Effects of Single Low Dose of Dexamethasone before Noncardiac and Nonneurologic Surgery and General Anesthesia on Postoperative Cognitive Dysfunction—A Phase III Double Blind, Randomized Clinical Trial

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Abstract

Postoperative cognitive dysfunction (POCD) is a multifactorial adverse event most frequently in elderly patients. This study evaluated the effect of dexamethasone on POCD incidence after noncardiac and nonneurologic surgery. METHODS: One hundred and forty patients (ASA I-II; age 60–87 years) took part in a prospective phase III, double blind, randomized study involving the administration or not of 8 mg of IV dexamethasone before general anesthesia under bispectral index (BIS) between 35–45 or 46–55. Neuropsychological tests were applied preoperatively and on the 3rd, 7th, 21st, 90th and 180th days after surgery and compared with normative data. S100β was evaluated before and 12 hours after induction of anesthesia. The generalized estimating equations (GEE) method was applied, followed by the posthoc Bonferroni test considering P<0.05 as significant. RESULTS: On the 3rd postoperative day, POCD was diagnosed in 25.2% and 15.3% of patients receiving dexamethasone, BIS 35–45, and BIS 46–55 groups, respectively. Meanwhile, POCD was present in 68.2% and 27.2% of patients without dexamethasone, BIS 35–45 and BIS 46–55 groups (p<0.0001). Neuropsychological tests showed that dexamethasone associated to BIS 46–55 decreased the incidence of POCD, especially memory and executive function. The administration of dexamethasone might have prevented the postoperative increase in S100β serum levels. CONCLUSION: Dexamethasone can reduce the incidence of POCD

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in elderly patients undergoing surgery, especially when associated with BIS 46–55. The effect of dexamethasone on S100β might be related with some degree of neuroprotection.

Trial Registration: www.clinicaltrials.gov NCT01332812

Introduction

Postoperative cognitive dysfunction (POCD) is frequently reported following general anesthesia, especially in elderly patients and after cardiac surgery. POCD was defined as a cognitive decline in two or more neuropsychology functions, according to the International Study of Postoperative Cognitive Dysfunction (ISPOCD) study group. Global cognitive function was evaluated by a neuropsychology battery, and the Z-score method was applied as a measure of cognition[1].

The ISPOCD demonstrated that in geriatric patients submitted to non-cardiac surgery under general anesthesia, this adverse event affected up to 26% of them, one week after the procedure. After three months of operation, POCD remained in up to 10% of that group[2,3]. In elderly patients, POCD increased the risk of comorbidities in the first year after surgery[4]. However, there is no consensus about precipitating factors and preventive measures for cognitive dysfunction in surgical patients. Besides age, the postoperative cognitive function may be compromised by hypoxia, hypotension, anesthetics and depth of anesthesia, surgical procedures and external factors such as quality of life[5]. Patients might present different levels of mental status. It can vary from mental confusion to memory loss. Clinically, it is shown as a decrease in the consciousness level, also known as delirium.

Surgery can result in a complex neuronal system response, which includes inflammation and may directly affect patient outcome[6]. Data support the concept that inflammation and brain injury are a possible pathogenic mechanism for POCD. S100b is a known biomarker related to brain injury. It is released into blood circulation in early stages of brain suffering when glial cells are activated [7].

Corticosteroids such as dexamethasone are often used as additional drugs in anesthesia to mitigate its side effects, such as pain, vomiting and fatigue, all of which are physical symptoms that compromise cognitive functioning[8,9]. The use of dexamethasone was never investigated as a possible protective factor against cognitive impairment in surgery.

This study aimed to evaluate the effect of dexamethasone on the incidence of postoperative cognitive dysfunction in elderly patients undergoing surgery under general anesthesia. It is registered in www.clinicaltrials.gov Identifier: NCT01332812.

Materials and Methods

Study design and subject enrollment

The study was conceived as a randomized, double-blind and prospective clinical trial. After approval by the "Comissão de Etica para Analise de Projeto de Pesquisa do Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo"(CAPPesq-HCFMUSP) S1 File, and "Comissão Nacional de Etica em Pesquisa"(CONEP) S2 File, and receiving written informed consent, 140 patients (aged 60 years or older) who were candidates for elective non-cardiac and nonneurologic surgery in a university hospital between January 2011 and February 2012 were enrolled in the study, and the neuropsychological assessment was completed in March 2013. www.clinicaltrial.gov was not realized before the beginning of the study patient recruitment period, because at that moment, in Brazil, only CAPPesq-HCFMUSP and CONEP

registrations were required for that. Later, the www.clinicaltrial.gov registration was performed. Identifier: NCT01332812.

