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Effects of milrinone on cerebral perfusion and postoperative cognitive function in spine surgery: Secondary analysis of a CONSORT-compliant randomized controlled trial

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Abstract

Objective: To compare the effects of milrinone, sodium nitroprusside (SNP), and nitroglycerin (NTG) on induced hypotension, cerebral perfusion, and postoperative cognitive function in elderly patients undergoing spine surgery.

Methods: Sixty patients >60 years scheduled for lumbar fusion surgery were assigned to receive milrinone (group M), SNP (group S), or NTG (group N). The administration of the study drug was initiated immediately after perivertebral muscle retraction and was stopped after completion of interbody fusion. Target blood pressure was a decrease of 30% in systolic blood pressure from baseline or mean blood pressure of 60 to 65 mm Hg. The regional cerebral venous oxygen saturation (rS_VO_2), as a measure of cerebral perfusion, and the change in perioperative Mini-Mental State Examination (MMSE) score, as a measure of postoperative cognitive function, were assessed.

Results: During the administration of the study drug, the overall and lowest intraoperative rS_VO_2 values were significantly higher ($P = .01$ and $P = .01$, respectively), and the duration of rS_VO_2 <60% was shorter in group M than in the other groups ($P = .03$). In group M, intraoperative rS_VO_2 was not different from the basal value, whereas in groups S and N, rS_VO_2 was significantly lower than the basal value during the administration of the study drug, but then returned to the basal value after terminating the study drug. Basal MMSE scores were comparable among the 3 groups. The MMSE score on postoperative day 5 was higher in group M than the other groups.

Conclusions: Milrinone used to induce hypotension resulted in better intraoperative cerebral perfusion and postoperative cognitive function compared to SNP and nitroglycerin.

Abbreviations: ASA = American Society of Anesthesiologists, CI = cardiac index, CO = cardiac output, Hb = hemoglobin, MBP = mean blood pressure, MMSE = Mini-Mental State Examination, NTG = nitroglycerine, PCA = patient-controlled analgesia, POCD = postoperative cognitive decline, RCT = randomized-controlled trial, rS_VO_2 = regional cerebral venous oxygen saturation, SBP = systolic blood pressure, SNP = sodium nitroprusside, VAS = visual analogue scale.

Keywords: controlled, elderly, frail, Hypotension, milrinone, phosphodiesterase 3 inhibitors, postoperative complications

1. Introduction

Induced hypotension is effective for reducing perioperative hemorrhage and facilitating visualization of the surgical field during spine surgery.[1–4] However, the majority of patients undergoing spine surgery are elderly; therefore, the application of induced hypotension is limited in clinical practice due to concerns regarding hypoperfusion of major organs, particularly the brain.[5–7] Hence, the characteristics of each drug and its effect on patient hemodynamics must be considered to select the most appropriate agent to induce hypotension.

Milrinone is mainly used in patients with congestive heart failure. It exhibits both vasodilatory and inotropic effects.[8] One study demonstrated that milrinone can be used to induce hypotension.[9] Also, compared to pure vasodilators frequently used for inducing hypotension in spine surgery, such as sodium nitroprusside (SNP) and nitroglycerine (NTG), milrinone is associated with higher cardiac output (CO), resulting in higher renal perfusion and urine output.[10] Therefore, we hypothesized that in elderly patients at risk of hypoperfusion in major organs, milrinone might have a favorable effect on intraoperative cerebral perfusion, which could decrease the incidence of postoperative cognitive decline (POCD).

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The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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We evaluated the hypothesis that hypotension induced with milrinone would result in better intraoperative cerebral perfusion and postoperative cognitive function, compared to SNP and NTG, in elderly patients undergoing spine surgery in a secondary analysis of a randomized-controlled trial (RCT).

