Effects of Dexamethasone on Cognitive Decline after Cardiac Surgery

A Randomized Clinical Trial

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ABSTRACT

Background: Cardiac surgery can be complicated by postoperative cognitive decline (POCD), which is characterized by impaired memory function and intellectual ability. The systemic inflammatory response that is induced by major surgery and cardiopulmonary bypass may play an important role in the etiology of POCD. Prophylactic corticosteroids to attenuate the inflammatory response may therefore reduce the risk of POCD. The authors investigated the effect of intraoperative high-dose dexamethasone on the incidence of POCD at 1 month and 12 months after cardiac surgery.

Methods: This multicenter, randomized, double-blind, placebo-controlled trial is a preplanned substudy of the DExamethasone for Cardiac Surgery trial. A total of 291 adult patients undergoing cardiac surgery with cardiopulmonary bypass were recruited in three hospitals and randomized to receive dexamethasone 1 mg/kg (n = 145) or placebo (n = 146). The main outcome measures were incidence of POCD at 1- and 12-month follow-up, defined as a decline in neuropsychological test performance beyond natural variability, as measured in a control group.

Results: At 1-month follow-up, 19 of 140 patients in the dexamethasone group (13.6%) and 10 of 138 patients in the placebo group (7.2%) fulfilled the diagnostic criteria for POCD (relative risk, 1.87; 95% CI, 0.90 to 3.88; $P = 0.09$). At 12-month follow-up, 8 of 115 patients in the dexamethasone group (7.0%) and 4 of 114 patients (3.5%) in the placebo group had POCD (relative risk, 1.98; 95% CI, 0.61 to 6.40; $P = 0.24$).

Conclusion: Intraoperative high-dose dexamethasone did not reduce the risk of POCD after cardiac surgery. **(ANESTHESIOLOGY 2014; 121:492-500)**

PATIENTS who undergo cardiac surgery are at risk of postoperative cognitive decline (POCD). POCD is defined as a decrease in performance on neuropsychological tests after undergoing surgery.[1,2] Clinically, patients may experience impaired memory function and intellectual abilities. POCD negatively affects quality of life and is associated with prolonged hospitalization and increased use of healthcare resources.[3,4] The incidence of POCD widely varies across different studies, depending on timing of assessment, measuring methods, and criteria defining cognitive decline. Previous studies reported an incidence of POCD between 8 and 50% at 2 months after cardiac surgery.[1,5]

Postoperative cognitive decline after cardiac surgery has been attributed to cerebral microemboli originating from cardiopulmonary bypass (CPB). However, randomized studies have not demonstrated that avoiding CPB improves

What We Already Know about This Topic

- Postoperative cognitive decline occurs in some individuals after major surgery, including cardiac surgery
- Although the etiology of postoperative cognitive decline is obscure, systemic inflammation may be a contributor

What This Article Tells Us That Is New

- In a preplanned secondary analysis of 291 cardiac surgical patients randomized to receive perioperative dexamethasone or placebo, the treatment groups did not differ in the incidence of postoperative cognitive decline 1 or 12 months after surgery
- These results fail to support the use of dexamethasone to prevent postoperative cognitive decline in heart surgery patients

This article is featured in "This Month in Anesthesiology," page 3A. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Preliminary results of this work have been presented during a lecture at the Annual Meeting of the European Association of Cardiothoracic Anaesthesiologists, Barcelona, Spain, June 8, 2013.

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cognitive outcome.[6–9] An alternative explanation is that the systemic inflammatory response, induced by the surgery itself and also by the use of CPB, is responsible for POCD.[10] Although there is evidence that the inflammatory response to cardiac surgery is associated with transient cerebral edema[11,12] and disruption of the blood–brain barrier,[13,14] the evidence that this results in POCD is circumstantial. Grocott *et al.*[15] reported an association between postoperative hyperthermia, potentially related to an enhanced inflammatory response, and POCD in 300 patients undergoing coronary artery bypass surgery. After sepsis, cognitive deterioration is believed to be in part because of the systemic inflammatory response.[16,17] Data from animal models suggest that major surgery disrupts the blood–brain barrier and causes cognitive dysfunction.[18,19]

