is no significant difference between two group in POD (12% vs 19.6%,  $P=0.144$ ). The average value of intraoperative BIS were lower in BIS group (43.75 vs 50.69,  $P=0.001$ ). The postoperative hospitalisation time 9.99 vs 12.41,  $P=0.001$ ) and the mortality (5.4% vs 14.4%,  $P=0.042$ ) was significantly decreased while the satisfaction is higher in BIS group (39% vs 24.7%,  $P=0.009$ ).

**Conclusions.** Using BIS can decrease delayed neurocognitive recovery and postoperative neurocognitive disorder, while it is not associated with POD. BIS-monitoring can validly lessen the postoperative hospitalisation and mortality, and increase the satisfaction of patients.

**Clinical trial registration.** Chinese Clinical Trial Registry, ChiCTR2000032463.  
<http://www.chictr.org.cn/showproj.aspx?proj=33065>

## Introduction

Postoperative cognitive dysfunction (POCD), which was renamed of delayed neurocognitive recovery (up to 30 days) and postoperative neurocognitive disorder (up to 12 months), is a complication of the neurological system secondary to surgery and anesthesia, mainly manifested as memory, cognition and computing disorders, disability to combine tasks, psychomotor dexterity and so on<sup>[1, 2]</sup>. It was associated with dementia<sup>[3]</sup> for the similar mechanism of amyloid  $\beta$  peptide oligomerisation and deposition probably<sup>[4]</sup>. Meanwhile, postoperative delirium (POD) is always acute onset and fluctuating, mainly performed inattention, a disorder in thinking, perception memory, psychomotor behaviour, sleep–wake schedule and change of consciousness level, etc<sup>[5–7]</sup>. In non-cardiac surgery, when discharged from hospital, we can obtain the morbidity of POCD in patient 18–39 years are 36.6%, 40–59 years are 30.4%, older than 60 years are 41.15%, besides there still 12.7% of patients aged over 60 years were diagnosed

with POCD 3 months after the operation<sup>[8]</sup>. According to the type of surgery, the incidence of POD ranges from 10–55%. In elderly patients, the incidence of POD reaches 50%<sup>[9]</sup>. The incidence of the two diseases are high, particularly in elderly patients. This finding is consistent with many studies that age is an important risk factor for the two diseases<sup>[10–12]</sup>. With society's development and the increased level of medical care, the world has entered an aging society. The more and more elderly patients will receive surgery and anesthesia. The incidence of delayed neurocognitive recovery, postoperative neurocognitive disorder, and POD will increase quite dramatically. In that case, the social health and medical problems caused by these diseases have attracted the attention of many scholars<sup>[9]</sup>.

At present, some scholars summarise and classify cognitive dysfunction. For example, perioperative neurocognitive disorders(PND) be used to describe cognitive impairment of preoperative and postoperative period, which includes cognitive decline diagnosed before operation (neurocognitive disorder), POD and delayed neurocognitive recovery (up to postoperative 30 days), and postoperative neurocognitive disorder (up to postoperative 12 months)<sup>[13]</sup>.

Although the mechanism of neuroinflammation is well accepted, the unified pathogenesis of postoperative cognition impairment is still not clear<sup>[14]</sup>. There are still many studies that try to investigate effective methods to prevent it happen. With the popularization of intraoperative neuromonitoring which inhibit the experience of surgery by suppressing consciousness or ensuring disconnection of environment<sup>[15]</sup>, such as BIS, which analysis and integrates several different descriptors of the electroencephalogram (EEG) to form a single value<sup>[12, 16]</sup>. A large number of studies indicate that monitoring anesthesia with BIS can effectively reduce anesthesia exposure and reduce the occurrence of POD<sup>[17]</sup> and POCD, and accelerate the recovery of anesthesia<sup>[18, 19]</sup>. While F. M. Radtke<sup>[12]</sup> elucidated monitoring depth of anesthesia did not alter the morbidity of POCD after the operation on 7th day and 90th day. The study of the relationship between the use of BIS and delayed neurocognitive recovery, postoperative neurocognitive disorder, POD is few and controversial<sup>[20]</sup>.

Therefore, this study aims to explore the correlation between BIS-monitoring and the incidence of delayed neurocognitive recovery, postoperative neurocognitive disorder and POD in laparoscopic gastrointestinal surgery.

## Methods

This trial was a single-centre prospective randomised controlled trial. 220 patients who would experience laparoscopic gastrointestinal surgery were equally assigned to the BIS group and the control group at The Second People's Hospital of Yibin, Sichuan, China (ChiCTR 2000032463). This trial was approved by the Medical Ethics Committee of The Second People's Hospital of Yibin and received informed consent from every patient.