Inclusion criteria were as follows: candidates for noncardiac and nonneurologic surgery under general anesthesia that was not expected to exceed 6 hours, no history of brain disease, dementia or other psychiatric disorders that affect cognition, literate, and no continuous use corticosteroids, antidepressants or opioids preoperatively.

The mental state was preliminarily assessed using the Mini-Mental State Examination (MMSE), which is validated for the Brazilian population as a brief screening instrument designed to measure and quantify the global cognitive state, assessing reasoning, spatial-temporal orientation, memory, and schooling. The test uses for the Brazilian people a cut-off of 18 points for subjects who have completed up to 4 years of formal academic study and 23 points for individuals with higher levels of education. Patients were excluded if they had an MMSE score below 18 or 23 by educational level[10].

Preoperative evaluation and neuropsychological assessment. Demographic data were analyzed, including education, marital status, occupation, and current medication. Signs and symptoms of depression were assessed preoperatively using the Beck Depression Inventory (BDI), which consists of 21 questions that explore depressive symptoms on a scale of 0 to 4, where zero represents no symptoms and four is the maximum symptomatology. A total of 14 points was considered indicative of the presence of moderate depressive symptoms[11]. The quality of life was investigated using the Short Form Health Survey (SF-36) to investigate health-related conditions, activities of daily living, productivity, emotional problems, relationships, and motivation, and one question about the perception of the patients itself[12].

The Telephone Interview for Cognitive Status (TICS) was used as a standardized test to assess neuropsychological functioning when assessing cognitive skills. This test was used when screening personally was impractical or when patients were unable to attend the clinic. This test consists of a structured interview with 11 items that assess the skills of spatial and temporal orientation, mental control, memory, general information, language, and calculations[13].

POCD diagnosis was performed by TICS and Neuropsychological Battery, near the seventh postoperative day.

The specific neuropsychological battery test, based on the International Studies of POCD 1 and 2 translated and adapted for the individually studied population, was performed one day before surgery (baseline) and on the 3rd, 7th, 21st, 90th and 180th postoperative day. The cognitive functions assessed were memory, attention and executive function in aspects such as strategy, elaboration of thought and inhibiting the control of actions. Tests used for the evaluation of these skills are redundant, especially for the assessment of attention.

Memory was evaluated using the Rey-Auditory Verbal Learning Test (RAVLT), which consists of a list of 15 words to be memorized and recalled on three successive attempts, with delayed recall after 15 to 25 minutes, evaluating the number of words recalled and the number of errors made for each presentation[14].

The Symbol Digit Modified Test (SDMT) was applied for the evaluation of short-term memory, visual search skill, and attention. SDMT is a graphical task where the individual has to fill in symbols exemplified in the spaces below the corresponding number within 180 seconds. The result is measured as the number of symbols drawn and the number of errors[14].

Attention was also evaluated using the Trail Making Test (TMT) for the assessment of selective and alternating attention. In part A of the test, the subject must consecutively draw lines connecting numbered circles. In part B, the subject must draw lines connecting circles alternately with letters and numbers in a sequence. The result is measured as time and trail errors [14].

Criteria for POCD diagnosis. TICS values were used to evaluate the evolution of general cognition postoperatively and were applied in every phase's pre and postoperatively. For the diagnosis of POCD, a composite cognitive index was established defined by the occurrence of cognitive impairment in TICS and at least 1 of 8 possible deficits of the others neuropsychologist tests. Changes in neuropsychological tests have been compared with the results of tables of normative subjects matched for age, gender, and formal education[15].

Assessment of serum levels of S100β. Serum levels of S100β protein were obtained from venous blood samples collected before anesthesia induction and 12 hours after surgery. Samples were placed in dry tubes and centrifuged; serum was removed and stored to -80°C until the analysis; and S100β protein was measured by a commercially available S100β enzyme-linked immune absorbent assay, (ELISA) kit (Diasorin, Italy). A quantitative monoclonal 2-site ELISA microplate assay in which the last antibody added to the reaction system is labeled with peroxidase. After the addition of a peroxidase substrate, the reaction produces a final color product read in a spectrophotometer. S100β levels were expressed as micrograms per milliliter [16].

