Postoperative Neurocognitive Disorders After Closed-Loop Versus Manual Target Controlled-Infusion of Propofol and Remifentanil in Patients Undergoing Elective Major Noncardiac Surgery: The Randomized Controlled Postoperative Cognitive Dysfunction-Electroencephalographic-Guided Anesthetic Administration Trial

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**BACKGROUND:** The aim of the study was to investigate whether closed-loop compared to manual bispectral index (BIS)-guided target-controlled infusion of propofol and remifentanil could decrease the incidence of postoperative neurocognitive disorders after elective major noncardiac surgery.

**METHODS:** Patients aged >50 admitted for elective major noncardiac surgery were included in a single-blind randomized (ratio 2:1) trial. The anesthetic protocol was allocated by randomization into either closed-loop or manual BIS-guided propofol and remifentanil titration. The BIS target range was 40–60. All patients had cognitive assessment the day before surgery and within 72 hours after surgery using a battery of neuropsychological tests. The primary outcome was the rate of postoperative neurocognitive disorders. Postoperative neurocognitive disorders were defined as a decrease >20% from baseline on at least 3 scores. Intergroup comparison of the primary outcome was performed using the χ² test.

**RESULTS:** A total of 143 and 61 patients were included in the closed-loop and manual groups, respectively (age: 66 [8] vs 66 [9] years). The primary outcome was observed in 18 (13%) and 10 (16%) patients of the closed-loop and manual groups, respectively (relative risk [95% CI], 0.77 [0.38–1.57], P = .47). Intraoperative propofol consumption was lower (4.7 [1.4] vs 5.7 [1.4] mg·kg⁻¹·h⁻¹, mean difference [MD] [95% CI], −0.73 [−0.98 to −0.48], P < .0001) and the proportion of time within the BIS target range higher (84 [77–89] vs 74 [54–81]%, MD [95% CI], 0.94 [0.67–1.21], P < .0001) in the closed-loop group.

**CONCLUSIONS:** Closed-loop compared to manual BIS-guided total intravenous anesthesia provided a significant reduction in episodes of an excessive depth of anesthesia while decreasing intraoperative propofol requirement but no evidence for a reduction of the incidence of postoperative neurocognitive disorders after elective major noncardiac surgery was observed. (Anesth Analg 2021;133:837–47)

**KEY POINTS**
- **Question:** Could closed-loop compared to manual target-controlled infusion of propofol and remifentanil lower the rate of postoperative neurocognitive disorders after elective major noncardiac surgery?
- **Findings:** Closed-loop compared to manually-driven BIS-guided total intravenous anesthesia provided a significant reduction in episodes of an excessive depth of anesthesia while decreasing intraoperative propofol requirement but no evidence for a reduction of the incidence of postoperative neurocognitive disorders after elective major noncardiac surgery was observed.
- **Meaning:** This randomized controlled trial failed to demonstrate that the propofol sparing effect provided by closed-loop anesthesia is sufficient alone to decrease the risk of postoperative neurocognitive disorders after elective major noncardiac surgery.
About 25% of patients aged ≥60 years experience postoperative cognitive dysfunction (POCD) within 7 days after major noncardiac surgery.1 According to recent recommendations, early POCD, as defined by the international study of post-operative cognitive dysfunction (ISPOCD) group1,2 that occurs within the first month after surgery, refers to postoperative neurocognitive disorders (PND).3 PND is characterized as a postoperative decrement from baseline in different cognitive functions (especially memory and executive functions) compared to age-matched healthy control.1 PND has been associated with an impaired recovery, a prolonged hospital length of stay, a higher rate of dementia, and increased mortality.4,5 The underlying mechanisms leading to PND are complex and remain incompletely understood.6 Thus, no specific therapy is currently available, and the treatment of PND is mainly based on prevention.

Since dose-related neurotoxic effects of anesthetic drugs have been reported in animal experiments,7–9 some authors suggested that decreasing the dose delivered and avoiding an excessive depth of anesthesia could lower the incidence of PND.10–12 In this field, lighter anesthesia targeting higher bispectral index (BIS) values has been associated with a lower rate of PND after total knee replacement in a recent randomized trial.13 However, these data remain controversial.14 The difficulty of accurately maintaining a BIS value within a specified target range with manual titration of the anesthetic drugs could explain the discrepancies among the different studies.