During cardiac surgery, high doses of corticosteroids can be used to suppress the postoperative inflammatory response syndrome.[20] The DExamethasone for Cardiac Surgery (DECS) trial, published in 2012, failed to demonstrate a beneficial effect of dexamethasone on major complications after cardiac surgery but found that patients receiving dexamethasone had a shorter hospital stay and a lower risk of postoperative delirium and infections.[21] If inflammation plays a role in the pathogenesis of POCD, suppression of the inflammatory response could potentially reduce the incidence or severity of POCD. Dexamethasone is a potent synthetic glucocorticoid with a long duration of action; its biological half-life is approximately 36 to 54 h.[22] Dexamethasone suppresses the release of proinflammatory cytokines and acute-phase mediators in patients exposed to cardiac surgery with CPB.[23,24]

In this study, we assessed the effect of an intraoperative high dose of dexamethasone on cognitive outcome of patients who underwent cardiac surgery with the use of CPB. We hypothesized that the incidence of POCD at 1 month after surgery would be lower in patients who received dexamethasone compared with those who received placebo.

Materials and Methods

Study Design and Participants

This study on the effect of dexamethasone on the occurrence of POCD was carried out as a preplanned substudy of the DECS trial (ClinicalTrials.gov registration no. NCT00293592). The DECS trial was a multicenter, randomized, double-blind, placebo-controlled, parallel-arm study conducted in The Netherlands. The DECS trial studied the effect of dexamethasone on major perioperative complications after cardiac surgery. A detailed report of the DECS trial has been published in 2012.[21] The Institutional Review Board of the University Medical Center Utrecht, as well as the Institutional Review Boards of each of the participating centers, approved this specific substudy, which adhered to all relevant national laws and guidelines. All patients gave written informed consent. This substudy was carried out at three of the eight DECS trial centers (University Medical Center Utrecht, Utrecht, The Netherlands; Erasmus University Medical Center, Rotterdam, The Netherlands; and Isala Clinics, Zwolle, The Netherlands). Between August 2010 and October 2011, patients planned for elective cardiac surgery who participated in the DECS trial in one of these centers were invited to undergo neuropsychological testing before surgery and at 1 and 12 months after surgery. Exclusion criteria were significant impairments of vision, hearing or motor skills (such as hemiplegia), and mental illness that precluded the ability to complete the baseline cognitive assessment. Patients who had already given informed consent but could not complete a baseline assessment were excluded from this substudy. As per the inclusion criteria of the parent trial, all patients underwent cardiac surgery with the use of CPB.

Randomization and Masking

Patients were randomized (1:1) to receive a single IV bolus of dexamethasone (1 mg/kg, maximum 100 mg) or placebo (NaCl 0.9%), administered by the attending anesthesiologist, shortly after induction of general anesthesia. The pharmacy of the University Medical Center Utrecht prepared the trial medication in computer-randomized blocks of 40 sequentially numbered, indistinguishable vials, containing a clear solution of either dexamethasone 20 mg/ml or NaCl 0.9%. Patients, their treating physicians, and the investigators were blinded for treatment allocation.

Surgery and Anesthesia

The anesthetic technique was based on either total IV anesthesia or a combination of IV opioids and muscle relaxants in combination with volatile anesthetics. Antegrade crystalloid cardioplegia with St. Thomas solution was used. The use of corticosteroid-containing solutions for cardioplegia or bypass circuit prime was not allowed. Access to the heart was achieved *via* a median sternotomy. The CPB machines generated nonpulsatile flow and were equipped with microporous membrane oxygenators with integrated 40-μM arterial line filters (Quadrox I; Maquet, Rastatt, Germany) and heparin-coated circuits (Bioline; Maquet). Blood gas management was according to the α-stat principle. Direct retransfusion of cardiotomy blood was allowed, also if a cell-saver device was used. Heparin and protamine were used for anticoagulation and reversal of coagulation, respectively. Body temperature was reduced to 34°C during CPB, followed by rewarming to a rectal temperature of more than 35°C before separation from CPB.