Randomization and anesthesia technique. Immediately before anesthesia induction patients were randomized to receive or not 8 mg of dexamethasone, stratified into subgroups according to the bispectral index (BIS) and allocated into BIS 46–55 or 35–45 subgroups inside the operating room. The randomization was performed using the website http://www.randomizer.org/form.htm, recorded on paper and stored in sealed opaque envelopes to be opened in the operating room. Anesthesiologists were aware of the BIS allocated arm when the patients entered in the operating room, but patients, neuropsychologists, laboratory technicians and outcome assessors involved in the study were kept blinded to the stratification group to which each patient belonged. The study groups were identified only after the evaluation of all patients and statistical analysis.

In the operating room, standard monitoring included continuous registration of electrocardiogram at DII, pulse oximetry, non-invasive blood pressure, end tidal CO_2 and bispectral index (BIS). General anesthesia was induced with propofol (1.0–2.5 mg/kg), fentanyl (2.0–3.0 μg/kg) and cisatracurium (0.10–0.2 mg/kg). Maintenance of anesthesia was performed with propofol target-controlled infusion according to Schneider's pharmacokinetic model for the intended BIS-value subgroup. The remifentanil (0.10 to 1.0 μg/kg/ min) or fentanyl (intermittent doses of 2.0–3.0 μg/kg) were added according to anesthesiologist judgment, plus cisatracurium in supplemental doses (0.03–0.05 mg/kg). Glycaemia was controlled perioperatively; after anesthesia induction. Insulin was given when blood glucose concentrations exceeded 180 mg/dL. At the end of surgery and after tracheal extubation, patients were transferred to the post-anesthesia care unit. The control of postoperative pain was conducted following institutional protocols.

The CONSORT criteria (www.consort-statement.org) was followed S3 File.

Statistical analyses

It was estimated a sample size of 138 patients in the study. The sample size was based upon a 40% POCD incidence in elderly patients as previously described in the literature[17]. As was showed before, there is a possible improvement of 20% in POCD with dexamethasone use during surgery[18]. It was considered a maximum error of 5%, and a statistical power of 80%. The results of neuropsychological tests used to evaluate cognitive function were described for the two groups; each one stratified in two arms. The tests values were analyzed according to the 6 phases of evaluation (Fig 1). The interaction between time point and groups were tested. The results were shown as means and standard deviation. The comparison between the four groups,