2. Methods

We performed a secondary analysis of an RCT comparing the effects of milrinone, SNP, and NTG in elderly patients undergoing spine surgery.[10] The patients included in the secondary analysis, and the study protocol, were to the same as those of the original study. The original study was approved by the Ethical Committee of Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea (approval number: KC11MISE0628) and was retrospectively registered with the Clinical Research Information Service (http://cris.nih.go.kr, ID: KCT0000313). Written informed consent was obtained from all patients before randomization.

The original study enrolled patients aged >60 years with American Society of Anesthesiologists (ASA) physical status I–III, and who were scheduled for elective posterior lumbar interbody fusion. The exclusion criteria were: heart failure (New York Heart Association grade III–IV), clinically significant arrhythmia, history of cerebrovascular disease, cognitive dysfunction, illiteracy, and inability to provide informed consent.

The original study was a prospective, double-blind, balanced (1:1) randomized, controlled parallel-group trial. No changes were made to the design or protocol during the study. The patients were randomly assigned to one of 3 groups: group M (milrinone), group S (SNP), or group N (NTG). Randomization was performed using a computer-generated randomization sequence by an investigator who was not involved in patient care. The group allocation was concealed in sealed opaque envelopes given to an anesthesia nurse not involved in patient care or assessment. The nurse opened the envelope immediately before the induction of anesthesia and prepared a covered syringe pump containing the study drug. A single anesthesiologist conducted the entire course of anesthesia, including administration of the study drug according to the target blood pressure. A separate anesthesiologist recorded all outcomes. A single surgeon performed all surgeries using the same technique. Patients, anesthesiologists, and the surgeon in charge were all blinded to the group assignments during the entire study.

Upon arrival in the operating room, routine standard monitoring with a cerebral oximetry sensor (Invos 5100C Cerebral/Somatic Oximeter; Somanetics Corp, Troy, MI, USA) was performed every 5 minutes. Anesthesia was induced with 1.5 mg/kg propofol, and 0.5 mg/kg atracurium was given to facilitate tracheal intubation with a cuffed tube. After tracheal intubation, an arterial line was inserted into the radial artery and connected to the FloTrac/Vigileo system (Edwards Lifesciences, Irvine, CA, USA).

Anesthesia was maintained with sevoflurane (1.0–1.5 age-adjusted minimal alveolar concentration) and 50% nitrous oxide to maintain bispectral index (A-2000TM SP; Aspect Medical Systems, Norwood, MA, USA) values of 45 to 55. To maintain muscle relaxation, atracurium was administered continuously at a dose of 5 μg/kg/minutes until the end of surgery. Minute ventilation was adjusted to maintain a peak inspiratory of pressure <20 cm H_2O and end-tidal carbon dioxide of 30 to 35 mm Hg. The patients were positioned prone on a Wilson frame and care was taken to avoid hemodynamic changes, disruption of ventilation, and eye and nerve injuries. During the surgery, maintenance lactated Ringers solution was administered at a rate of 10 ml/kg/hour, and 0.5 to 2.0 mg nicardipine was administered when the systolic blood pressure (SBP) increased by more than 10% of the baseline value. Perioperative blood lost was replaced with 6% hydroxyethyl starch at a ratio of 1:1. Packed red blood cells were transfused to achieve the target hemoglobin (Hb) level of >10 g/dl.

Administration of the study drug was initiated immediately after perivertebral muscle retraction, and stopped after completing interbody fusion. The administration protocol for the study drugs was based on our preliminary study target of a 30% decrease in SBP or mean blood pressure (MBP) of 60 to 65 mm Hg (unpublished data). In group M, a loading dose of 50 μg/kg/minutes milrinone was administered for 10 minutes followed by continuous administration of 0.6 μg/kg/minutes. In group S, a loading dose of 2 μg/kg/minutes SNP was administered for 10 minutes followed by continuous administration of 0.5 μg/kg/minutes. In group N, a loading dose of 3 μg/kg/min NTG was administered for 10 minutes followed by continuous administration of 1.0 μg/kg/minutes. The maintenance dose in each group was adjusted to maintain the target blood pressure mentioned above. During the surgery, 5 to 10 mg ephedrine was administered, when SBP was <70% of the baseline value or MBP was <60 mm Hg.