Neuropsychological Testing

The cognitive outcome was determined by administering a battery of five neuropsychological tests, including eight main variables at 1 day before surgery and 1 month and 12 months after surgery. The battery included the tests recommended in the Statement of Consensus on the Assessment of Neurobehavioral Outcomes after Cardiac Surgery.[25] The test battery was designed to measure short- and intermediate-term memory, attention and concentration, and psychomotor skills. An alternative list of words was used every time

the Rey Auditory Verbal Learning task was administered to minimize learning effects (for an explanation of the different tests and the cognitive domains covered, see table 1, Supplemental Digital Content 1, http://links.lww.com/ALN/B58).

Research assistants, who were extensively trained for this specific test battery by an experienced neuropsychologist, carried out the neuropsychological tests. A strict, written test protocol was used to minimize interobserver variability. The test battery took 30 to 40 min to complete. Patients who were unable to come to the hospital for follow-up were tested at home.

Control Group

In studies that use repeated neuropsychological tests, misinterpretation of the outcome can be caused by practice effects and natural variation in cognitive test performance.[26] To control these effects, we recruited 54 age- and sex-matched volunteers from the cardiology outpatient clinic. These volunteers in the control group had documented coronary artery or valve pathology, but they either did not need surgery because they were managed medically, did not want to undergo surgery, or were followed up by the cardiologist because they underwent a cardiac intervention in the past. Volunteers were tested with the same test battery and protocol, by the same investigators as the trial participants, at baseline and 1-month follow-up.

Outcome

Primary Outcome Measure. The primary endpoint of this secondary analysis was the incidence of POCD at 1 month after surgery, defined as a decline in performance on neuropsychological assessment beyond natural variation. We used Jacobson and Truax Reliable Change Index (RCI) to control natural variation and practice effects in cognitive test performance, as measured in the control subjects. To calculate the RCI for an individual patient, the baseline score from each test was subtracted from the follow-up score, giving Δ_x. The same was done in the control group, giving Δ_{xc}. The mean change on that test in the control group was then subtracted from Δ_x to eliminate practice effects. To create an *Z*-score, and to eliminate the effect of natural variation in test performance, this result was then divided by the SD of Δ_{xc}. The RCI is the result of the sum of the *Z*-scores of all tests, divided by the SD of the sum of the *Z*-scores in the control group SD [$\Sigma Z_{control}$]. We defined POCD in an individual patient as an RCI equal to or less than −1.96, or *Z*-score equal to or less than −1.96 in at least two different tests.[26] Patients who had a postoperative stroke within the 1-month observation period were also scored as POCD cases. Stroke was defined as a new clinical neurologic deficit and signs of new ischemic cerebral infarction on a computed tomography scan or magnetic resonance imaging scan. Stroke cases were evaluated by the parent trials' critical event adjudication committee.

Secondary Outcome Measures. The incidence of POCD at 12-month follow-up was measured using the same criteria as described in the previous alinea. In addition to the dichotomized cognitive outcome at both time points, we also directly compared the (continuous) RCI. A positive RCI value indicates improvement, whereas a negative value indicates decline in cognitive test performance.

Statistical Analysis

Analyses were conducted according to randomization. For the primary outcome (incidence of POCD at 1-month follow-up), we calculated the relative risk (RR) with 95% CI and tested the between-group difference in incidence using the chi-square test. For comparison of mean and median values of the continuous secondary outcome measures, we used Student *t* test or Mann–Whitney U test, as appropriate.

Because the number of patients lost to follow-up was relatively small, we report a complete case analysis of the primary outcome. To study the effects of loss to follow-up, we performed an extreme case analysis, where first all patients in the placebo group and then all patients in the dexamethasone group who were lost to 1-month follow-up were counted as POCD cases. In both groups, patients who had died were counted as POCD cases as well.

A preplanned subgroup analysis for the primary outcome was performed for two age groups (cutoff value based on the median age of the study population), sex, and isolated coronary artery bypass surgery *versus* other types of surgery. To assess heterogeneity in the subgroup analyses, logistic regression analysis was performed with a 0.10 threshold for significance. In all other analyses, we considered a *P* value of 0.05 to be statistically significant. All conducted hypothesis tests were two sided. We used IBM SPSS version 19 (IBM SPSS, Armonk, NY) for all analyses.