Closed-loop controller allows the automated titration of both propofol and remifentanil guided by the BIS.15 Automated titration of anesthetic agents has been shown to increase the time spent within the BIS target range or adequate anesthesia while decreasing both number and length of episodes of an excessive depth of anesthesia (ie, BIS value <40).16,17 Recently, Cotoia et al18 reported that closed-loop anesthesia could decrease emergence delirium, but the impact of closed-loop anesthesia on PND has never been studied.

The hypothesis of the POCD-ELA trial19 was that closed-loop target-controlled infusion of propofol and remifentanil could lower the rate of PND by reducing the risk of an excessive depth of anesthesia. The POCD-ELA randomized study was designed to investigate whether closed-loop compared to manual target-controlled infusion of propofol and remifentanil guided by BIS monitoring could decrease the incidence of PND after elective major noncardiac surgery.

METHODOLOGY

Study Design

The POCD-ELA study was a single-center, single-blind, parallel-group, randomized superiority trial conducted between February 2013 and July 2018 in the University Hospital of Besancon (Besancon, France). The study protocol was approved by the Institutional Review Board CPP Est-II, University Hospital of Besancon (no. 12/654, Eric Toussriott, MD, PhD) on November 5, 2012, and by the French National Health Products Safety Agency (Agence National de Sécurité du Médicament, Saint-Denis, France) on January 25, 2013. The study was conducted in accordance with the French bioethics law (Art. L. 1121-1 of the law no.
2004-806, August 9, 2004). Written informed consent was obtained from all subjects participating in the trial. The POCD-ELA trial was a substudy of the ELA trial that was registered before patient enrollment on www.clinicaltrials.gov under the identifier NCT01198639 on September 10, 2010 (principal investigator: Marc Fischler, MD). The trial protocol has been previously published elsewhere. This manuscript adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines.

**Study Population**

Patients >50 years of age, scheduled for major elective noncardiac surgery expected to last >1 hour and performed under general anesthesia, were eligible. Exclusion criteria were patients whose native language was not French, American Society of Anesthesiologists physical status >III, brain or cephalic surgery, medical history of neurological or psychiatric disorder, cardiac pacing, current psychoactive substances use (eg, benzodiazepines, antidepressant or neuroleptics agents), and contraindication to propofol or remifentanil administration. Information about the study was given both orally and in writing during the anesthesia consultation performed at least 2 days before surgery. Patients were included in the study after providing written, informed consent to participate.

**Anesthetic Management**

Preoperative fasting was started at midnight the day before surgery. On arrival in the operating room, standard monitoring was set up. A BIS electrode was positioned on the patient’s forehead and connected to a BIS Vista monitor (Covidien, Dublin, Ireland). The BIS value was recorded every 5 seconds and was considered valid when the signal quality index was >50. All patients received a target-controlled infusion of propofol and remifentanil. Effect-site concentrations of propofol and remifentanil were calculated by using the pharmacokinetic models of Schnider et al and Minto et al, respectively. A computer was connected as an interface between the BIS monitor and the propofol and remifentanil infusion pumps (Alaris GH Medical, Hampshire, United Kingdom) via an RS232 serial port (Infusion Toolbox 95w version 4.11 software). With the exception of propofol and remifentanil delivery, the anesthetic protocol was at the discretion of the anesthesiologist in charge of the patient. Ketamine infusion was prohibited.

Postoperative pain management and decision for discharge from the hospital were left at the discretion of the physicians in charge of the patient.

**Randomization and Study Drug Administration**

Patients included in the study were randomly assigned to either the closed-loop or manual group the day before surgery. A permuted-block randomization list with varying block sizes (block sizes of 2 and 4) was performed using a specialized website. According to the ELA study protocol, the allocation ratio between closed-loop and manual groups was 2:1, and the randomization was stratified by age (< or ≥70 years) and cancer (yes/no). Patients and primary outcome assessors (neuropsychologists) were blinded to the treatment allocated, and investigators were blinded to the randomization block size.

In the closed-loop group, anesthesia was performed using a dual closed-loop controller allowing automated propofol–remifentanil titration guided by BIS monitoring, as described elsewhere. Briefly, propofol and remifentanil were automatically titrated by the controller to maintain the BIS value as close as possible to 50, between a target range of 40–60.

In the manual group, propofol and remifentanil were manually titrated by the anesthesiologist in charge of the patient to maintain the BIS value within the same target range.