| | | CONTROL GROUP | | | | DEXAMETHASONE GROUP | | | | p-value | | |
| | | BIS 35-45 (N=40) | | BIS 46-55 (N=32) | | BIS 35-45 (N=36) | | BIS 46-55 (N=32) | | | | |
	Day	Mean ± SD	POCD%	Mean± SD	POCD%	Mean± SD	POCD%	Mean ± SD	POCD%	Group	Time point	Interaction
TICS	POp	28.3±1.5	---	28.3±1.3	---	28.3±1.6	—	28.1±1.6	---			
	3rd	22.5±2.1	68.2	25.8±3.8	27.2	26.8±4.6	25.2	26.7±5.5	15.3	<0.001	<0.001	<0.001
	7th	23.7±1.2	35.3	24.7±1.3	21.2	29.5±4.7	22.1	31.3±4.6	18.5			
	21st	23.0±2.0	44.2	25.5±4.6	37.2	30.4±3.6	2.3	32.5±1.4	---			
	90th	24.8±2.2	21.6	28.8±3.9	9.1	31.0±3.6	2.2	33.0±3.7	---			
	180th	25.4±2.6	25.3	26.7±3.7	21.7	31.2±3.1	3.1	32.6±1.6	---			
RAVLT Immediate	POp	5.3±1.8	---	5.2±1.8	---	5.3±1.8	—	5.2±1.7	---			
	21st	4.3±1.4	37.5	5.3±1.9	21.8	6.2±2.4	5.4	6.3±1.9	9.3	<0.001	<0.001	0.002
	180th	5.6±1.3	74.6	5.8±1.1	53.4	6.6±1.8	2.7	6.4±2.0	3.1			
RAVLT Delay	POp	6.1±2.5	---	6.5±2.9	---	5.8±2.3	—	6.4±3.0	---			
	21st	5.8±1.3	42.5	6.1±3.1	18.7	9.2±5.0	11	9.1±1.7	---	<0.001	<0.001	<0.001
	180th	6.0±2.3	20.5	7.0±2.0	28.2	8.7±2.5	2.7	7.8±2.7	---			
TMT-A	POp	84.3±39.2	---	84.4±19.7	---	79.6±23.3	—	99.6±32.8	---			
	21st	77.0±43.1	52.5	149.8±90.7	37.3	146.4±87.5	8.3	64.1±20.1	6.2	<0.001	<0.001	<0.001
	180th	76.5±39.4	77.5	122.8±74.8	34.1	80.9±42.4	13.8	78.3±37.1	9.3			
TMT-B	POp	153.0±60.6	---	169.8±54.2		162.8±54.4	—	186.8±59.3	---			
	21st	224.2±122.9	32.5	258.8±150.0	31.1	202.4±93.4	24.8	140.1±70.9	9.3	<0.001	<0.001	<0.001
	180th	179.0±87.4	42.5	255.2±124.9	31.2	105.5±38.5	8.2	145.0±66.6	6.2			
SDMT	POp	34.4±17.0	---	39.5±19.5	---	28.0±16.6	—	34.3±21.0	---			
	21st	39.2±17.7	22.5	30.3±14.9	16.3	30.1±20.9	24.3	50.4±14.0	6.2	0.058	<0.001	<0.001
	180th	37.7±8.5	16.5	44.6±22.8	5.1	54.8±24.2	—	50.5±22.3	---			
SF-36 General Health	POp	84.0±7.1	---	84.5±7.5	---	83.2±9.7	—	81.5±8.9	---			
	21st	75.5±15.3	---	74.5±14.4	---	75.9±16.0	—	73.4±15.7	---	0.966	<0.001	0.851
	180th	70.3±17.1	---	69.3±21.8	---	72.1±18.1	—	73.0±14.0	---			
SF-36 Mental Health	POp	76.7±11.4	---	75.5±12.0	---	78.1±9.5	—	76.2±20.8	---			
	21st	71.7±22.8	---	66.1±13.8	---	73.4±15.4	—	75.2±15.8	---	0.007	<0.001	0.048
	180th	64.3±22.1	---	63.2±19.5	---	76.6±13.7	—	75.6±12.1	---			
BDI	POp	4.6±2.9	---	4.9 ±3	---	4.6±3.4	—	4.7±2.5	---			
	21st	9.8±6.0	---	11.0±8.4	---	6.7±6.0	—	6.3±4.4	---	<0.001	<0.001	0.013
	180th	9.7±6.6	---	14.2±9.9	---	8.1±4.4	—	5.8±3.4	---			

Fig 1. Pre and postoperative results of the specific test: for global cognitive, memory, attention, executive functions, and Quality of life and depressive symptoms, compared to normative data [a]. BIS: bispectral index; POCD: postoperative cognitive disorder; TICS: Telephone interview for cognitive status; RAVLT immediate: Rey Auditory- verbal learning test (immediate); RAVLT delay: Rey Auditory- verbal learning test (delay); TMT-A: Trail making test- A; TMT-B: Trail making test-B; SDMT: symbol digit modalities—Test; SF-36 general health: Short form health survey (general health); SF-36 Mental Health: Short form health survey (mental health); BDI: Back depression inventory. [a] Normative values. Data are mean ± SD and percentage for patients with POCD. TICS: 27±3; VLT: immediate 6.3±2.1; delay 10.2±2.5; TMT-A $\geq$ 55 and TMT-B $\geq$137; SDMT 50.1±8.1; SF-36 scale >60±10; BDI <12; Pop = Preoperative; Postoperative days = 3rd; 7th; 21st; 90th and 180th; [b] *p-value for the Generalized Estimating Equations (GEE).

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according to the six evaluation phases were analyzed by using Generalized Estimation Equation (GEE). Data was evaluated under the intention to treat analysis[15].

Changes in neuropsychological tests have been compared with the results of the table of normative subjects (Fig 1), matched for age, gender, and formal education, using Z-score analysis[19]. General linear mixed modeling was applied. Imputation treated the Missing data,

which did not exceed 12%. Bonferroni multiple comparisons were used to complete the evaluation Statistical calculations. They were performed using SPSS12 and GraphPad Prism version 6.00 for Mac (GraphPad Software, La Jolla California USA www.graphpad.com).