Intravenous patient-controlled analgesia (PCA) infusion was initiated after extubation. PCA consisted of 10 to 15 μg/ml fentanyl in normal saline at a continuous infusion rate of 1 ml/hour, with a 1 ml bolus and a lockout time of 10 minutes. If a patient experienced pain of severity >5 on a visual analog scale, 50 mg tramadol was injected intravenously. If such pain was persistent, 30 mg ketoracin or 75 mg diclofenac was injected intravenously.

The outcome measures were obtained during the original study. The primary outcome was intraoperative cerebral perfusion, which was assessed by cerebral oximetry. The secondary outcome was the change in perioperative cognitive function, which was assessed by the Mini-Mental State Examination (MMSE).

Right- and left-sided regional cerebral venous oxygen saturation (rS_VO_2) values were obtained simultaneously, and the lower values were used for analysis. The rS_VO_2 and hemodynamic data, including SBP, MBP, CO, and the cardiac index (CI), were recorded at the following 7 points: before induction (T0); before (T1), and after (T2) the loading dose; at 30 (T3), 60 (T4), and 90 (T5) min after the loading dose; and at 30 minutes after terminating the study drug (T6). Arterial blood sampling was performed every 30 minutes to confirm the lowest PaO_2 and Hb values. The lowest rS_VO_2 value during surgery and the duration of rS_VO_2 <60% were recorded.

The MMSE was performed 1 day before and 5 days after surgery. The MMSE score was obtained during the daytime to minimize the impact of circadian rhythms on alertness. Consciousness status (i.e., alert) and sufficient pain control (VAS <5) were confirmed before administering the MMSE to avoid bias. No morphine was administered due to the risk of mental clouding from active morphine metabolites. We randomized the order of test items to minimize learning effects. The incidence of POCD, defined as a decrease >2 points from the baseline MMSE score, was recorded. No changes were made to the outcome assessments during the study.

SPSS software for Windows (version 24.0; SPSS Inc., Chicago, IL, USA) was used for the analysis. Data are presented as mean ± SD or absolute values. One-way analysis of variance (ANOVA) was used to compare intergroup differences in continuous variables. The Chi-Squared test or Fishers exact test was used to compare categorical variables. Hemodynamic and $rSVO_2$ values were compared using repeated-measured ANOVA and one-way ANOVA if a significant difference was found among the groups. Paired *t*-tests with the Bonferroni correction for multiple comparisons were performed to identify any significant changes from baseline values. A *P* value <.05 was considered significant.

3. Results

In total, 72 patients were assessed for eligibility and 60 were enrolled in the study. Twenty patients were allocated to each group. All patients completed the study, and there were no missing or lost data. None of the patients were excluded during the study due to hemodynamic instability or side effects of the study drugs. The study flow chart is presented in Figure 1.

Patient characteristics, including age, sex, height, weight, and ASA physical status were similar among all 3 groups. Intraoperative variables, including the duration of surgery, level of the fused spine, lowest PaO_2, and lowest Hb, were also similar among the 3 groups (Table 1).

Intraoperative hemodynamic variables are shown in Table 2. Values before administration of the study drugs were similar among the 3 groups. SBP and MBP were maintained within target values and were similar among all 3 groups throughout the study. CO and CI were comparable at T1 among the groups. After administration of the study drugs, CO and CI were significantly higher in group M than in groups S and N during all periods. In group M, CO and CI increased significantly compared to basal values, both during administration of the study drug and after its termination. In groups S and N, CO and CI decreased significantly compared to the basal values after administration of the study drug, but returned to basal values after its termination.