In one of our previous studies on POCD after cardiac surgery, we randomized 281 patients to coronary artery bypass surgery with or without CPB and found a 29% incidence of POCD in patients operated with CPB at 3-month follow-up.[6] For the current study, we anticipated a potential increase of this incidence because we measured POCD earlier after surgery, but thought that this would be balanced by a potential decrease in the incidence as we applied a more conservative definition of POCD.[27] We therefore assumed that the incidence of POCD at 1-month follow-up in the control group would be similar, that is, 29%. To detect a risk reduction of 50%, with a power of 80% at a two-sided significance level of 0.05, 252 patients would be required (126 in each of the two study groups). To compensate loss to follow-up, we aimed to recruit 290 patients.

Results

Study Population

Between August 2010 and October 2011, 291 patients were included in the study, completed baseline assessment, and randomized. The flow of patients through the study is shown in figure 1. Two patients from the placebo

group were excluded from the analysis; one withdrew informed consent before the 12-month follow-up assessment and the other patient was excluded for logistic reasons. Two patients (1.4%) in the dexamethasone group and three patients (2.1%) in the placebo group died before their 1-month cognitive follow-up appointment. Five patients in each group died before the 12-month cognitive follow-up assessment. During the 12-month follow-up period, two patients (one in each group) experienced a stroke and were counted as POCD cases. Patients' baseline demographic and surgical characteristics are presented in table 1. Despite randomization, patients in the dexamethasone group were slightly younger, had less diabetes mellitus, and more use of cell-saving devices. The control group consisted of 54 volunteers not undergoing cardiac surgery. The volunteers' average age was 64.6 yr, and 75.9% of the volunteers were men (for characteristics of the control group volunteers, see table 2, Supplemental Digital Content 1, http://links.lww.com/ALN/B58). On average, patients who received dexamethasone had lower peak body temperatures (mean, 37.2°C; SD, 0.8°C) during postoperative intensive care unit stay compared with patients who received placebo (mean, 37.6°C; SD, 0.7°C; $P < 0.01$)