Results

Three hundred and six patients were recruited for elective surgery under general anesthesia, but 83 patients were excluded because they are not in the inclusion criteria or declined to participate in the study or for other reasons not justified by the patient. Two hundred and twenty-three patients were assessed with the MMSE cognitive screening test, and 27 patients were excluded after failing to normative score (≤ 18 or ≤ 23 points) according to education levels. One hundred and ninety-six patients were assessed using neuropsychological battery tests adapted from ISPOCD and 140 patients were ultimately randomized and evaluated under the intention to treat[15] analysis up to an 180th postoperative day (Fig 2).

There was no statistical difference between groups concerning baseline and demographic data (Fig 3), and the intraoperative data are shown in (Fig 4). No reports of intraoperative recall were related. The mean bispectral index values were comparable between groups at baseline but differed according to anesthesia procedure (Fig 4). The results for global cognitive function evaluated by TICS (Fig 1) showed that the highest incidence of POCD on the 3rd postoperative day was observed in the BIS 35–45 group without preoperative dexamethasone shot (68.2%, p<0.0001). After six months, the same group showed the highest incidence of POCD, although the cognitive function improved compared to 3rd postoperative day (25.3%, p<0.0001). The group receiving BIS 46–55 and dexamethasone at anesthesia induction showed the lowest incidence of POCD during the study. Their global cognitive function according to TICS was recovered on the 21st, 90th and 180th postoperative days. The cut-off point was (27 ± 3) and the three cited postoperative days presented the values (32.5±1.4; 33±3.7 and 32.5±1.6), respectively.

Regarding memory function (immediate and delayed) assessed via RAVLT, Cognitive dysfunction was most impaired in the groups without dexamethasone, independently of their BIS group. There was a significant difference during postoperative phases between groups for immediate memory (p = 0.0002) and delayed recall (p = 0.001). Regarding immediate memory, the highest incidence of dysfunction was observed on the 180th day. (74.6% and 53.4%) For both groups: BIS 35–45 and BIS 46–55, respectively. For delayed recall the most impaired cognitive function was 42.5% in the BIS 35–45 group without dexamethasone on the 21st day. The BIS 46–55 plus dexamethasone group showed no dysfunction for delayed recall. For the Selection Attention Function assessed by the TMT in part A, Group BIS 35–45 without dexamethasone presented cognitive dysfunction in 77.5% (p<0.0001) on the 180th day. Meanwhile, its group ability to toggle attention, assessed by TMT part B showed an 42% of impairment on the 180th day (p = 0.001). For executive function, visual and motor skills, evaluated by the SDMT, The groups receiving dexamethasone showed no executive dysfunction on the 180th postoperative day (Fig 1).

Based on the SF-36 results, (Fig 1), all groups showed general good health at the end of the study (p = 0.09). All groups showed the absence of depressive symptoms in the preoperative assessment. At the end of the study, the group who received dexamethasone and BIS 46–55 showed a lower mean for depressive symptoms (5.8±3.4) assessed by the BDI (Fig 1).

S100β serum levels were significantly increased 12 hours after surgery in patients without dexamethasone submitted to either BIS 35–45 or BIS 46–55 (p<0.05) (Fig 5).