**Data Collected and Endpoint Measures**

Demographic data, medical history, current treatment, American Society of Anesthesiologists physical status, and type of surgery were recorded at inclusion. Intraoperative data describing the surgical procedure and the anesthetic management, use of vasoactive drugs, fluid loading, and red cell transfusion were obtained from the computerized anesthesia monitoring sheet. BIS values, propofol, and remifentanil targeted effect-site concentrations, and total doses of propofol and remifentanil infused during anesthesia were recorded by the computer for subsequent analysis.

The primary endpoint of the study was the PND rate within 72 hours after surgery. For this purpose, patients underwent a neuropsychological assessment by trained neuropsychologists at 2 time points: the day before surgery (baseline) and within 72 hours after surgery (postoperative assessment) before discharge from the hospital. The neuropsychological tests were performed in a quiet environment free from distraction and interruption, after checking for the absence of hypoglycemia or hypotension and uncontrolled pain (visual analog scale for pain >3).

The neuropsychological assessment included 7 tests listed below, presented in the order of administration within the battery: memory impairment screen, Isaacs set test, mini-mental state examination, crossing-off test, Mattis dementia rating scale, Victoria Stroop test, and trail making test. These tests yielded 11 primary scores and covered 4 cognitive domains: (1) memory (memory subscale of the Mattis dementia rating scale); (2) attention/processing speed (trail making test part A, crossing-off test, attention subscale of the
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Mattis dementia rating scale, word condition and dot condition of the Victoria Stroop test): (3) global cognitive efficiency (mini-mental state examination); and (4) executive functioning (Isaacs set test, initiation/perseveration subscale of the Mattis dementia rating scale, trail making test part B and interference condition of the Victoria Stroop test). For the latter 2 tests (trail making test part B and interference condition of the Victoria Stroop test), the difference score trail making test (B − A) and the ratio score between the time required to name the colors in the interference and the dot conditions of the Victoria Stroop test (ie, high interference score) were used to obtain a measure of executive function independently of processing speed.

To control for practice effect associated with repeated cognitive testing, we first considered to define PND as a Z score value >1.96 for at least 2 tests or a Z score composite value (mean Z scores value of each neuropsychological score) >1.96.1 This method implied the comparison to an age-matched, nonsurgical control group undergoing the same neuropsychological tests and retests than patients included in the study. After analysis of the results obtained in the study, the decision was made by the scientific study committee not to include the age-matched control group for futility (see below statistical paragraph). In the absence of matched control group, PND was thus defined by a decrease in an individual’s score >20% from baseline on at least 3 scores (20%) of neuropsychological scores.31–33

Secondary outcomes were (1) the total dose of propofol and remifentanil infused; (2) the percentage of time spent within the BIS target range of 40–60; (3) the percentage of time spent with a BIS value <40; (4) the proportion of time spent with a BIS value >60; (5) time spent with a suppression ratio >5; and (6) score of each neuropsychological tests at baseline and post-operative assessments.

**Statistical Analysis**
The Shapiro-Wilk test was used to test the normality of the distribution of quantitative data. Continuous variables are expressed as mean ± standard deviation, median (interquartile range 25%–75%), or number (percentage), as appropriate. Intergroup comparisons were performed using the $\chi^2$ or Fisher exact (expected count <5 for at least 25% of the cells) tests for qualitative variables and the Student $t$ or the Mann-Whitney $U$ tests for quantitative variables, as appropriate. The

![Diagram](https://via.placeholder.com/150)

Figure 1. Flow chart of patients’ inclusions in the POCD-ELA study according to the CONSORT statement. CONSORT indicates Consolidated Standards of Reporting Trials.
primary outcome was compared between the closed-loop and the control groups using the $\chi^2$ test. The postoperative score of each neuropsychological test was compared between the 2 groups while adjusting for the baseline score value using analysis of covariance. Moreover, a separate analysis was conducted as a sensitivity analysis using a Mann-Whitney $U$ test to compare the baseline as well as the postoperative score values of each neuropsychological test between the closed-loop and the control groups (not normally distributed variables). The statistical analysis included all patients who underwent neuropsychological testing at baseline and postoperative. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc, Cary, NC), and the significance level was fixed at 0.05.

