

# Replacement of dexmedetomidine loading with midazolam for sedation in elderly patients with spinal anesthesia

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## Abstract

**Background:** Dexmedetomidine is an effective sedative during spinal anesthesia. However, it requires a loading dose, which can result in transient hypertension, hypotension, bradycardia, and/or sinus arrest. In addition, the time required to reach an appropriate depth of sedation may cause anxiety to the patients. Therefore, we examined whether an intravenous bolus of midazolam could replace the loading dose of dexmedetomidine for sedation during surgery in elderly patients who received spinal anesthesia.

**Methods:** Patients aged over 60 years who scheduled to undergo total knee arthroplasty under spinal anesthesia were enrolled in this study. The patients were randomized into 2 groups. Patients in dexmedetomidine group (group D) (n=20) were administered a loading dose of dexmedetomidine (1.0 µg/kg over 10 min) intravenously followed by dexmedetomidine maintenance (0.5 µg/kg/h). Patients in group MD (n=20) were administered an intravenous midazolam (0.05 mg/kg) followed by dexmedetomidine maintenance (0.5 µg/kg/h) intravenously. Heart rate (HR), mean arterial blood pressure (MBP), peripheral oxygen saturation (SpO<sub>2</sub>), and patient state index (PSI) were recorded. Ramsay sedation scale (RSS) scores were evaluated at 10 minutes after drug administration and the end of surgery.

**Results:** A total of 40 subjects were enrolled in the present study. At baseline, there was no between-group difference in HR. Ten minutes after drug administration, group D had lower HR than group MD (62.1±9.4 versus 69.6±13.4, P=.047). PSI was significantly lower in group MD at 10 minutes after drug administration (82.8±13.0 versus 72.0±16.0, P=.024); there was no between-group difference at 30 and 60 minutes, and lower values in group D at the end of surgery (70.2±22.6 versus 79.7±10.9, P=.011). The RSS score showed statistically significantly deeper sedation in group MD 10 minutes after drug administration, but no difference at the end of surgery.

**Conclusions:** An intravenous bolus of midazolam is a viable alternative to dexmedetomidine loading for sedation during surgery in elderly patients who received spinal anesthesia. This is especially effective for patients who are at high risk for bradycardia or who want a faster sedation.

**Abbreviations:** ASA = American Society of Anesthesiologists, group D = dexmedetomidine group, group MD = midazolam/dexmedetomidine group, HR = heart rate, MBP = mean arterial blood pressure, NRS = numeric rating scale, PACU = post-anesthesia care unit, PSI = patient state index, RSS = Ramsay Sedation Scale, SpO<sub>2</sub> = peripheral oxygen saturation.

**Keywords:** dexmedetomidine, midazolam, sedation, spinal anesthesia

## 1. Introduction

Dexmedetomidine is a highly selective alpha 2 adrenergic receptor agonist and has sedative and analgesic effects without

respiratory depression.<sup>[1,2]</sup> It is increasingly used as a sedative during spinal anesthesia. However, it requires a loading dose, which can result in transient hypertension, hypotension, bradycardia, and/or sinus arrest.<sup>[3-7]</sup> Elderly patients may be more susceptible to these hemodynamic side effects.<sup>[8]</sup> In addition, the time required to reach an appropriate depth of sedation may cause anxiety to the patients.

Midazolam is 1 of the classic sedatives and is commonly used for sedation during spinal anesthesia. It has a fast onset and short recovery time. It also provides better intraoperative amnesia and minimal hemodynamic effects.<sup>[9-11]</sup> However, it occasionally can result in deeper sedation, respiratory depression, and confusion, especially when administered to elderly patients.<sup>[12,13]</sup>

Therefore, we examined whether an intravenous bolus of midazolam could effectively replace the loading dose of dexmedetomidine for sedation during surgery in elderly patients who received spinal anesthesia.

## 2. Materials and methods

This study was approved by the hospital's Institutional Review Board, and written informed consent was received from all subjects. Patients were included in the study if they were over 60 years of age, classified as American Society of Anesthesiologists

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(ASA) physical status I or II, and scheduled for total knee arthroplasty under spinal anesthesia. Exclusion criteria included allergies or adverse drug reactions to midazolam or dexmedetomidine, heart block, uncontrolled hypertension, psychiatric disorder, or a history of sleep apnea and airway obstruction. Using computer-generated randomization, patients were randomized to receive either dexmedetomidine (group D) or midazolam/dexmedetomidine (group MD) for sedation during surgery.