Patients were enrolled in the BIS group and the control group according to the computer-generated random sequence. Firstly, staff A designed two anesthesia plans and put them in envelopes. Secondly,

staff B screened the patients and extracted the envelopes. Thirdly, staff C would implement the anesthesia plan according to the envelope and record the data. Fourth, cognitive function was evaluated and recorded by staff D. Finally, staff E analyzed all the data and obtained the results. The staff participating in the study was blinded to the other data and well trained for a week before the trial started.

The inclusion criteria are as follows: the anesthesia time was longer than 2 hours, the age of patient was older than 18 years, American Society of Anesthesiologists' physical status (ASA) was I-III.

The exclusion criterion was patient with a history of mental and neurological disorders, excessive drinking and drug abuse, addiction to opioids or tranquilizers; severe organ functional diseases, stroke; mini-mental state examination (MMSE) score<20 (Because there are many rural people with no educational background in China, we choose the lower score as the standard); cannot complete the questionnaire; fail to complete the operation or anesthesia.

This trial's main outcome was the incidence of delayed neurocognitive recovery on 7th day and 1month, postoperative neurocognitive disorder at 6th month and 1 year, POD from 1st day to 7th day. In our trial, the surgeons were fixed of two, which could effectively reduce the difference caused by the surgeons. Most of the patients are diagnosed with gastrointestinal cancer in the trial. They need to be re-hospitalised for chemotherapy after the operation, therefore the long-term cognitive function can be easily acquired. A series of scales will lead to adverse effects and affect patients' completion and accuracy<sup>[21]</sup>. The MMSE scale is easy to complete and reliable (most patients with a low education level in our study, so the acceptance of this scale is higher). We select this scale as the only screen tool before surgery and evaluate the cognition function, including the memory, recollection, attention, computational ability, and writing and painting abilities in post-operation<sup>[1, 22, 23]</sup>. All patients were tested with the MMSE one day before the surgery. We use the scale of MMSE and CAM (The Confusion Assessment Method), which derived from the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R)<sup>[5, 12]</sup> to diagnosed the postoperative cognitive function. A patient was considered delayed neurocognitive recovery (at 7th day and 1month), postoperative neurocognitive disorder (at 6th month and 1 year) when postoperative MMSE score is greater than or equal to 2 points compared to preoperative scores<sup>[24][25]</sup>; or be deemed to POD while CAM scores greater than 22. If there are any doubts about the scale score, we invite a specialist neurologist to re-diagnose it.

All patients were no premedication. Before induction, we have already placed the electrode sensor of BIS index (Covidien 186 – 0106, YZB/USA 0793–2013) on the patient's forehead and record the number every 5 minutes. When the BIS group was maintained the BIS index between 40 and 60 during anesthesia, the control group was kept at the appropriate depth of anesthesia by the anesthesiologist's experience. The BIS monitor was covered and blinded to the anesthesiologists. Then we design to use propofol 2mg/kg, midazolam 0.05mg/kg, sufentanil 0.4mg/kg, cisatracurium 0.1mg/kg to complete the induction, and maintain an appropriate depth of anesthesia with propofol 4-12mg/kg/min and remifentanil 0.1-0.3ug/kg/min. The right invasive radial artery pressure was monitored and the artery blood-gas was analyzed (Abbott Point of Care inc, CG8+).

During the anesthesia, mean arterial blood pressure was maintained at about 20% of its baseline. Otherwise, ephedrine, metaraminol, or nitroglycerin was needed. Heart rate was kept at 50 to 100 beats per minute. Atropine and esmolol were needed if they exceeded the range. PetCO<sub>2</sub> was held at 35 to 45 mmHg by adjusting the ventilation parameters. The patients would be withdrawn from the study if they refused the trial, developed serious complications or broke the blindness. EEG, PR, SPO<sub>2</sub>, NIBP, IBP, PetCO<sub>2</sub>, BIS index were monitored and recorded in all patients for data-collection.

Finally, the patient's characteristic data, such as age, sex, weight, height, body mass index (BMI), education status (years), ASA, preoperative complications, etc. were collected. The surgery data, including infusion volume, blood transfusion volume, bleeding volume, urine volume, the dosage of anesthetics, the dose of vasoactive drugs, recovery time after the operation, concentration of CRP (C-reactive protein), BIS value, etc. Moreover, post-operation data consists of the incidence of delayed neurocognitive recovery, postoperative neurocognitive disorder and POD, the satisfaction of anesthesia, length of postoperative hospitalisation, complications, and mortality were also recorded.

## Statistical analysis

Data were performed using the Statistical Product and Service Solutions Group version 22.0. Data conformed to normal distribution are described by mean  $\pm$  standard deviation, while those that do not conform to normal distribution are shown as median and range interquartile. Comparisons were made using T-tests or Rank sum test for continuous variables and Chi-square test or Fisher's exact test for dichotomous variables. A value of *P* less than 0.05 was considered to be a significant statistical difference.