The sample size calculation was based on the hypothesis of an expected rate of PND of 26% in the control group and of 10% in the closed-loop group. Considering a loss to follow-up rate of 5%, an $\alpha$ risk of .05, and a $\beta$ risk of .20, a total sample size of 204 patients was calculated (68 patients in the manual arm and 136 patients in the closed-loop arm). The inclusion of an age-matched nonsurgical control group was planned at the end of the study for Z score calculation. Based on the analysis of score of each neuropsychological test at baseline and postoperative assessments, a significant difference in the incidence of PND between the closed-loop and the control groups was unlikely, and the decision was made not to include an age-matched control group for futility.

**RESULTS**

A total of 238 patients were included during the study period, and 61 and 143 patients were analyzed in the manual and closed-loop groups, respectively (Figure 1). The baseline characteristics of patients were similar between the 2 groups (Table 1).

**Anesthetic Management**

Data describing the intraoperative management in the 2 groups are presented in Table 2. Intraoperative propofol consumption was significantly lower, and intraoperative remifentanil consumption significantly higher in the closed-loop group (Table 2). Patients in the closed-loop group spent a higher proportion of time within the BIS target range of 40–60 and a lower proportion of time with a BIS value <40 (Table 2).

**Neuropsychological Assessment**

The neuropsychological scores at baseline did not differ between the 2 groups (Figure 2). A PND (primary outcome) occurred in 18 (13%) and 10 (16%) patients of the closed-loop and manual groups, respectively (relative risk [95% confidence interval], 0.77 [0.38-1.57], $P = .47$) (Figure 3). Scores of each neuropsychological test at postoperative assessment were not significantly different between the groups in the analyses, adjusting for baseline values as well as in unadjusted analyses (Figure 2). Secondary outcomes are given in Table 2.

**DISCUSSION**

This study showed that closed-loop compared to manually-driven BIS-guided total intravenous anesthesia provided a decrease in the rate of an excessive depth of anesthesia episodes and intraoperative propofol consumption requirement, but no evidence for a reduction of the incidence of PND after elective major noncardiac surgery was observed.

This result is inconsistent with previously published studies and deserves further analysis. First, the incidence of PND in the manual group was low, as compared to the previously published data. This may be related to the use of BIS monitoring to guide anesthetic agents administration in this group. This is in accordance with the study from Chan et al, evaluating BIS-guided general anesthesia in major noncardiac surgery.
Third, the proportion of time spent within the BIS target range in the manual group was higher than that reported in previous studies, suggesting that the remifentanil dose had no relevant impact on hemodynamic stability. Finally, PND was not significantly different between the 2 groups previously described elsewhere. To our knowledge, there is no link between the remifentanil dose and the risk of perioperative cognitive disorders. Moreover, the rate of intraoperative administration of vasopressor did not significantly differ between the 2 groups suggesting that the remifentanil dose had no relevant impact on hemodynamic stability. Finally, PND was not only related to deep anesthesia but also to other mechanisms, such as surgical procedure, patients comorbidities, or intraoperative hemodynamic management. In particular, there is a significant body of literature suggesting that the systemic inflammatory response following surgery could be the leading trigger for postoperative decline in cognition. Several preclinical and some clinical studies showed that postsurgical systemic inflammatory response is associated with significant neuroinflammation characterized by morphological and functional changes of microglia and astrocytes, complement activation, proinflammatory chemoattractant synthesis, endothelial dysfunction, and blood-brain barrier opening. The lack of impact of tighter control of anesthesia level that we observed in the closed-loop group may support noncardiac surgery. However, this beneficial effect of intraoperative BIS monitoring remains a matter of debate, depending on several experimental conditions. In this regard, Wildes et al recently reported that BIS-guided volatile anesthesia failed to decrease the incidence of postoperative delirium after major surgery. The definition of POCD, the tests used to assess cognition, the method to determine a cognitive threshold of neurotoxicity of an excessive depth of anesthesia were avoided in this group by the Hawthorne effect.