None of the patients received premedication. After the patient arrived in the operating room, routine intraoperative monitoring including non-invasive blood pressure, electrocardiography, pulse oximeter, and patient state index (PSI) using SedLine Sedation Monitor (Masimo, Irvine, CA) were initiated. The patient was asked to rate their baseline level of anxiety on a 10-point numeric rating scale (NRS), where 0 represented 'calm and comfortable' and 10 represented 'very anxious and stressed.' With the patient in the right or left lateral recumbent position, spinal anesthesia was performed. After the anesthetic drug was injected, the patient was promptly moved to the supine position. After confirmation of sensory blockade, baseline Ramsay Sedation Scale (RSS) scores were evaluated.<sup>[14]</sup>

Patients in group D (n=20) were administered a loading dose of dexmedetomidine (1.0 µg/kg over 10 min) intravenously followed by a maintenance dose of 0.5 µg/kg/h. Patients in group MD (n=20) were administered an intravenous midazolam dose of 0.05 mg/kg immediately followed by a maintenance dose of dexmedetomidine of 0.5 µg/kg/h intravenously. All patients breathed spontaneously and 100% oxygen was supplied via simple oxygen mask at a rate of 6L/min throughout the operation. Rescue sedation with midazolam 0.02 mg/kg was available to patients in both groups and was administered if the patient complained of alertness, which was defined as failure to induce sedation when it developed at 10 minutes after drug administration.

Heart rate (HR), mean arterial blood pressure (MBP), peripheral oxygen saturation (SpO<sub>2</sub>), and PSI were recorded at 10 minutes, 30 minutes, and 60 minutes after drug administration, and the end of surgery. RSS scores were evaluated at 10

minutes after drug administration and the end of surgery. HR, MBP, SpO<sub>2</sub>, and NRS of anxiety were recorded immediately before leaving the post-anesthesia care unit (PACU) after surgery. All adverse events including bradycardia (HR < 50 beats/min), hypotension (MBP < 60 mmHg sustained for >10 min), oxygen desaturation (SpO<sub>2</sub> < 90%), or nausea during surgery and in the PACU were recorded.

The primary outcome measure of this study was the HR at 10 minutes after drug administration. Sample size was calculated based on a difference of HR at 10 minutes in a previous study (61.3 ± 11.7 versus 52.9 ± 5.7 beats/min),<sup>[15]</sup> a 2-sided α of 0.05, and a power of 80%. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as absolute numbers (%). Continuous variables were compared using the Student's t-test or the Mann-Whitney U test. Categorical variables were compared using the chi-square or the Fisher's exact test. Hemodynamic data, SpO<sub>2</sub>, and PSI were analyzed using repeated measures ANOVA. In the case of a significant difference on repeated measures ANOVA, the Student's t-test was used for post-hoc testing. RSS scores were compared using Mann-Whitney U test. P values < .05 were considered statistically significant. All statistical analyses were performed using the IBM SPSS Statistics for Windows/Macintosh software version 23.0 (IBM Corp., Armonk, NY).

### 3. Results

A total of 40 subjects were enrolled in the present study. There were no significant differences in the subjects' age, sex, height, weight, ASA class, level of sensory block, operation time, and preoperative NRS of anxiety between the 2 groups (Table 1).

Although there was no difference in baseline measurements of HR between groups, patients in group D had lower HR at 10 minutes after drug administration compared with those in group MD (group D versus group MD, 62.1 ± 9.4 versus 69.6 ± 13.4 beats/min, P = .047) (Fig. 1A). However, there was no significant difference in HR between the 2 groups after 30 minutes. The changes in MBP and SpO<sub>2</sub> were not different between the 2 groups (Fig. 1B and C). PSI showed a significantly lower value in