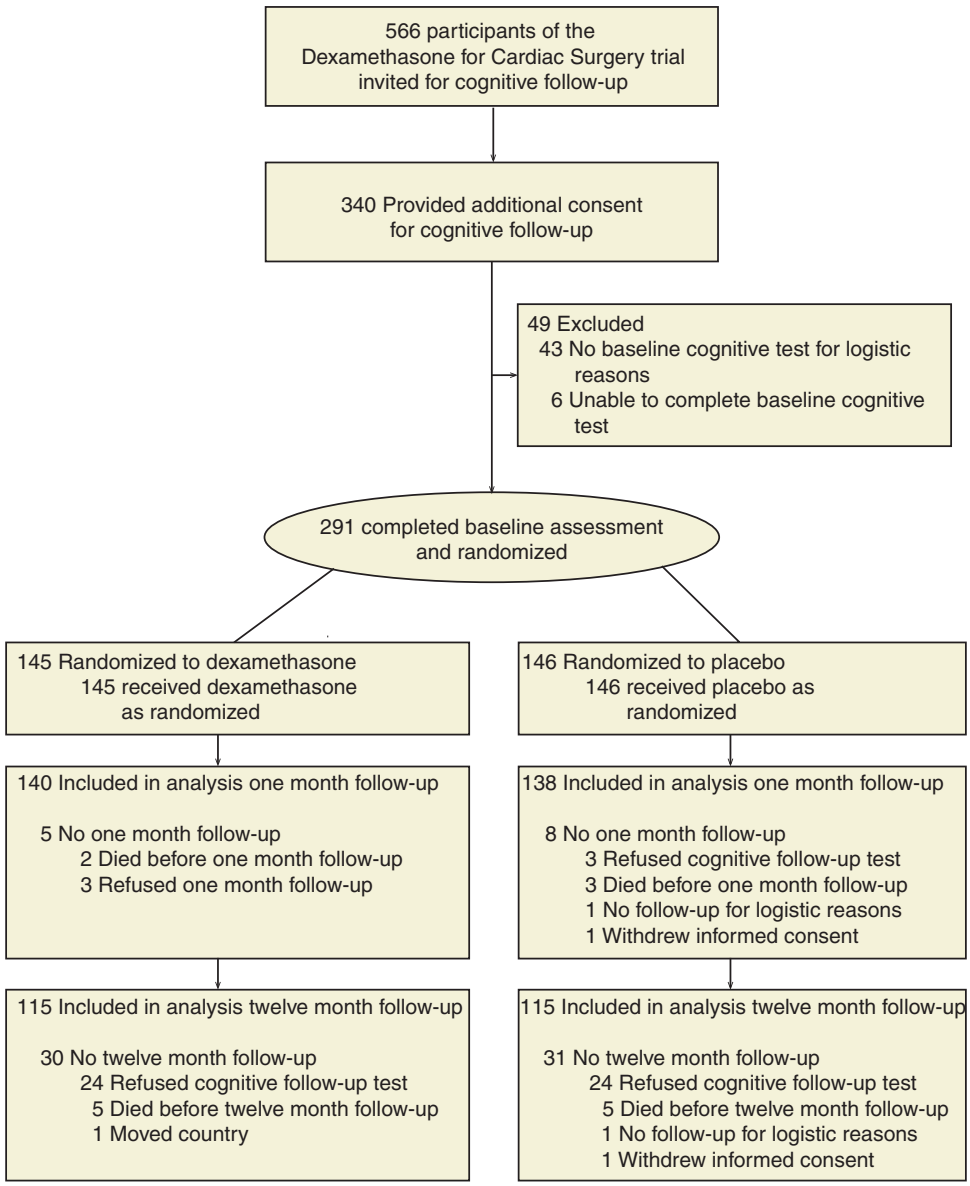

Fig. 1. Enrollment flowchart. Flow of patients through this substudy of the DExamethasone for Cardiac Surgery (DECS) Trial on cognitive dysfunction.

Table 1. Demographic, Clinical, and Surgical Characteristics*

	Dexamethasone N = 140	Placebo N = 138
Demographics		
Age, mean (SD), yr	63.4 (12.3)	65.4 (11.5)
Male sex	103 (73.6)	109 (79.0)
Weight, mean (SD), kg	82.8 (14.8)	83.3 (15.7)
Height, mean (SD), cm	176 (9.7)	175 (7.8)
Level of education, median (IQR)†	5 (4–6)	5 (4–6)
Coexisting medical conditions		
Hypertension	72 (51.4)	79 (57.2)
Diabetes mellitus	16 (11.4)	28 (20.3)
Insulin dependent	7 (5.0)	8 (5.8)
Noninsulin dependent	9 (6.4)	20 (14.5)
Treatment for pulmonary disease	16 (11.4)	16 (11.6)
Previous cerebrovascular event	11 (7.9)	5 (3.6)
Stroke	5 (3.6)	3 (2.2)
Transient ischemic attack	6 (4.3)	2 (1.4)
Peripheral vascular disease	17 (12.1)	18 (13.0)
Preoperative creatinine, mean (SD), mg/dl‡	1.02 (0.21)	1.07 (0.31)
Cardiac status		
Recent myocardial infarction (<90 d)	8 (5.7)	10 (7.2)
Left ventricular function§		
Moderate	26 (18.6)	34 (24.6)
Poor	2 (1.4)	4 (2.9)
Euroscore, median (IQR)	4 (2–7)	4 (2–6)
Type of surgery		
Isolated CABG	46 (32.9)	54 (39.1)
CABG plus valve	22 (15.7)	17 (12.3)
Single valve	58 (41.4)	51 (37.0)
Surgery on multiple valves	1 (0.7)	4 (2.9)
Other procedures	13 (9.3)	12 (8.7)
Repeat surgery	11 (7.9)	9 (6.5)
Use of cell-saving device	91 (65.0)	69 (50.0)
Use of tranexamic acid	131 (93.6)	129 (93.5)
Type of anesthesia		
Intravenous	53 (37.9)	42 (30.4)
Volatile	87 (62.1)	96 (69.6)
Duration of procedure, mean (SD), min	218 (70)	212 (67)
Duration of extracorporeal circulation, mean (SD), min	126 (59)	120 (54)
Duration of aortic cross-clamping, mean (SD), min	93 (45)	87 (43)

* Data are shown as number (%), unless otherwise indicated. † Level of education according to Verhage Classification of Dutch Education Levels, ranging from less than elementary school (1) to university degree (7). ‡ SI-conversion: to convert creatinine to μmol/l, multiply by 88.4. § Definition of left ventricular function classes: moderate, ejection fraction 30–50%; poor, ejection fraction <30%.