Figure 2 shows the rS_VO_2 before and after administration of the study drug. Basal rS_VO_2 was similar among all 3 groups, but was significantly higher in group M than the other 2 groups during administration of the study drug ($P=.01$). In group M, intraoperative rS_VO_2 values were not different from the basal value. In groups S and N, rS_VO_2 was significantly lower than the basal value during administration of the study drug and did not differ from the basal value after terminating infusion.

The lowest intraoperative rS_VO_2 was higher and the duration of rS_VO_2 <60% was shorter in group M than the other 2 groups. The basal MMSE scores were comparable among the 3 groups. The MMSE scores decreased on postoperative day 5 in all groups. However, the MMSE score was significantly higher in group M than the other groups (Table 3).

Ten patients (16.7%) showed POCD on postoperative day 5; 2 patients in group M, 4 patients in group S, and 4 patients in group N ($P=.74$). The lowest rS_VO_2 value and the duration of rS_VO_2 <60% were significantly different between patients with and without POCD (Table 4).

4. Discussion

The results of this secondary analysis of an RCT comparing milrinone, SNP, and NTG demonstrate that hypotension induced with milrinone, compared to SNP and NTG, resulted in better intraoperative cerebral perfusion and postoperative cognitive function in elderly patients undergoing spine surgery. However, milrinone did not decrease the incidence of POCD compared to the other vasodilating agents. Induced hypotension with milrinone has been shown in previous studies to exert beneficial effects on renal perfusion and quality of the surgical field.[9,10] Although the use of milrinone failed to decrease the incidence of POCD in this study, the results suggest that hypotension induced with milrinone preserves intraoperative cerebral perfusion.

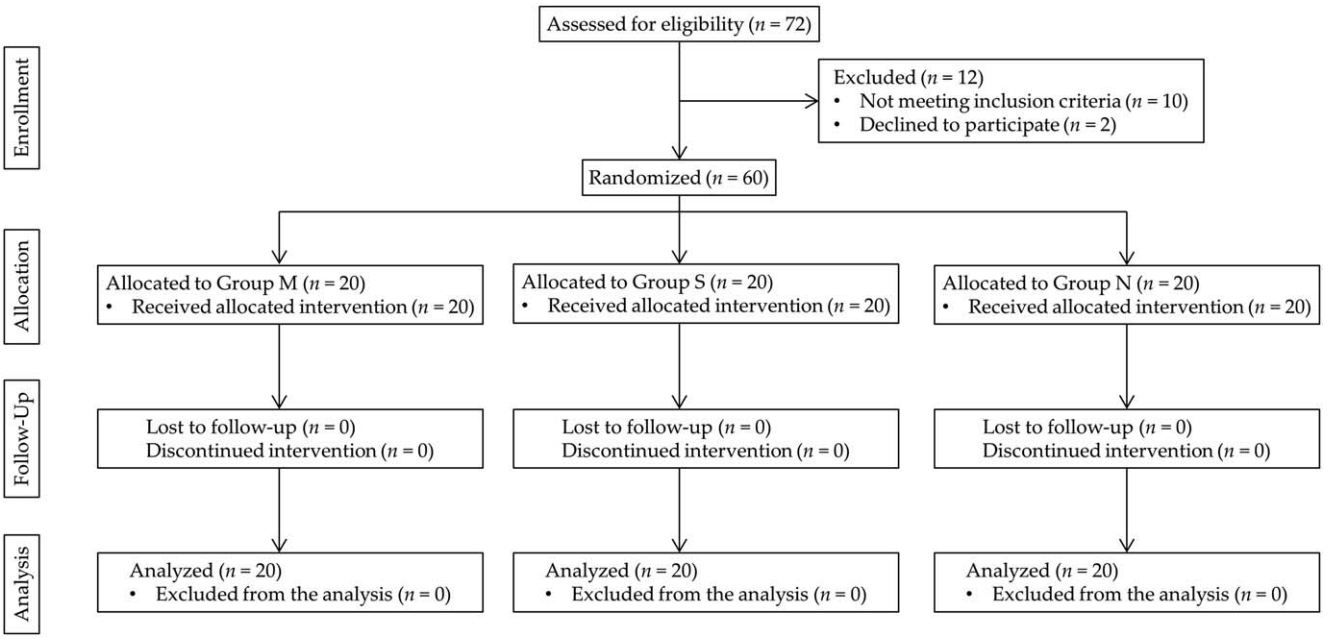

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart of the study.