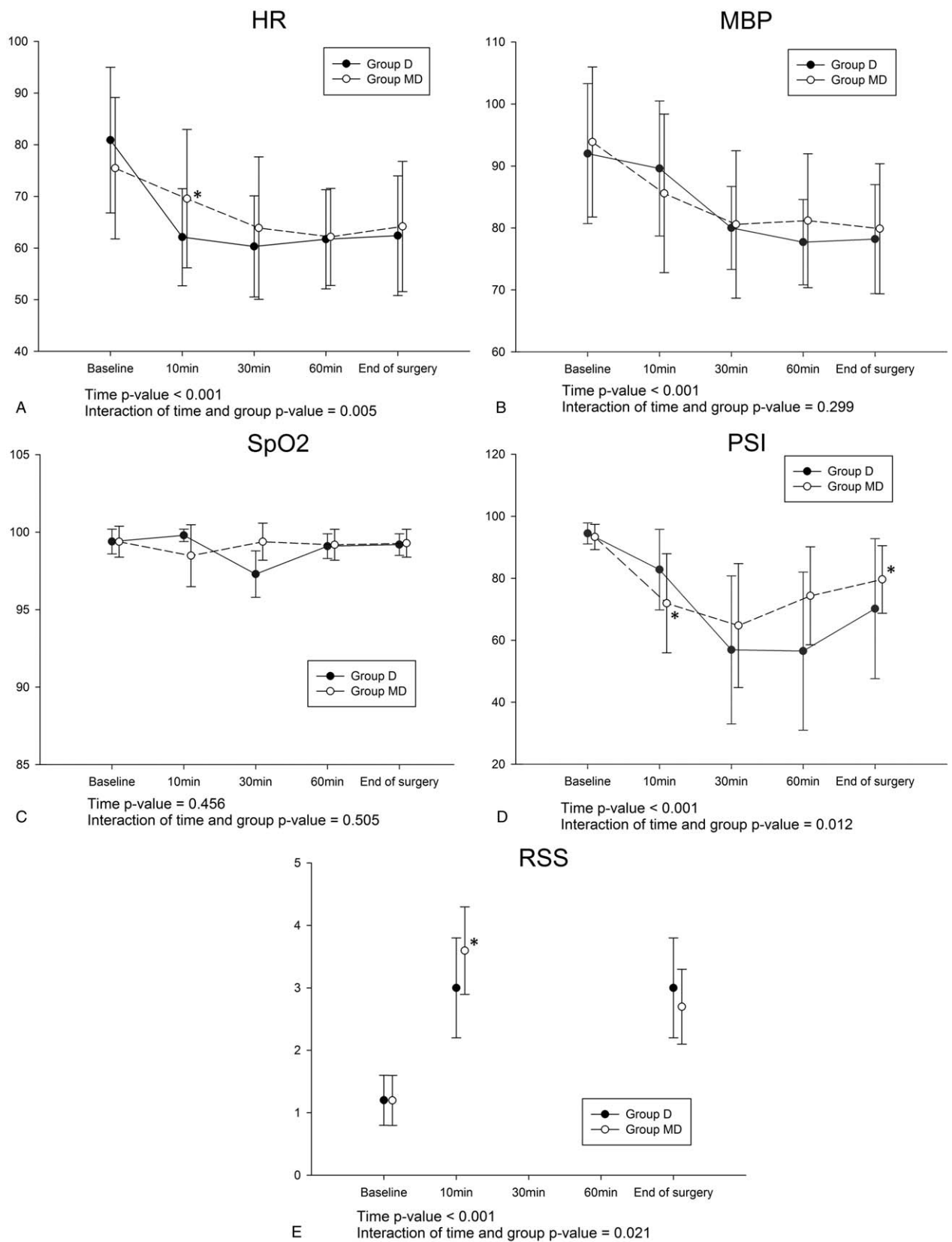
**Table 1**  
Patient characteristics and clinical data.

	Group D* (n=20) Mean ± SD or N (%)	Group MD† (n=20) Mean ± SD or N (%)	P value
Age, yr	69.2 ± 5.9	69.8 ± 5.3	.740
Sex			
Male	17 (85%)	19 (95%)	.302
Female	3 (15%)	1 (5%)	
Height, cm	154.9 ± 7.8	153.2 ± 7.6	.501
Weight, kg	64.2 ± 8.3	62.3 ± 9.2	.508
ASA			1.000
I	0 (0%)	1 (5%)	
II	20 (100%)	19 (95%)	
Level of sensory block			.367
T10	5 (25%)	6 (30%)	
T8	11 (55%)	6 (30%)	
T6	3 (15%)	7 (35%)	
T4	1 (5%)	1 (5%)	
Operation time, min	104.0 ± 9.0	99.5 ± 11.7	.180
Preoperative NRS of anxiety	6.1 ± 1.8	5.7 ± 2.0	.566

ASA = American Society of Anesthesiologists; NRS = numerical rating scale, SD = standard deviation.

\* Patients administered a loading dose of dexmedetomidine followed by a maintenance dose of dexmedetomidine.

† Patients administered an initial dose of midazolam followed by a maintenance dose of dexmedetomidine.