Discussion

This study found that patients receiving a single dose of dexamethasone at induction of anesthesia presented a lower incidence of postoperative cognitive dysfunction. When this
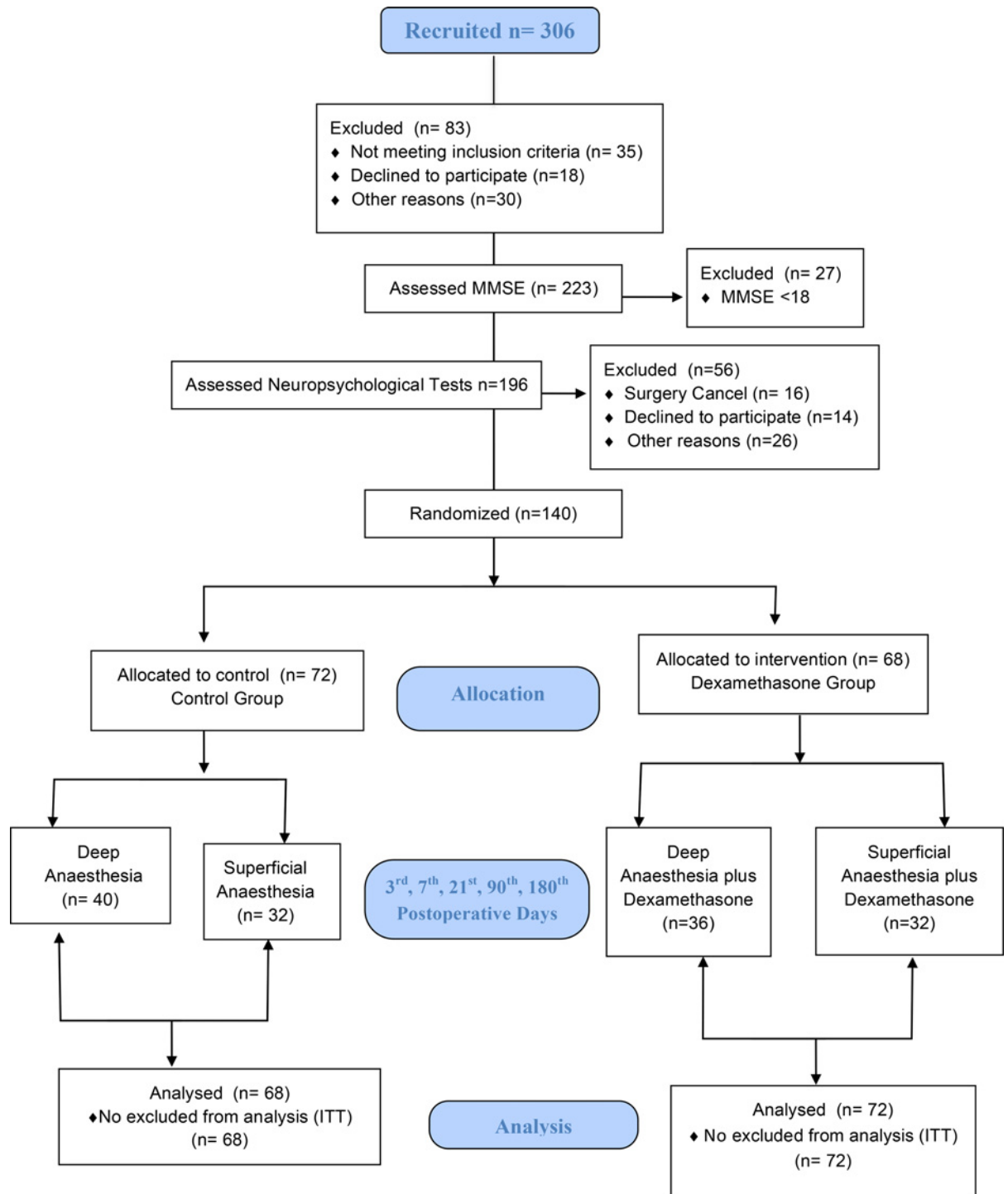
Fig 2. Study Fluxogram. MMSE: Mini-Mental State Examination; ITT: Intention to treat.

corticosteroid was associated with BIS 46–55 rather than BIS 35–45, their cognitive functions established more rapidly. A better quality of life was also observed in the postoperative period in the dexamethasone groups, as a lower incidence of depressive symptoms.

| | CONTROL GROUP | | DEXAMETHASONE GROUP | | |
	BIS 35-45 (N=40)	BIS 46-55 (N=32)	BIS 35-45 (N=36)	BIS 46-55 (N=32)	*p-value
Gender, % female	52.5	74	58.3	59.4	0.84
Age (years)	67.2±5.2	68.7±7.7	68±6.3	69.2±5.3	0.96
Height (cm)	163.3±8.2	158.7±9.3	158.7±9.3	161.9±9.1	0.06
Weight (kg)	71.8±13.4	65.4±13	72.1±12.5	71.1±14	0.14
Body mass index (kg/m²)	28.6±5.5	25±5	29.4±5	27.2±5	0.03
Years of education	5±4.7	4.8±5	3.8±4	5.4±5.5	
1-3 years, %	54.0	61.3	72.2	69.2	0.93
4-11 years, %	25.0	22.5	16.8	10.3	
> 12 years, %	20	16.1	11.0	16.8	
Income**	2.7±2	2.5±3	2.5±2.3	2.2±2.7	
1 salary, %	85	77.4	66.7	80	
2 salaries, %	2.5	---	2.8	---	0.34
6 salaries, %	10	13	30.5	13.3	
10 salaries, %	2.5	9.7	---	6.7	
Marital status					
Married, %	57	54.8	55.5	56.2	
Single, %	10	6.4	8.3	9.4	0.91
Divorced, %	7.5	6.4	8.3	9.4	
Widower, %	25	32.2	28	25	
Employment					
Employee, %	17.5	3.2	11.1	15.6	
Retired, %	72.5	74.2	69.4	68.7	0.52
Unemployment, %	10	22.6	19.4	15.6	
MMSE	23.5±3.2	24.5±3.5	25.2±3	24.6±3	0.65