## Results

Five patients in each group were excluded because the MMSE score was less than 20. Two patients' surgery in the BIS group was delayed and 5 patients' surgery in the control group was delayed. Besides, 1 patient in the BIS group and 3 patients in the control group were dropped out for the anesthesia time less than 120 min. Two patients refused to undertake the experiment after having signed the BIS group's informed consent. Eventually, 100 patients in the BIS group and 97 in the control group were recruited (Fig. 1).

There was no significant difference in the education status, ASA, age, height, weight, BMI, preoperative complications (coronary heart disease, hypertension, and diabetes) between the two groups (Table 1).

Table 1

Preoperative information of patients' characteristics. Data was showed in mean  $\pm$  standard deviation, median (range interquartile) and number (%). P value less than 0.05 mean significant difference.

Characteristic	BIS group (n = 100)	Control group (n = 97)	P
Height (cm)	162.64 $\pm$ 7.69	161.72 $\pm$ 6.02	0.351
Weight (kg)	59.45 $\pm$ 7.64	59.78 $\pm$ 10.64	0.805
BMI	22.61 $\pm$ 3.49	22.95 $\pm$ 3.70	0.512
Age (yr)	62.98 $\pm$ 10.77	61.69 $\pm$ 10.27	0.391
Education status (yr)			0.252
Illiteracy	1 (1.0%)	6 (6.2%)	
Primary school	31 (31.0%)	36 (37.1%)	
Junior school	38 (38.0%)	32 (33.0%)	
High school	27 (27.0%)	21 (21.6%)	
University	3 (3.0%)	2 (2.1%)	
ASA			0.943
I	25 (25.0%)	13 (13.4%)	
II	53 (53.0%)	75 (77.3%)	
III	22 (22.0%)	9 (9.3%)	
Gender			0.232
Male	66 (66.0%)	56 (57.7%)	
Female	34 (34.0%)	41 (42.3%)	
Preoperative complications			
Hypertension	23 (23.0%)	16 (16.5%)	0.252
Diabetes	4 (4.0%)	2 (2.1%)	0.429
Coronary heart disease	8 (8.0%)	5 (5.2%)	0.421

There was no significant difference between the two groups in transfusion volume, anesthesia time, operation time, bleeding volume, mean arterial pressure (MAP), mean concentration of C-reaction protein (mg/L) (Table 2). However, the dosage of propofol (1810.00  $\pm$  533.33 vs 1336.08  $\pm$  461.75,  $P < 0.001$ ), cisatracurium (37.61  $\pm$  13.59 vs 30.57  $\pm$  8.08,  $P < 0.001$ ), and remifentanyl (2207  $\pm$  766.25 vs 1970.62  $\pm$  870.23,  $P = 0.044$ ) is higher in the BIS group, while the dose of sufentanil (43.86  $\pm$  7.60 vs 46.90  $\pm$  10.73,

$P = 0.023$ ) is lower than that in the control group. The MAP is similar in the two group, while the use of vasoactive drugs (5.0 vs 18.6%,  $P = 0.003$ ) is higher in the control group.

Table 2

Details in peri-operation. Data were showed in mean  $\pm$  standard deviation, median (range interquartile). P value less than 0.05 means significant difference.

	BIS group (n = 100)	Control group (n = 97)	P
Operation time (min)	235.65 $\pm$ 62.42	229.59 $\pm$ 75.87	0.542
Anesthesia time (min)	261.74 $\pm$ 63.09	253.28 $\pm$ 76.76	0.400
Liquid Infusion (ml)	2021.10 $\pm$ 583.09	2037.11 $\pm$ 687.59	0.860
Volume of bleeding (ml)	277.30 $\pm$ 105.14	236.70 $\pm$ 206.11	0.082
Dosage of anesthesia (ml)			
Propofol (mg)	1810.00 $\pm$ 533.33	1336.08 $\pm$ 461.75	< 0.001
Remifentanil ( $\mu$ g)	2207 $\pm$ 766.25	1970.62 $\pm$ 870.23	0.044
Cisatracurium (mg)	37.61 $\pm$ 13.59	30.57 $\pm$ 8.08	< 0.001
Sufentanil ( $\mu$ g)	43.86 $\pm$ 7.60	46.90 $\pm$ 10.73	0.023
Dose of vasoactive drugs	5 (5.0%)	18 (18.6%)	0.003
Intraoperative MABP (mmHg)	89.22 $\pm$ 4.92	90.73 $\pm$ 7.31	0.093
Intraoperative mean BIS	43.75 $\pm$ 6.78	50.69 $\pm$ 6.33	< 0.001
Concentration of CRP (mg/L)	32/97 $\pm$ 22.80	36.86 $\pm$ 28.43	0.292