**Figure 1.** Changes in HR (A), MBP (B), SpO<sub>2</sub> (C), PSI (D), and RSS score (E), \**P* < .05 between the 2 groups. Group D: Patients administered a loading dose of dexmedetomidine followed by a maintenance dose of dexmedetomidine; Group MD: Patients administered an initial dose of midazolam followed by a maintenance dose of dexmedetomidine. HR=heart rate, MBP=mean arterial blood pressure, PSI=patient state index, RSS=Ramsay Sedation Scale SpO<sub>2</sub>=peripheral oxygen saturation.

**Table 2**

**Comparison of heart rate, mean arterial blood pressure, peripheral oxygen saturation, and numeric rating scale of anxiety just before leaving the post-anesthesia care unit.**

	Group D* (n=20)	Group MD† (n=20)	P value
	Mean ± SD	Mean ± SD	
HR	63.9 ± 11.8	66.6 ± 11.5	.478
MBP	81.0 ± 7.3	83.4 ± 9.6	.382
SpO <sub>2</sub>	99.4 ± 0.7	99.4 ± 0.8	.826
NRS of anxiety	2.5 ± 2.0	1.6 ± 1.2	.096

HR=heart rate, MBP=mean arterial blood pressure, NRS=numeric rating scale, SD=standard deviation, SpO<sub>2</sub>=peripheral oxygen saturation.

\*Patients administered a loading dose of dexmedetomidine followed by a maintenance dose of dexmedetomidine.

†Patients administered an initial dose of midazolam followed by a maintenance dose of dexmedetomidine.

group MD at 10 minutes after drug administration (group D versus group MD, 82.8 ± 13.0 versus 72.0 ± 16.0,  $P=.024$ ), no difference between the 2 groups at 30 minutes and 60 minutes, and lower values in group D at the end of surgery (group D versus group MD, 70.2 ± 22.6 versus 79.7 ± 10.9,  $P=.011$ ) (Fig. 1D). The RSS score showed statistically significantly deeper sedation in group MD 10 min after drug administration (group D versus group MD, 3.0 ± 0.8 versus 3.6 ± 0.7,  $P=.010$ ), but no difference at the end of surgery (Fig. 1E).

The HR, MBP, SpO<sub>2</sub>, and NRS of anxiety just before leaving the PACU were not significantly different between the 2 groups (Table 2). There were no significant differences in adverse effects including failure to induce sedation, bradycardia, hypotension, nausea, and desaturation between the 2 groups (Table 3).

#### 4. Discussion

Dexmedetomidine can provide adequate sedation during spinal anesthesia,<sup>[16]</sup> but side effects such as bradycardia, hypotension, and transient hypertension may occur and loading time is required until adequate sedation. The main finding of this study is that intravenous administration of midazolam and immediate maintenance with dexmedetomidine compared with loading dexmedetomidine results in less reduction in HR and a deeper level of sedation in a shorter time during spinal anesthesia in elderly patients.

In group MD, PSI, and RSS showed deeper sedation at 10 minutes after the administration of small dose of midazolam compared with group D. This can be explained by the rapid onset of midazolam. On direct observation, patients were seen to be entering sleep mode faster. Patients undergoing surgery find

entering the operating room to be a stressful situation, and being awake during the loading time of dexmedetomidine adds to the stress; therefore, reducing the awake time by administering an intravenous bolus of midazolam is beneficial. This may be 1 of its most important advantages. Previous studies comparing the same 2 groups as our study using bispectral index (BIS) showed that BIS at 10 minutes was similar between the 2 groups.<sup>[15]</sup> However, they infused maintenance dexmedetomidine 10 minutes after the administration of midazolam, whereas in our study dexmedetomidine was administered immediately after administration of midazolam; therefore, there would have been deeper sedation at 10 minutes. Although the PSI is a clinically validated measure of the effect of anesthesia and sedation,<sup>[17,18]</sup> further studies are needed to validate PSI when dexmedetomidine is administered. Although not statistically significant in our study, 2 patients in group D complained of awake state even after 10 minutes of drug administration and required additional midazolam. This supports the fact that a bolus of midazolam followed by continuous infusion of dexmedetomidine can achieve rapid sedation compared with dexmedetomidine loading.

The PSI values were lower in group D from 30 minutes of drug administration to the end of surgery. However, the RSS at the end of surgery was similar. This suggests that over-sedation may have occurred in group D. As the half-life of dexmedetomidine is 2 hours, recovery may be delayed if an excessive dose is administered.<sup>[19]</sup> Therefore, we can expect to avoid over-sedation and early recovery by replacing the loading of dexmedetomidine with midazolam. Future studies should investigate the effect of postoperative recovery.