Table 1

Patient characteristics and intraoperative variables.

	Group M (n=20)	Group S (n=20)	Group N (n=20)	*P* value
Age (years)	71.4±3.5	70.5±4.8	68.9±4.2	.18
Sex (Male/Female)	7/13	6/14	9/11	.70
Height (cm)	156.0±8.8	154.2±10.4	158.9±9.0	.28
Weight (kg)	61.0±8.4	57.9±10.4	63.2±7.3	.17
ASA physical status (I/II/III)	2/14/4	5/14 /1	5/12/3	.86
Level of the fused spine (1/2/3)	3/8/9	3/15/2	2/13/5	.12
Duration of surgery (minutes)	202±42	192±36	193±31	.68
Lowest PaO_2 (mm Hg)	151.1±28.0	160.2±26.8	151.4±22.7	.45
Lowest hemoglobin (g/dl)	9.0±0.6	8.9±0.6	8.8±0.6	.44

Values are expressed as numbers or mean ± standard deviation. ASA, American Society of Anesthesiologists.

A major advantage of using milrinone for induced hypotension during spine surgery is that the inotropic effect of milrinone might increase major organ perfusion despite low blood pressure. The 2 most popular drugs for inducing hypotension are SNP and NTG. Contrary to an animal study, in which administration of SNP or NTG did not result in decreased CO,[11] co-administration of vasodilators and general anesthesia in elderly patients resulted in decreased CO during induced hypotension. Inhaled anesthetics are associated with dose-related depression of cardiac contractility and, by extension, CO,[12] where this effect is even more pronounced in elderly patients in whom the β-receptor-mediated compensatory mechanism has decreased.[13] On the other hand, the inotropic effect of milrinone was expected to increase CO, which in turn increased major organ perfusion while maintaining a low blood pressure. In the original study, higher urine output was considered an indirect indicator of the maintenance of renal perfusion;[10] in this secondary analysis, higher rS_VO_2 was considered an indirect indicator of the maintenance of cerebral perfusion.

Table 2

Intraoperative hemodynamic variables.

	Group M (n=20)	Group S (n=20)	Group N (n=20)
SBP (mm Hg)			
T1	120±9	124±15	127±12
T2	89±7	87±4	87±5
T3	89±7	88±5	86±5
T4	91±7	90±5	86±4
T5	91±7	89±6	86±4
T6	120±13	126±12	120±14
MBP (mm Hg)			
T1	91±5	93±10	96±9
T2	65±5	65±3	65±2
T3	63±3	64±3	64±2
T4	65±2	65±2	65±2
T5	65±3	66±3	65±2
T6	85±10	92±8	87±8
CO (L/minutes)			
T1	3.9±0.8	3.9±0.8	4.1±0.7
T2	4.1±0.9	3.4±0.7*	3.3±0.7*
T3	4.3±1.4	3.3±0.7*	3.3±0.5*
T4	4.5±1.4	3.2±0.7*	3.3±0.7*
T5	4.6±1.3	3.3±0.6*	3.3±0.6*
T6	4.9±1.2	3.8±0.7*	3.9±0.6*
CI (L/minutes/m^2)			
T1	2.6±0.4	2.6±0.4	2.6±0.3
T2	2.8±0.4	2.4±0.4*	2.4±0.5*
T3	2.9±0.7	2.3±0.4*	2.4±0.6*
T4	3.0±0.5	2.4±0.4*	2.5±0.6*
T5	3.1±0.5	2.4±0.4*	2.4±0.5*
T6	3.2±0.6	2.7±0.4*	2.7±0.3*

Values are expressed mean ± standard deviation.