CABG = coronary artery bypass grafting; IQR = interquartile range.

Cognitive Outcome

At 1-month follow-up, 19 of 140 patients in the dexamethasone group (13.6%) and 10 of 138 patients in the placebo group (7.2%) fulfilled the diagnostic criteria for POCD. The difference was not statistically significant (RR, 1.87; 95% CI, 0.90 to 3.88; $P = 0.09$). At 12-month follow-up, 8 of 115 patients in the dexamethasone group (7.0%) and 4 of 114 patients (3.5%) in the placebo group fulfilled the diagnostic criteria for POCD. The difference was not statistically significant (RR, 1.98; 95% CI, 0.61 to 6.40; $P = 0.24$).

Patient scores on the different tasks are presented in table 2. At 1-month follow-up, the RCI was −0.38 in the dexamethasone group and −0.13 in the placebo group ($P = 0.10$). At 12-month follow-up, the RCI was 0.63 and 0.82, respectively ($P = 0.21$). The neuropsychological test results of the control group are presented in table 3.

Subgroup Analysis

Figure 2 shows the results of the preplanned subgroup analysis of the primary outcome. There was no differential effect of dexamethasone on the incidence of POCD at 1-month follow-up in any of the subgroups analyzed.

Table 2. Neuropsychological Test Results and RCI

Test	Main Variables	Dexamethasone Group			Placebo Group		
		Baseline (n = 140) Mean (SD)	1 Month (n = 140) Mean (SD)	12 Months (n = 115) Mean (SD)	Baseline (n = 138) Mean (SD)	1 Month (n = 138) Mean (SD)	12 Months (n = 114) Mean (SD)
Corsi Blocks	Total score	41.6 (15.9)	43.0 (16.9)	47.4 (16.2)	39.7 (14.1)	41.2 (17.2)	47.4 (17.1)
Rey Auditory Verbal Learning	Immediate recall score	37.6 (10.5)	40.4 (11.6)	43.6 (12.2)	37.6 (9.9)	41.2 (11.2)	43.5 (11.3)
Rey Auditory Verbal Learning	Delayed recall score	7.1 (3.1)	7.8 (3.5)	9.2 (3.3)	7.0 (2.9)	7.8 (3.4)	8.7 (3.5)
Grooved Pegboard*	Time, dominant hand, s	91.1 (30.0)	93.5 (48.1)	88.3 (29.2)	92.8 (31.6)	91.1 (29.6)	87.9 (24.8)
Trailmaking test A*	Time, s	39.5 (13.9)	38.7 (18.1)	40.2 (19.1)	40.4 (14.1)	38.0 (13.6)	38.9 (14.5)
Trailmaking test B*	Time, s	69.3 (40.0)	70.6 (50.1)	67.2 (42.6)	72.6 (40.4)	73.1 (45.4)	67.1 (43.2)
WAIS Digit Span	Span	5.8 (1.3)	5.7 (1.2)	5.8 (1.3)	5.7 (1.2)	5.7 (1.1)	5.9 (1.1)
WAIS Digit Span	Total score	14.2 (3.8)	14.3 (4.0)	15.0 (3.9)	14.1 (3.9)	14.2 (3.7)	15.3 (3.8)
RCI†			−0.38	0.63		−0.13	0.82

* In timed tasks, lower scores reflect better performance. RCI values of these variables were inverted so that positive RCI values always indicate improvement and negative RCI values indicate decline in test performance. † The RCI is the sum of the *Z*-scores of the different tests, divided by the SD of this sum in the control group. Positive values indicate improvement, and negative values indicate decline in overall test performance. *P* value of the overall RCI at 1-month follow-up; 0.10, at 12-month follow-up.

RCI = reliable change index; WAIS = Wechsler Adult Intelligence Scale.