There was no significant difference in postoperative ICU admission between two group (6% vs 5.2%,  $P = 0.796$ ). In the BIS group, the time of post-operation recovery (24.76  $\pm$  9.36 vs 29.49  $\pm$  9.72,  $P = 0.001$ ), the length of postoperative hospitalisation (9.99  $\pm$  3.94 vs 12.41  $\pm$  4.61,  $P < 0.001$ ), and the mortality (5.4% vs 14.4%,  $P = 0.042$ ) was less than that in the control group. Meanwhile the satisfaction of patient ( $P = 0.009$ ) in the BIS group is better than that in the control group (Table 3).

Table 3

The information of the patients after the operation. Data were shown in mean  $\pm$  standard deviation, median (range interquartile), and number (%). P value less than 0.05 mean a significant difference.

	BIS group (n = 100)	Control group (n = 97)	P
Stop medication-discharged (min)	24.76 $\pm$ 9.36	29.49 $\pm$ 9.72	0.001
ICU admission	6 (6%)	5 (5.2%)	0.796
Postoperative hospital stay (d)	9.99 $\pm$ 3.94	12.41 $\pm$ 4.61	< 0.001
Satisfaction			0.009
0	0	0	
1	25 (25.0%)	44 (45.4%)	
2	36 (36.0%)	29 (29.9%)	
3	39 (39.0%)	24 (24.7%)	
Death	5 (5.4%)	13 (14.4%)	0.042

Table 4

The main outcome of delayed neurocognitive recovery, postoperative neurocognitive disorder, and postoperative delirium.

	BIS group	Control group	P
Delayed neurocognitive recovery			
7th day (B = 100, C = 97)	3(3.0%)	21(21.6%)	< 0.001
1 month (B = 100, C = 95)	3(3.0%)	20(21.1%)	< 0.001
Discharge (B = 100, C = 96)	1(1.0%)	8(8.3%)	0.035
Postoperative neurocognitive disorder			
6th month (B = 97, C = 94)	6(6.2%)	20(21.3%)	0.002
1 year (B = 91, C = 86)	4(4.4%)	14(16.3%)	0.009
POD (B = 100, C = 97)	12(12.0%)	19(19.6%)	0.144

There is a significant difference between the two groups when comparing BIS with delayed neurocognitive recovery and postoperative neurocognitive disorder (Table 4).

The incidence of delayed neurocognitive recovery and postoperative neurocognitive disorder showed a downward trend in general. The lowest morbidity of delayed neurocognitive recovery in the two groups is at discharge time (1% vs 8.3%). The highest morbidity of postoperative cognitive dysfunction is 21.6% in



the control group. The highest incidence of 6.2% at postoperative 6th month in the BIS group was still lower than that at each time points in the control group (Table 4).

Figure 2 showed the mean score of MMSE in the BIS group increased moderately until discharge time point and then decreases. At the same time, there was a decrease in the control group except for discharge time point. The result shows that the BIS value in the BIS group is lower than the control group (43.75 vs 50.69,  $P < 0.001$ ).

In order to further explore the relationship of BIS values and the incidence of cognitive dysfunction, we divided patients in control group who experience the BIS value beyond 40–60 into postoperative cognitive impairment group (including delayed neurocognitive recovery and postoperative neurocognitive disorder) and non-postoperative cognitive impairment group. There was no significant difference between the two group in the time distribution of BIS number out of the standard range (Table 5).

Table 5

Time distribution of BIS beyond range in control group. (Np means the number of postoperative cognitive impairment group, Nn means the number of non- postoperative cognitive impairment group)

	No postoperative cognitive impairment (min)	postoperative cognitive impairment (min)	<i>P</i>
POCD 7th day (Np = 21, Nn = 76)			
BIS<40	20.0 (0.0,55.0)	40.0 (10.0,67.5)	0.144
BIS>60	40.0 (11.25,82.5)	15.0 (7.5,60.0)	0.155
POCD 1 month (Np = 20, Nn = 75)			
BIS<40	20.0 (0.0,60.0)	32.5 (6.25,57.5)	0.523
BIS>60	30.0 (10.0,75.0)	40.0 (11.25,68.75)	0.745
POCD discharge (Np = 8, Nn = 88)			
BIS<40	22.5 (0.0,55.0)	42.5 (2.5,73.75)	0.502
BIS>60	40.0 (10.0,75.0)	25.0 (6.25,62.5)	0.562
POCD 6th month (Np = 20, Nn = 74)			
BIS<40	20.0 (0.0,56.25)	32.5 (11.25,63.75)	0.231
BIS>60	40.0 (10.0,71.25)	22.5 (6.25,66.25)	0.433
POCD 1 year (Np = 14, Nn = 72)			
BIS<40	20.0 (0.0,58.75)	32.50 (3.75,65.0)	0.657
BIS>60	35.0 (10.0,68.75)	27.5 (5.0,57.5)	0.441

The occurrence of POD in the BIS group and control group is 12% and 19.6% in the first three days, and there is no statistical difference between the two groups.