Fig 3. Baseline and demographic data. MMSE: Mini-Mental State Examination; *p-value >0.05; **Salary rates equivalent to current Brazilian minimum salary in 2012 ($331.129 USD); *** Data are mean ± SD or per cent.

In anesthesia practice, patients who have postoperative injuries, such as pain, nausea, and vomiting return to daily activities in more time than patients who presented fewer postoperative symptoms. Nowadays, dexamethasone is commonly used in the perioperative setting by anesthetists, both for its antiemetic properties and its ability to reduce airway swelling and fatigue. Our findings corroborate some of the observations made in other studies on corticosteroids such as the decrease in the postoperative recovery time. The inhibitory effect of dexamethasone on inflammation could also prevent some undesirable neuropsychological adverse events such as cognitive dysfunction, delirium, and even stroke[8,20]. Until now, no specific study have evaluated the possible effects of dexamethasone on the incidence of POCD in patients undergoing general surgery.

Although some controversy remains, several authors were able to demonstrate a relationship between the degree of cognitive dysfunction and S100β protein[6,21], which is consistent with our present findings. In the present study, S100β postoperative injuries serum levels were significantly elevated after surgery regardless BIS values. The glial cells are activated, In the early stages of brain injury, and S100β is released into blood circulation[7]. The dexamethasone group presented a smaller incidence of cognitive dysfunction. During surgical procedures without direct brain involvement; S100B increase might be due a variety of clinical states that might cause BBB disruption[20,22].

In our study, an enormous neuropsychological battery evaluated the cognitive function. Some cognitive functions are assessed by more than one test. So, we have chosen a specific test

| | CONTROL GROUP | | DEXAMETHASONE GROUP | | |
	BIS 35-45 (N=40)	BIS 46-55 (N=32)	BIS 35-45 (N=36)	BIS 46-55 (N=32)	*p-value
Heart rate					
After induction	72.2±12.52	71.9±15.7	72.3±12.3	71.4±14.4	0.93
Before induction	68±14.4	67±14.3	71±11.6	68.6±13.7	0.63
End of surgery	64.2±13	65.2±9.4	67.4±11.5	66.6±11.3	0.65
Systolic Blood Pressure (mmHg)					
Before induction	148.1±27	149.6±21	157.1±27	157.3±17.1	0.13
After induction	112.3±26	107±26.1	100±25.4	112.5±33.6	0.64
End of surgery	112.2±21.1	122.6±22.5	112±21.3	117±25.3	0.65
Diastolic Blood Pressure (mmHg)					
Before induction	82±15.2	83.7±13	88±15.2	84.5±11.6	0.15
After induction	65±18	61±15	60.3±16.1	65.5±16	0.13
End of surgery	64±14.2	67±13.5	65.6±12.4	65.5±15	0.83
Pulse Oximetry (%)					
Before induction	96.2±1.5	96.2±1.7	96.2±2	96±2.5	0.84
After induction	98.1±1	98.1±1	98.2±1	98.2±1.5	0.98
End of surgery	97.5±1.6	98±1	97.6±1.4	98±1.3	0.86
Temperature (ºC)					
Before induction	35.5±1.4	35.3±2.4	35.6±1	36.3±1.5	0.47
After induction	35.5±1.3	35.9±1	35.8±0.6	35.9±0.4	0.23
End of surgery	35.8±0.5	35.6±1.2	35.6±1.1	35.8±0.6	0.63
Volume Replacement (mL)					
	1969.5±750.4	1942±661.2	1859.7±524.4	1787.5±605.8	0.63
Blood Glucose (mg / dl)					
1st hour	127.1±42.1	102±17	111±20.6	119.2±27	0.12
2nd hour	126±72.1	108±10.1	120.4±29.1	136±40.5	0.53
3rd hour	82±9.07	110±17	127±20.2	145±35.6	0.15
Length of Surgery (min)	136.7±50.3	173.3±171.3	141.7±37	150.6±56	0.43
Length of Anaesthesia (min)	209±62.4	221.3±94.4	220±49.8	222.1±62.3	0.84
Anaesthetic drugs					
Midazolam (mg)	2.0±0.6	1.7±0.4	2.1±1	2.1±0.9	0.31
Propofol (mg)	1093.2±451.5	855.4±509.6	1051.5±405.6	931.8±411.7	0.15
Fentanyl (μg)	370.7±223.9	328.2±173.8	305.5±117	312.5±128.2	0.35
Remifentanil (μg)	2068.3±9440.9	1282.3±703.1	1682.4±1146.9	1465.5±1106	0.01
Cisatracurium (mg)	12.7±3.3	14.1±4.1	12.7±3.7	12.8±4.2	0.34
BIS					
Awake	97.1±1.9	96.7±2.9	95.8±4.2	97±1.9	0.22
1th hour	38±5.5	49.1±11.1	36.7±5.2	46.6±13.4	<0.0001
2nd hour	41.2±8.1	46.2±5.4	38.6±8.8	47.5±11	0.001
3rd hour	44±11.1	48.4±13.5	47.1±18.7	59.9±17.8	0.03