Table 3. Neuropsychological Test Results of the Control Group (N = 54)

Test	Main Variables	Baseline Mean (SD)	1 Month Mean (SD)
Corsi Blocks	Total score	49.1 (16.4)	53.8 (20.6)
Rey Auditory Verbal Learning	Immediate recall score	43.9 (9.9)	45.3 (10.6)
Rey Auditory Verbal Learning	Delayed recall score	8.6 (3.5)	9.2 (3.5)
Grooved Pegboard*	Time, dominant hand, s	90.7 (35.3)	89.8 (40.2)
Trailmaking test A*	Time, s	39.4 (21.0)	37.0 (20.1)
Trailmaking test B*	Time, s	60.5 (36.7)	55.0 (37.5)
WAIS Digit Span	Span	6.2 (1.0)	6.4 (1.0)
WAIS Digit Span	Total score	16.2 (2.9)	17.2 (3.1)

* In timed tasks, lower scores reflect better performance.

WAIS = Wechsler Adult Intelligence Scale.

Sensitivity Analysis

We performed an extreme case type sensitivity analysis where first all patients in the placebo group who were lost to 1-month follow-up were counted as POCD cases. In both groups, patients who died were counted as POCD cases as well. In the first scenario, POCD would occur in 21 of 145 patients (14.5%) in the dexamethasone group and in 17 of 145 patients (11.7%) in the placebo group ($P = 0.60$). In the second scenario, all patients in the dexamethasone group who were lost to 1-month follow-up were counted as POCD cases. This resulted in an incidence of 24 of 145 (16.6%) *versus* 13 of 146 (6.8%) in the dexamethasone and placebo groups, respectively ($P = 0.08$).

Post Hoc *Analysis*

To address the unexpectedly low incidence of POCD obtained with the chosen definition, we also report the incidence of POCD defined as an RCI equal to or less than −1.96, or *Z*-score equal to or less than −1.96 in at least *one* different test. With this more liberal diagnostic cutoff point, 38 of 140 patients in the dexamethasone group (27.1%) and 27 of 138 patients in the placebo group (19.6%) fulfilled the diagnostic criteria for POCD at 1-month follow-up (RR, 1.39; 95% CI, 0.90 to 2.14; $P = 0.14$). At 12-month follow-up, the incidence was 15.7 and 8.8%, respectively (RR, 1.78; 95% CI, 0.86 to 3.70; $P = 0.11$).

Discussion

This randomized trial in 291 cardiac surgery patients found no benefit of intraoperative administration of high-dose dexamethasone on the incidence of POCD as compared with placebo, at either 1 month or 12 months after surgery. To our knowledge, this is the first randomized trial that has evaluated the hypothesis that suppression of the postoperative inflammatory response in cardiac surgical patients with corticosteroids may improve postoperative cognitive outcome.

The incidence of POCD at 1-month follow-up in the current study was lower than anticipated. This is an important limitation because it negatively affects the power of the

Forest plot of subgroup analyses of the effect of dexamethasone on the incidence of POCD at one month follow-up

Subgroup	No. of Patients: Dexamethasone	No. of Patients: Placebo	No. of Events: Dexamethasone	No. of Events: Placebo	Relative Risk (95% CI)	*P* for homogeneity
Age						
<65	66	59	5	3	1.49 (0.37–5.97)	
≥65	71	71	13	7	1.86 (0.79–4.38)	
Sex						
Men	104	108	15	6	2.65 (1.07–6.56)	
Women	36	30	4	4	0.78 (0.20–2.87)	
Surgery						
CABG	43	52	4	3	1.61 (0.38–6.82)	
Other	97	68	15	7	1.90 (0.81–4.44)	
Total	140	138	19	10	1.87 (0.90–3.88)	

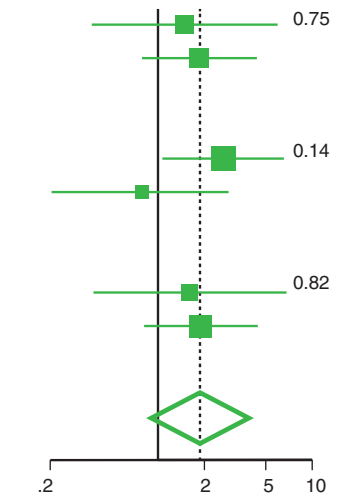

Fig. 2. Forest plot of subgroup analyses of the effect of dexamethasone on the incidence of postoperative cognitive decline (POCD) at 1-month follow-up. The effect estimates for the primary outcome in the subgroup analyses are shown. The size of each data marker correlates with the total number of patients in that subgroup. CABG = coronary artery bypass surgery.