## Discussion

Our study's main finding was that BIS monitoring during anesthesia reduces the incidence of delayed neurocognitive recovery and postoperative neurocognitive disorder. This may be because the BIS value within the normal range reduces the effects of neuroinflammation<sup>[26]</sup> associated with lighter anesthesia and the toxic effects of drugs associated with deeper anesthesia. And the patient in BIS group who were continuously under deeper anesthesia (mean BIS = 43.75) within the normal range can decrease postoperative cognitive impairment.

Moreover, the further analysis of BIS value beyond 40–60 with postoperative cognition function shows no significant difference. The result unmasks that the time under deep anesthesia (BIS<40) and light anesthesia (BIS>60) between patients with POCD and patients without POCD were similar in the control group, thus the risking factor is not just the BIS value but the value combined with the duration.

The curve of the score with MMSE from Fig. 1 shows that the mean score of MMSE in the two groups showed the trend of increasing and decreasing. This may illustrate that the BIS-monitor effectively reduces postoperative cognitive impairment or even improves postoperative cognitive function<sup>[27]</sup>.

It could be a possibility that most patients perform well when answering the questionnaire with a better mood and familiar with the environment of hospital at the discharge time, besides the learning effect were exist.

Our study demonstrated that the postoperative cognitive disorder at different time points is a change of fluctuation and downtrend. According to the data, the postoperative cognitive disorder is a common complication after surgery, whose onset time may be very late. Although most of the symptoms of patients are reversible, some people still suffer from a decline in cognitive function. Moreover, the highest morbidity is 23.6%, which was similar to the result of Chan MT's study<sup>[18]</sup>. In general, the occurrence of delayed neurocognitive recovery and postoperative neurocognitive disorder was higher in the control group at all time points, which shows using BIS can effectively decrease the occurrence of postoperative cognitive impairment<sup>[17, 28]</sup>. In our study the BIS group who received high doses of anesthesia had a more stable cardiovascular response, better postoperative recovery and satisfaction, so the examination was more acceptable and well performed which may lead to a lower cognitive dysfunction in BIS group.

our result is accordance with Chan MT<sup>[19]</sup> that BIS-guided anesthesia can decrease the risk of POCD and POD at 3 months after surgery in 921 elderly patients underwent non-cardiac surgery. We also found that the median BIS value was 53 vs 38.6 in BIS group with a lower dose of anesthetic and control group, which is opposite to our BIS value in BIS and control group (43.75 vs 50.69). It may contribute to the larger doses of narcotic drugs used in our study.

At the same time, Farag E<sup>[29]</sup> discovered that in 74 patients the deeper (median BIS 39 vs 51) anesthesia were associated with better cognitive function 4–6 week postoperatively for the possible reason of lower BIS. Deeper anesthesia means lower metabolic of the brain, which can increase the tolerance to ischemia and hypoxia, reducing the body's stress response<sup>[18]</sup>. These results were similar to the finding of Tasbihgou SR<sup>[30]</sup> that deepening anesthesia attenuated the brain changes associated with hypoxia in rats. These studies illustrate a deep anesthesia associated with inhibition of inflammation<sup>[31]</sup> and burst suppression may be the protective factors of POCD<sup>[32]</sup>. This may be consistent with our findings that patients with a relatively lower value (43.75 vs 50.69) have a lower incidence of delayed neurocognitive recovery and postoperative neurocognitive disorder.

Meanwhile, Radtke FM<sup>[12]</sup> researched BIS with POCD and POD in 1155 patients. The result shows BIS does not change the incidence of POCD in the post-operation of 7th and 90th day. This may be because the two groups of patients' BIS values were similar, while huge differences exist in our study (43.75 vs 50.69,  $P<0.001$ ). The observation period in our study was longer, and the results of 3 months after operation were not included. Cao YH<sup>[1]</sup> also points out that there were no statistically significant differences in BIS group than that in the control group (15.15% vs 33.33%) after 7 days. There is inconsistent with our study because the sample size of this study is small. Moreover, postoperative cognition impairment incidence was higher than our study in both groups because of an incredible trauma by liver transplantation. Comparing to the stress response to surgical trauma, anesthesia may have a more negligible effect on cognition impairment.