* indicates $P < .05$ compared to the group M. SBP, systolic blood pressure; MBP, mean blood pressure; CO, cardiac output; CI, cardiac index; T1, before loading dose; T2, after loading dose; T3, 30 minutes after loading dose; T4, 60 minutes after loading dose; T5, 90 minutes after loading dose; T6, 30 minutes after termination of study drug.

The possible adverse effects of milrinone include hemodynamic changes and arrhythmias.[14] Milrinone may cause ventricular tachyarrhythmia, which can result in cardiac ischemia or sudden cardiac death. However, arrhythmias associated with milrinone are rare and tend to occur in patients with pulmonary hypertension.[8] As expected, none of the patients in the present study exhibited arrhythmias perioperatively. Milrinone may cause an increase in venous vessel capacitance, resulting in headache, syncope, and severe hypotension. Hypotension occurs dose-dependently.[14] The dosing regimen for milrinone, SNP, and NTG used in the present study was validated in previous studies.[1,2,9] Moreover, achieving adequate blood pressure, namely a 30% decrease in SBP or a MBP of 60 to 65 mm Hg, was the goal of the present study. Therefore, the investigators meticulously avoided severe hypotension; as a result, the patients did not exhibit any adverse effects.

Cerebral oximetry is a noninvasive method for monitoring cerebral oxygenation and perfusion usually used for cardiac anesthesia.[15,16] Although rS_VO_2 measured with cerebral oximetry is not cerebral perfusion per se, it can be used as an indirect indicator of cerebral perfusion. In this study, intraoperative changes of the rS_VO_2 values were similar to the CO changes in each group, and various factors such as MBP, $PaCO_2$, PaO_2, and Hb, which could affect rS_VO_2, were comparable among the 3 groups. Therefore, our findings suggest that the inotropic effect of milrinone resulted in maintenance of, higher rate of cerebral perfusion compared to other study drugs. We expect that milrinone may be protective in at-risk elderly patients who have pre-existing cerebral hypoperfusion and require induced hypotension during surgery.

The most consistently reported risk factors for POCD are preexisting cognitive impairment, older age, lower educational achievement, major, prolonged, or emergency surgical procedures, and postoperative pain.[17–22] In the present study, the prevalence rates of these risk factors were similar among the 3 groups. Patients with a history of cerebrovascular disease and/or cognitive dysfunction were excluded from the study. The MMSE score 1 day before surgery, age, and extent of surgery were similar