### Table 2. Anesthetic Management in the Closed-Loop and Manual Groups

<table>
<thead>
<tr>
<th>Anesthetic management</th>
<th>Closed-loop group (n = 143 patients)</th>
<th>Manual group (n = 61 patients)</th>
<th>Effect size</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of anesthesia (min)</td>
<td>192 ± 89</td>
<td>208 ± 80</td>
<td>−0.20 (−0.43 to 0.04)</td>
<td>.207</td>
</tr>
<tr>
<td>Total intraoperative dose of propofol (mg·kg⁻¹·h⁻¹)</td>
<td>4.7 ± 1.4</td>
<td>5.7 ± 1.4</td>
<td>−0.73 (−0.98 to −0.48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Total intraoperative dose of remifentanil (µg·kg⁻¹·min⁻¹)</td>
<td>0.15 ± 0.05</td>
<td>0.12 ± 0.03</td>
<td>.72 (0.45-0.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Regional anesthesia (%)</td>
<td>103 (72)</td>
<td>40 (66)</td>
<td>1.09 (0.89-1.34)</td>
<td>.357</td>
</tr>
<tr>
<td>T&lt;sub&gt;BIS.40 (%)&lt;/sub&gt;</td>
<td>12 (7–17)</td>
<td>19 (11–42)</td>
<td>−0.76 (−1.02 to −0.50)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T&lt;sub&gt;BIS40-60 (%)&lt;/sub&gt;</td>
<td>84 (77–89)</td>
<td>74 (54–81)</td>
<td>0.94 (0.67-1.21)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T&lt;sub&gt;BIS.60 (%)&lt;/sub&gt;</td>
<td>3 (2–36)</td>
<td>4 (2–46)</td>
<td>−0.43 (−0.64 to −0.22)</td>
<td>.223</td>
</tr>
<tr>
<td>Time with SR &gt;5 (%)</td>
<td>0 (0–2)</td>
<td>0 (0–5)</td>
<td>−0.21 (−0.44 to 0.02)</td>
<td>.223</td>
</tr>
<tr>
<td>Intraoperative management</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative atropine (%)</td>
<td>32 (22)</td>
<td>13 (21)</td>
<td>1.05 (0.59-1.86)</td>
<td>.866</td>
</tr>
<tr>
<td>Intraoperative bolus of vasopressor (%)</td>
<td>99 (70)</td>
<td>37 (61)</td>
<td>1.14 (0.91-1.44)</td>
<td>.234</td>
</tr>
<tr>
<td>Intraoperative bolus of antihypertensive drug (%)</td>
<td>21 (15)</td>
<td>4 (7)</td>
<td>2.24 (0.80-6.25)</td>
<td>.165</td>
</tr>
<tr>
<td>Intraoperative blood loss ≥500 mL</td>
<td>43 (30)</td>
<td>15 (24)</td>
<td>1.22 (0.74-2.03)</td>
<td>.427</td>
</tr>
<tr>
<td>Red blood cell transfusion within 72 h after surgery (%)</td>
<td>12 (8)</td>
<td>3 (5)</td>
<td>1.71 (0.50-5.83)</td>
<td>.560</td>
</tr>
<tr>
<td>Intraoperative vascular filling</td>
<td>Crystalloids (mL)</td>
<td>2170 (1270)</td>
<td>2054 (979)</td>
<td>0.10 (−0.14 to 0.33)</td>
</tr>
<tr>
<td>Colloids (%)</td>
<td>31 (22)</td>
<td>9 (15)</td>
<td>1.47 (0.75-2.90)</td>
<td>.254</td>
</tr>
<tr>
<td>Time of neuropsychological assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 (median)</td>
<td>8 (6)</td>
<td>2 (3)</td>
<td>.439</td>
<td></td>
</tr>
<tr>
<td>Day 2 (median)</td>
<td>119 (83)</td>
<td>55 (90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 3 (median)</td>
<td>16 (11)</td>
<td>4 (7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± standard deviation. T<sub>BIS.40</sub>, T<sub>BIS40-60</sub>, and T<sub>BIS.60</sub> percentage of anesthesia time spent with a BIS value <40, between 40 and 60, and >60, respectively.

aEffect size is mean difference (95% confidence interval) and relative risk (95% confidence interval) for quantitative and qualitative variables, respectively.

bP value for Student t test.

cData are number of patients (percentage).

dData are median (interquartile range).

*P value for Mann-Whitney U test.

fP value for χ² test.

gP value for Fisher exact test.
Figure 2. (Continued)
the hypothesis that surgery rather than anesthesia is responsible for postoperative decline in cognition.

The present study has several strengths. First, eligible patients were not included if they had psychoactive treatment. Second, patients suspected of having cognitive preexisting cognitive impairment were excluded. At last, all anesthetic procedures were performed by 4 investigators and the neurocognitive assessment by 2 trained neuropsychologists, reducing the heterogeneity in the management of the patients.