Several studies have shown that lower BIS implies a larger dose of anesthetic was needed, which contributes to the risk factor of POCD, such as intra-operative hypotension<sup>[5]</sup> and increased toxicity of drugs<sup>[17]</sup> are detrimental to postoperative cognitive function<sup>[18][27][33]</sup>.

In our study, the relatively lower mean BIS value of this research is in the normal range. Although the anesthetic dose was increased and the use of vascular active drug use was less in the BIS group, no noticeable difference in the mean ABP between the two groups. Therefore, our study's relatively lower BIS value is appropriate, and using BIS monitoring can decrease the incidence of postoperative cognitive disorder.

Morbidity of POD is 19.6% in the control group, which was consistent with L.Evered's result<sup>[13]</sup> (15–53%), and it occurred mainly in the first three days<sup>[34]</sup> due to the effects of anxiety, pain<sup>[35]</sup>, and residual anesthetic. However, there was no significant statistical difference in this study.

The reasons may be as follows. Firstly, the postoperative cognitive disorder occurs more frequently in elderly patients with poor outcomes and increased mortality<sup>[11]</sup>. However, some patients were less than 60 years old, although the two groups' mean age was over 60 years old and similar (62.98 vs 61.69,  $P=0.391$ ). Secondly, the sample size was small to show the obvious difference. Thirdly, the satisfaction of the patients in the two groups is high (no dissatisfaction exist) for the well postoperative analgesia, consultation, and comfort from 1 to 7 days after operation, which may be the protector for POD<sup>[36]</sup>. Finally, there were stable of circulation at the peri-operation, patients without serious complication, and hypo-active<sup>[5]</sup> of POD may be missed.

When BIS is maintained in a fixed range of 40–60, it can reduce the inflammation reaction and intraoperative awareness induced by light anesthesia. At the same time, it decreases the harm of hypotension and burst suppression caused by deep anesthesia. Hence the BIS monitor reduces the time of post-operation recovery ( $24.76 \pm 9.36$  vs  $29.49 \pm 9.72$ ,  $P=0.001$ ), and the length of postoperative hospitalization ( $9.99 \pm 3.94$  vs  $12.41 \pm 4.61$ ,  $P<0.001$ ), meanwhile prompt the satisfaction of patient ( $P=0.009$ ).

The lower average value of BIS group patients led to a higher intraoperative dose of anesthetic drugs. In contrast, the control group had a lower dose of anesthetic drugs and a higher dosage of vasoactive drugs due to sign of an unstable cardiovascular system, then led to an increase in sufentanil use for postoperative analgesia, which may lead to a longer recovery from anesthesia and lower satisfaction.

Furthermore, the significantly shorter postoperative recovery time and the shorter length of postoperative hospital stay in the BIS group means patients recover from surgery and diseases better. A significantly lower mortality rate after surgery was obtained in BIS group (5.4% vs 14.4%,  $P = 0.042$ ).

Finally, CRP concentration in the two groups associated with inflammation is no significant difference, which probably accounts for the mean BIS value in the standard range of 40–60. Delayed neurocognitive recovery, postoperative neurocognitive disorder, and POD were frequent complications after the operation. The detailed pathogenesis remains unclear<sup>[37]</sup>. The risk factor was increasing age<sup>[24]</sup>, poor education<sup>[5]</sup>, preoperative complications, pre-operation cognitive impairment, poor functional status, depression, alcohol abuse, the duration and type of anesthesia, homeostasis, hypotension, infection, hypoxia, pain, and so on<sup>[6, 8, 27, 36, 38, 39]</sup>. Besides, a more significant risk factor may be surgery because it has been mentioned that surgery is more likely to lead to cognitive decline than anesthetic<sup>[40]</sup>.

At present, there are no golden standard<sup>[41, 42]</sup> of diagnosis and effective treatment<sup>[36]</sup> for delayed neurocognitive recovery, postoperative neurocognitive disorder and POD. With the wide use of BIS, there are few and controversial studies on the relationship between BIS and postoperative cognitive impairment. To provide a method for the treatment of postoperative cognitive impairment. Therefore, we decided to do a prospective, randomised clinical trial to investigate whether there is a correlation between BIS and delayed neurocognitive recovery, postoperative neurocognitive disorder and POD.

In general, the operation type is single, the surgeon is fixed, and there were no ASA IV patients in the two groups, so the results are more reliable. Meanwhile, consultation and comfort are provided in time. The most important is our study involves the outcome of long-term and short-term cognitive.

There are several shortcomings in this study. Firstly, MMSE cannot accurately judge the specific brain functional areas' damage or the false-negative results of delayed neurocognitive recovery and postoperative neurocognitive disorder caused by mutual compensation of functional brain areas. Secondly, there was no other control group in the general population that excludes normal cognitive changes. Thirdly, our study included a small proportion of diabetes which was associated with POCD<sup>[43]</sup>.