study. We have applied a strict definition of POCD that corrects for learning effects and natural variability in neuropsychological test performance over time, which reduces the number of incorrect POCD diagnoses. A smaller incidence than reported in some studies was already anticipated, but because the cognitive follow-up was planned so early (1 month) after surgery, we still expected an incidence of POCD of approximately 30% at the time of the design of the study.[1,28,29] The primary analysis found no statistically significant difference between dexamethasone and placebo and, if anything, suggest a harmful effect rather than a benefit of dexamethasone. The *post hoc* application of a more liberal definition of POCD resulted in an incidence of POCD much closer to what was anticipated, but this changed neither the direction of the effect or its statistical significance. It is therefore not very likely that a study with more statistical power would have found a benefit of dexamethasone. In contrast, we cannot exclude a harmful effect of dexamethasone on POCD.

Control group volunteers performed better at baseline on the Corsi Blocks test and Rey Auditory Verbal Learning, but the differences were smaller at the follow-up tests. Because study patients were tested the day before surgery, psychological stress may have influenced their cognitive test performance. A difference in absolute cognitive test performance between patients and controls is not likely to be relevant because the RCI method used control data only to extract natural variability that occurs when a cognitive test is administered to the same patients multiple times.

Both adverse and beneficial effects of corticosteroids on memory function and other cognitive functions have been described in human and animal studies.[30,31] The findings of the current study do not support the hypothesis that POCD is caused by the postoperative inflammatory response. Of note, the investigators of the Corticosteroid Randomization after Significant Head Injury trial hypothesized that methylprednisolone could improve cerebral outcome after traumatic brain injury. However, in their study of 10,008 adult patients, they found an increased risk of death or severe disability in the methylprednisolone group.[32] The investigators did not administer neuropsychological tests to assess cognitive function. Possible explanations for the excess mortality in the methylprednisolone group were uncontrolled hyperglycemia and secondary adrenal insufficiency.[33,34] In our study, patients who received dexamethasone also had significantly higher glucose levels during intensive care unit stay. In the parent trial (n = 4,494), the highest serum glucose level observed in the intensive care unit was (mean, SD) 195 (50) mg/dl in the dexamethasone group *versus* 177 (59) mg/dl in the placebo group ($P < 0.001$).[21] It is conceivable that higher glucose levels have negatively affected cognitive outcome of the patients randomized to dexamethasone.

The choice of steroid and mode of administration should be closely regarded when interpreting the findings of this study. Prolonged exposure to high concentrations of glucocorticoids can be toxic to neural structures, especially the glucocorticoid receptor–rich hippocampus.[35] Although we

administered only one high dose of dexamethasone, its duration of action is 36 to 54 h. A different mode of administration, such as multiple smaller doses, or the administration of a steroid from another class, such as hydrocortisone, may have had a different effect. To our knowledge, the effects of other dexamethasone dosing regimes or other classes of steroids on POCD after cardiac surgery have not yet been studied.

A strength of the study is the loss to follow-up of less than 5% at 1-month follow-up, which is very satisfactory compared with other studies reporting cognitive outcomes after cardiac surgery.[5] The considerably higher 21% loss to 12-month follow-up, however, is a limitation. Patients who refused to participate in the 12-month follow-up could be more likely to have developed POCD. However, patients who were scored as POCD cases at 1-month follow-up were not more likely to become lost to follow-up at 12-month (POCD cases 82% followed up, other patients 84% followed up; $P = 0.72$). The baseline matching difference between the groups is also a limitation of this study.

In conclusion, in this randomized clinical trial in 291 cardiac surgical patients, the risk of POCD was not reduced by administration of intraoperative high-dose dexamethasone.

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Competing Interests

The authors declare no competing interests.

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