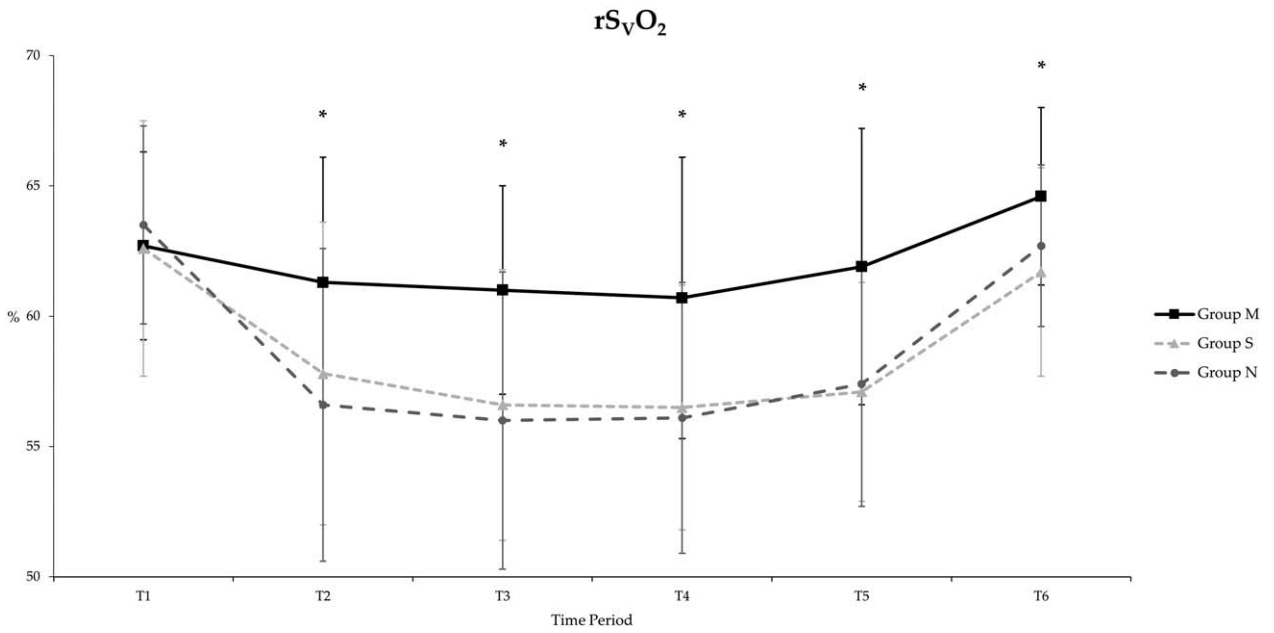

Figure 2. Intraoperative cerebral oximetry values. Error bars represent standard deviations. * indicates $P < .05$ compared to group M. T1, before the loading dose; T2, after the loading dose; T3, 30 minutes after the loading dose; T4, 60 minutes after the loading dose; T5, 90 minutes after the loading dose; T6, 30 minutes after terminating the study drug.

among the 3 groups. Perioperative management, including drug treatments and pain management, were strictly controlled in all 3 groups according to the study protocol.

It has been demonstrated that a lower rS_VO_2 is related to more frequent and severe postoperative cognitive impairment in many clinical settings.[23–25] In particular, several studies have reported correlations between cerebral desaturation and POCD in elderly patients undergoing orthopedic surgery. The degree of cerebral desaturation is correlated with POCD in patients undergoing total hip arthroplasty and total knee arthroplasty.[26,27] Several studies have shown that anesthetic management based on intraoperative cerebral oximetry monitoring prevents POCD

Table 3

Intraoperative regional cerebral venous oxygen saturation and perioperative Mini-Mental State Examination.

	Group M (n = 20)	Group S (n = 20)	Group N (n = 20)	*P* value
rS_VO_2				
lowest value (%)	57.2 ± 3.4	53.8 ± 4.9*	53.3 ± 4.8*	.01
duration of < 60% (minutes)	67.5 ± 54.6	114.9 ± 60.0*	109.5 ± 70.2*	.03
MMSE				
preoperative	27.0 ± 0.8	26.7 ± 1.0	26.9 ± 0.9	.45
POD 5	25.9 ± 1.0 †	24.4 ± 1.6 *†	24.8 ± 1.4 *†	<.01

Values are expressed mean ± standard deviation.
* indicates $P < .05$ compared to the group M, † indicates $P < .05$ compared to basal score. rS_VO_2, regional cerebral venous oxygen saturation; MMSE, Mini-Mental State Examination; POD, post-operative day.

Table 4

Comparison of patients with and without decline in postoperative cognitive function.