## Conclusion

Delayed neurocognitive recovery and postoperative neurocognitive disorder are common reversible and long-term complications after the operation. Using BIS can decrease delayed neurocognitive recovery and postoperative neurocognitive disorder in the whole age group, and can validly cut down the postoperative hospitalisation stay, the mortality and increase the satisfaction of patients.

# Declarations

## Ethics approval and consent to participate

This trial was approved by the Medical Ethics Committee of the Second People's Hospital of Yibin (referral number 2020-055-01, 26/04/2020) and received informed consent from every patient. The study was registered prospectively with Chinese Clinical Trial Registry (ChiCTR-2000032463, 29/04/2020). The study was performed in accordance with the ethical standards of the Declaration of Helsinki.

## Consent for publication

Not applicable.

## Availability of data and materials

Data are available upon request from the corresponding author.

## Competing interests

The authors declare no competing interests.

## Funding

This study did not receive any funding.

## Authors' contributions

XQ Chen, LJ Li and DS Yu conceived, designed the study and drafted the manuscript. L Yang and AJ Li collected data. M Wu was the fixed surgeon in this study and completed the statistical analysis. All authors reviewed, revised and approved the final manuscript.

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Not applicable.

## Authors' information

The authors consider that Xingqu Chen and Linji Li should be regarded as co-first authors. Corresponding author is Deshui Yu (Email: ybanesthesia@sina.com)