Fig 4. Intraoperative data. Data are mean ± SD; BIS: bispectral index; *p-value for the Generalized Estimating Equations (GEE).

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for each cognitive function evaluation. It is not a big limitation but a concern regarding data analysis. We have tried to avoid data duplication that might lead to an overestimation of cognitive function impairment. For example, the selective attention was evaluated only by TMT-A. The long-term memory was assessed only by VLT.

| Biomarkers | Moment | CONTROL GROUP | | DEXAMETHASONE GROUP | |
		BIS 35-45 (N = 40)	BIS 46-55 (N=32)	BIS 35-45 (N=36)	BIS 46-55 (N=32)
S100β (µg/l)	Baseline	Mean± SD 0.06±0.06	Mean± SD 0.06±0.03	Mean± SD 0.11±0.10	Mean± SD 0.08±0.02
	Post Anesthesia	0.23±0.32*	0.24±0.31*	0.10±0.11	0.14±0.29

Fig 5. S100β serum level. BIS: bispectral index; Mean ± SD: Mean ± standard deviation. * = $p<0.05$ as compared to baseline biomarkers S100β level.

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Our study found significant differences between groups concerning the BIS values. POCD incidence was increased in BIS 46–55 compared to BIS 35–45. The data also showed a more rapid cognitive function restoration in the last group, mainly in the group that received dexamethasone. We can suggest that anesthesia depth might influence the POCD grade and its recovery. Some other studies have shown that superficial anesthesia may benefit the patient and prevent postoperative cognitive dysfunction[23,24].

Although our study demonstrated the benefit of dexamethasone associated with BIS 46–55 regarding prevention of cognitive dysfunction, other factors should be investigated. Demographic data might have a significant influence on cognitive reserve. People with a higher educational level tend to be healthier than people with a lower educational level old age, and comorbidities may contribute as risk factors for POCD. Cognitive decline is inevitable during the aging process, but this impairment may also be associated with surgery and anesthesia.

One limitation of the current study was the loss of follow-up for some patients. Sometimes, they were not able to attend the assessments face to face in the hospital.

In conclusion, dexamethasone when administered with BIS 46–55 can help to preserve most cognitive functions in surgery. Additional studies could contribute to defining the neuroprotective properties of dexamethasone in the prevention of postoperative cognitive dysfunction in patients undergoing surgery.

Supporting Information

S1 File. CAPpesq appoval.
(DOCX)

S2 File. Cappesq_no99806_Disfuncao_Cognitiva-TODOS_OS_DOCUMENTOS 5.
(ZIP)

S3 File. CONSORT Checklist Completed 021216.
(DOC)

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Author Contributions

Conceived and designed the experiments: LSSV VFAP MJCC RSP. Performed the experiments: LSSV VFAP APS LVP JRNV VFL. Analyzed the data: LSSV VFAP RSP APS VFL JRNV MJCC

KCN LMSA. Contributed reagents/materials/analysis tools: APS DOZ LVP JPO. Wrote the paper: LSSV VFAP.

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