Midazolam is well known to cause a paradoxical reaction such as restlessness and disinhibition instead of sedation in some patients.<sup>[20]</sup> However, this reaction was not observed because the patients in this study were maintained with dexmedetomidine after administration of midazolam. Although there were no statistical differences, the NRS of anxiety before leaving the PACU was lower in group MD, which may affect overall satisfaction with the surgery. In addition, considering previous studies, the use of midazolam is expected to have an amnestic effect during surgery.<sup>[9]</sup> In a study comparing midazolam alone and midazolam plus dexmedetomidine, patients receiving the combination of dexmedetomidine and midazolam showed a calmer, more cooperative, and more satisfying effect.<sup>[21]</sup> Therefore, it is possible that a bolus of midazolam followed by maintenance with dexmedetomidine may improve the patient's overall satisfaction as compared with dexmedetomidine loading or use of midazolam alone.

A systematic review reported lower HR for 24 hours when dexmedetomidine was used, compared with midazolam.<sup>[22]</sup> In our study, we also found that there was less decrease in HR 10 minutes after drug administration with the use of midazolam compared with dexmedetomidine loading, consistent with previous studies. However, there was no difference in HR measured after 30 minutes between the 2 groups because maintenance dexmedetomidine was administered to both groups. Initially, dexmedetomidine acts on the peripheral blood vessels to induce vasoconstriction and reactive bradycardia; in severe cases, cardiac arrest occurs.<sup>[4,7,23]</sup> However, midazolam can reduce adverse effects such as bradycardia because a large amount of dexmedetomidine administration in a short time can be avoided. In our study, severe bradycardia (<50 beats/min) also occurred in group MD. Although early reductions in HR in the group MD are less, caution should be paid to severe bradycardia. MBP is also reported to be lower in patients administered dexmedetomidine

**Table 3**

**Adverse effects.**

	Group D* (n=20)	Group MD† (n=20)	P value
	N (%)	N (%)	
Failure to induce sedation	2 (10%)	0 (0%)	.487
Bradycardia (<50 bpm)	4 (20%)	3 (15%)	1.000
Hypotension (ephedrine)	0 (0%)	2 (10%)	.487
Nausea	1 (5%)	0 (0%)	1.000
Desaturation (<90%)	0 (0%)	1 (5%)	1.000

\*Patients administered a loading dose of dexmedetomidine followed by a maintenance dose of dexmedetomidine.

†Patients administered an initial dose of midazolam followed by a maintenance dose of dexmedetomidine.



compared with midazolam,<sup>[24,25]</sup> but since our study maintained dexmedetomidine after administration of midazolam, there was no difference in MBP between the 2 groups.

Even a high dose of dexmedetomidine is rarely associated with respiratory problems. However, midazolam may cause respiratory depression by reducing hypoxic ventilator responses when administered in excessive doses.<sup>[26]</sup> Our study showed no difference in SpO<sub>2</sub> between the 2 groups. However, in group MD, 1 patient had decreased respiration and SpO<sub>2</sub> temporarily decreased to less than 90%; stable breathing was maintained after stimulating the patient and encouraging breathing again. Depending on the patient's age, weight, and other conditions, a bolus of midazolam may be excessive, so monitoring for respiration is essential. A future study should determine whether reduction in adverse effects such as respiratory depression while maintaining the same sedative status can be achieved with even smaller doses of midazolam.

There were several limitations in this study. The postoperative satisfaction score was not investigated. Further studies are needed to determine whether the replacement of dexmedetomidine loading with a bolus of midazolam will increase patient satisfaction. As mentioned above, different doses of midazolam were not compared. This study was underpowered to detect the differences in sedation state, as it was not the parameter to obtain sample size.

In conclusion, an intravenous bolus of midazolam is a viable alternative to dexmedetomidine loading for sedation during surgery in elderly patients who received spinal anesthesia. This is especially effective for patients who are at high risk for bradycardia or who want a faster sedation. Future studies are needed to identify the optimal doses of midazolam and dexmedetomidine to further avoid HR reduction and reduce side effects.

## Author contributions

**Conceptualization:** Jeong-Hyun Choi.

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**Writing – review & editing:** Jeong-Hyun Choi, Yong Hyun Cho. Jeong-Hyun Choi orcid: 0000-0003-1995-1220

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