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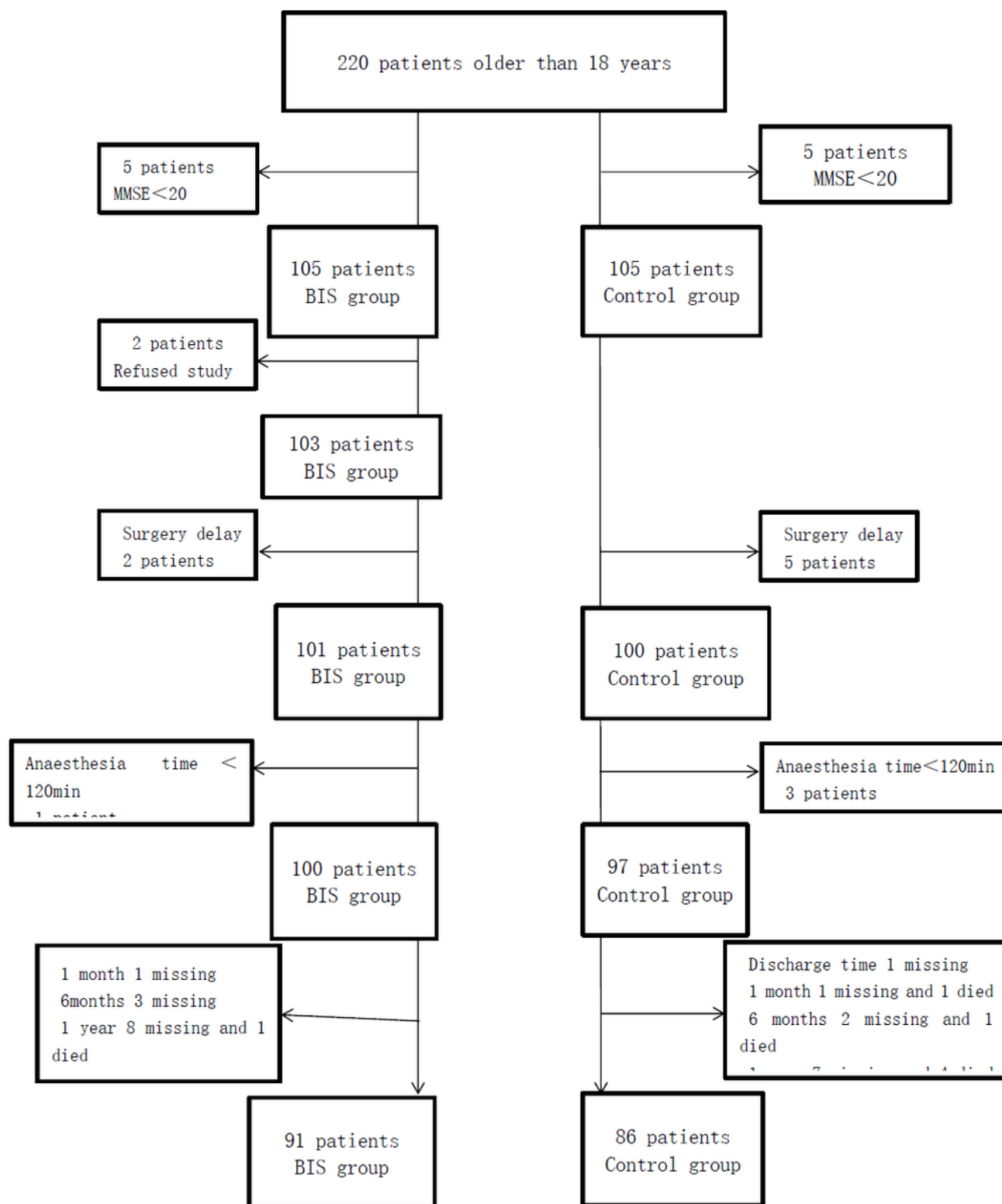
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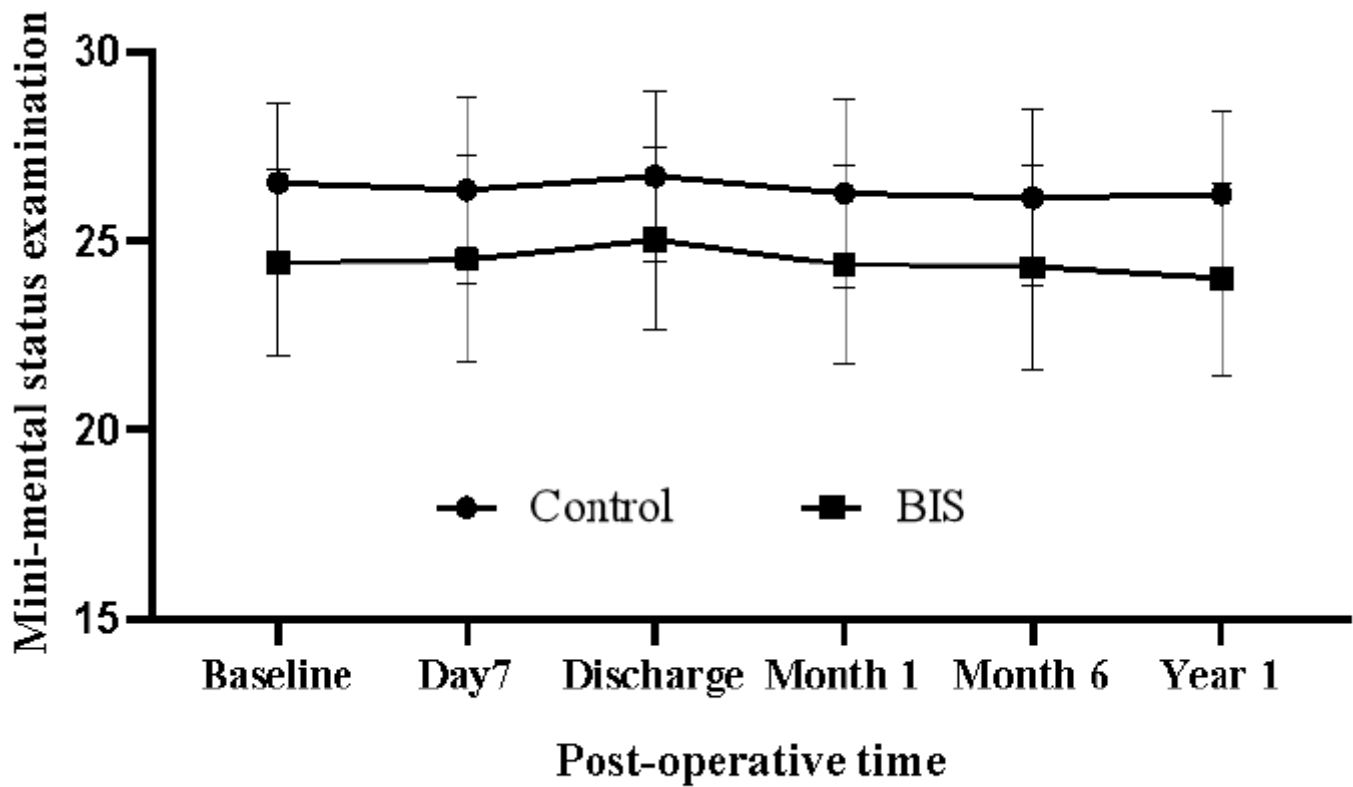
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## Figures



**Figure 1**

Flowchart of trial enrollment. MMSE, mini-mental state examination; BIS indicates bispectral index.



**Figure 2**

Figure showed the mean score of MMSE in the BIS group increased moderately until discharge time point and then decreases. At the same time, there was a decrease in the control group except for discharge time point. The result shows that the BIS value in the BIS group is lower than the control group (43.75 vs 50.69,  $P<0.001$ ).

**Supplementary Files**

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