![Figure 2](image)

Figure 2. Box-and-whisker plots of the distribution of the baseline and postoperative score values of neuropsychological tests exploring (A) memory, (B) attention/processing speed, (C) executive functioning, and (D) global cognitive efficiency in the closed-loop and manual groups. Box-and-whisker plots show the median, the first and the third quartiles, and the minimal and the maximal values of each score. Intergroup comparisons of the baseline and of the postoperative score values of each neuropsychological test was performed using the Mann-Whitney U test. $P$ value for ANCOVA are $P$ values for the comparison of the postoperative score of each neuropsychological test between the closed-loop and manual groups while adjusting for the baseline score using ANCOVA, including the baseline score as a covariate. ANCOVA indicates analysis of covariance; MDRS, Mattis dementia rating scale; MMSE, mini-mental state examination; TMT, trail making test; VST, Victoria Stroop test.
Limits of the Study and Control of Bias
This trial also has some limitations. First, the neuropsychological assessment was performed 72 hours after surgery, and long-term evaluation was not performed. In most studies, PND are screened within 7 days or 1 month after surgery. Whether PND observed within 3 postoperative days have the same clinical significance needs to be assessed. As it was not required by the ISPOCD1 definition of POCD, subjective complaints or symptoms of cognitive impairment were not investigated during the postoperative neuropsychological assessment, and some patients could not have strictly meet the criteria that defined early PND in the recent recommendations edited by Evered et al in 2018. Patients were not specifically screened for delirium in the present study, and we cannot exclude that some of them could meet criteria for postoperative delirium, reported to impair mild- and long-term recovery. Second, the patients included in the present study were younger and had few comorbidities when compared to patients included in previously published trials dealing with this topic, and could thus be considered at low risk of PND. Furthermore, most of the patients underwent laparoscopic or robotic surgery, and some of them received regional anesthesia combined with general anesthesia. These factors could have contributed to a reduction in postoperative inflammation. An age-matched nonsurgical control group was finally not included in the study by decision of the study scientific committee, because of the lack of intergroup difference in each neuropsychological test. This decision was pragmatic but prevented the control of a potential practice effect related to repeat cognitive testing and may have led to an underestimated PND rate. However, this should have no effect on the primary outcome, as the practice effect should be of the same magnitude in both groups. Another limitation is that the sample size calculation was based on an absolute 16% difference in PND rates between the groups, and the study was thus insufficiently powered to detect smaller differences. At last, all neuropsychological assessments were done during the hospital stay. The rate of PND could be overestimated in relation with confounding factors like environment and pain. However, significant efforts have been made to perform the test in the best possible condition to minor the effect of these environmental factors. Moreover, since the neuropsychological assessments were done at the hospital in all patients, a minor impact on the main result of the study can be assumed.

CONCLUSIONS
Closed-loop compared to manually-driven BIS-guided total intravenous anesthesia provided a significant reduction in episodes of an excessive depth of anesthesia while decreasing intraoperative propofol requirement, but no evidence for a reduction of the incidence of PND after elective major noncardiac surgery was observed. The hypothesis of improvement of postoperative cognitive recovery by a global approach of care, covering the preoperative (such as fasting), the intraoperative (depth of anesthesia, ventilation and fluids management), and the postoperative (pain relief, early rehabilitation) periods, in patients at high risk for PND, should be investigated in further studies.

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Figure 3. PND rate within 72 h after surgery in the closed-loop and manual groups.  P value is for intergroup comparison using the $\chi^2$ test. PND indicates postoperative neurocognitive disorders.
DISCLOSURES

Name: Nicolas Mahr, MD.
Contribution: This author helped conceive and design the study, acquire, analyze, and interpret the data, and draft the manuscript. He approved the manuscript to be published and attests to the integrity of the original data and the analysis reported in this manuscript.

Conflicts of Interest: None.

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Contribution: This author helped conceive and design the study, acquire, analyze, and interpret the data, and revise the manuscript critically for important intellectual content. She approved the manuscript to be published and attests to the integrity of the original data and the analysis reported in this manuscript.

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Contribution: This author helped conceive and design the study, acquire, analyze, and interpret the data, and revise the manuscript critically for important intellectual content. She approved the manuscript to be published and attests to the integrity of the original data and the analysis reported in this manuscript.

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Conflicts of Interest: None.

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REFERENCES