	Non-POCD (n = 50)	POCD (n = 10)	*P* value
$rSVO_2$			
lowest value (%)	55.5 ± 4.0	50.8 ± 6.1*	<.01
duration of <60% (minutes)	76.6 ± 45.5	200.8 ± 40.7*	<.01
MMSE			
preoperative	26.8 ± 0.9	27.0 ± 0.9	.56
POD 5	25.5 ± 1.1	22.8 ± 1.1*	<.01

Values are expressed mean ± standard deviation.
* indicates $P < .05$ compared to patients without decline. POCD, postoperative cognitive function decline; rS_VO_2, the values of cerebral oximetry; MMSE, Mini-Mental State Examination; POD, post-operative day.

after surgery, including spine surgery.[28–30] Another study involving elderly patients undergoing spine surgery demonstrated that the duration of cerebral desaturation is an independent risk factor for POCD.[31] In the present study, there was a significant difference in intraoperative rS_VO_2 between patients with and without POCD. The lowest rS_VO_2 value in patients with POCD was lower and the duration of rS_VO_2 <60% was longer. The postoperative MMSE score was higher in group M, which had a higher rS_VO_2 during surgery than the other groups. These findings were consistent with the results of previous studies.

Contrary to our expectations, the incidence of POCD was similar among all 3 groups despite the lower degree and shorter duration of cerebral desaturation after the administration of milrinone. In addition, the reported incidence of POCD in elderly patients undergoing major non-cardiac surgery was 26% at 1 week and 10% at 3 months.[23] However, the overall incidence of POCD in this study was lower compared to previous studies. These findings can be explained as follows. First, we aimed to maintain adequate blood pressure during induced hypotension. Although the lower limit of blood pressure considered safe to maintain major organ perfusion in elderly patients is not known, extreme cerebral hypoperfusion was kept to a minimum in this study. Kim et al. reported that the incidence of POCD is associated with a duration of rS_VO_2 <60% in elderly patients undergoing spine surgery.[31] The optimal cutoff value was 157 minutes with sensitivity of 75% and specificity of 72%. In this study, the duration of cerebral desaturation was relatively short in all groups. Second, we excluded patients with a history of cerebrovascular disease and cognitive dysfunction. Our patient selection criteria may have led to the low incidence of POCD. Third, meticulous anesthetic management was performed according to strict hemodynamic management, with administration of standardized fluid and blood products and frequent arterial blood sampling.

We used the MMSE to evaluate POCD because it combines high validity and reliability with brevity and ease of application.[32,33] The MMSE does not provide a complete evaluation of cognitive function, and additional tests could be used to increase sensitivity regarding the detection of cognitive dysfunction. However, certain cognitive function tests cannot be used during the immediate postoperative period, especially after spine surgery, due to the limited mobility of the patients. Also, the higher sensitivity of more extensive testing panels is associated with a longer testing time, which elderly patients may not be willing to undergo during the immediate postoperative period. The MMSE was chosen for use in our study to ensure patient cooperation with the cognitive function test procedure during the early postoperative period after major surgery.

There were several limitations to the present study. First, this study was conducted as a secondary analysis of a RCT; therefore, the sample size was based on a different primary outcome. Thus, the study might be underpowered. Second, POCD was followed-up for a relatively short period. The incidence of short-term POCD was low, and there was no significant difference in the incidence rate among the groups. However, considering that the incidence of long-term POCD is lower than that of short-term POCD, we postulated that the short follow-up period was sufficient.[18,19] Third, patients at high risk of developing POCD (history of cerebrovascular disease and cognitive dysfunction) were excluded from the study.

In conclusion, milrinone used to induce hypotension resulted in better intraoperative cerebral perfusion and postoperative cognitive function compared to the commonly used agents SNP and NTG. Considering the beneficial effect of milrinone on end organs, we recommend its use for induced hypotension in elderly patients undergoing spine surgery. Further studies with larger sample sizes, longer follow-up periods, and patients at high risk of developing POCD are warranted.

Author contributions

Conceptualization: Hoon Choi, Wonjung Hwang.
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Formal analysis: Hoon Choi, Wonjung Hwang.
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Software: Hoon Choi.
Supervision: Wonjung Hwang.
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Visualization: Hoon Choi.
Writing – original draft: Hoon Choi.
Writing – review & editing: Hoon Choi, Jaewon Huh, Jungmin Koo, Jiyoung Lee, Wonjung Hwang.

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