Original Article

Incidence of adverse events for procedural sedation and analgesia for cardioversion using thiopental in elderly patients: a multicenter prospective observational study

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Aim: The incidence and characteristics of thiopental-related adverse events (AEs) in elderly patients during procedural sedation and analgesia (PSA) have not been well studied. We aimed to characterize thiopental-related AE in elderly patients during PSA and compare the incidence of AE in elderly patients with non-elderly adults.

Methods: This is a secondary analysis of the Japanese Procedural Sedation and Analgesia Registry (JPSTAR). We included all adult patients who received thiopental for PSA in the emergency departments and excluded patients who received concomitant sedative(s) in addition to thiopental or patients with missing body weight data. We compared the incidence of AE between the non-elderly (18–64 years) and elderly groups (≥65 years).

Results: The JPSTAR had data on 379 patients who received thiopental for PSA and included 311 patients for analysis. Most (222/311, 71.3%) were elderly. Cardioversion was the most common reason for PSA (96.1%). The AE incidence between groups overall was similar, however, hypoxia was significantly more frequent in the elderly compared with the non-elderly group (10.3% versus 2.2%; adjusted odds 5.63, 95% confidence interval 1.27–25.0). The initial and total doses of thiopental were significantly lower in the elderly group than in the non-elderly group (1.95 mg/kg versus 2.21 mg/kg and 2.33 mg/kg versus 2.93 mg/kg, respectively).

Conclusions: Although elderly patients received lower doses of thiopental, hypoxic events were significantly more frequent in this group compared with the non-elderly patients. However, the AE incidence was similar.

Key words: Adverse effects, analgesia and anesthesia, cardioversion, elderly, thiopental

INTRODUCTION

WITH AN AGING world population, the number of people aged 65 years or over will double by 2050 from the current level.[1] Japan is the most aged country in the world and the percentage of those aged 65 years or over will reach 30.9% in 2030.[1] The number of patients visiting emergency departments (EDs) is increasing, including greater utilization by patients aged 65 years or over.[2] The Japanese Fire and Disaster Management Agency reported that 62.2% of patients transported to the EDs were 65 years or older.[3] Many elderly patients undergo ED-based procedural sedation and analgesia (PSA) in the world.[4,5] In Japan, as in other countries, 56.6% of patients undergoing PSA were 65 years or older.[6] Elderly patients have increased sensitivity to sedatives.[5] A previous study showed that while the total dose of sedatives decreased in the elderly, adverse events (AEs) from procedural sedation increased with age.[7]

The demand for sedatives used for mechanical ventilation rose sharply with the coronavirus disease 2019 (COVID-19) pandemic in 2020. Sedatives such as propofol, midazolam, and ketamine, which are frequently used in PSA, were in serious short supply.[8]

Although uncommon in North America,[9,10] physicians still use thiopental for PSA in many countries, including Japan, and the safety profile is comparable to other sedatives.[7,11–13] Thiopental during PSA might be a reasonable option when other sedatives are in short supply. The incidence and characteristics of thiopental-related AEs in elderly patients during PSA, however, are not well studied.

We aimed to characterize thiopental-related AEs in PSA and to compare the incidence of AEs in elderly patients with non-elderly adults. We hypothesized that AEs would be more common in elderly than non-elderly patients.

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Received 11 Oct, 2022; accepted 11 Dec, 2022

METHODS

Study design

WE ANALYZED DATA from the Japanese Procedural Sedation and Analgesia Registry (JPSTAR), a multicenter prospective registry of ED patients.[7] We defined PSA as "any systemic pharmacological intervention intended to facilitate a painful or uncomfortable procedure." The JPSTAR includes data from patients of all ages who received PSA whether in or outside the ED (e.g., radiology and endoscopy, suites). The JPSTAR excludes patients with airway management (e.g., endotracheal intubation) and treatment of delirium. Ten hospitals in Japan participated in the registry at the time of the analysis. All of the hospitals are urban and have residency programs. Previous results from the JPSTAR demonstrated that over half (56.6%) were 65 years of age or older.[7] Physicians who provided the PSA entered data into the JPSTAR registry using standardized data collection screens within the University of New Mexico–hosted REDCap server.[14,15] All JPSTAR sites regularly review data to ensure that all eligible patients undergoing PSA are included. Institutional review boards of all participating hospitals and University of New Mexico approved the design and the need for informed consent.

Population

We analyzed data from the JPSTAR collected between May 2017 and Aug 2021. We included all adult patients (≥18 years) who received thiopental for PSA (n = 379) in the analysis. We excluded patients with (i) concomitant use of thiopental and other sedatives (midazolam, n = 1; propofol, n = 4), (ii) missing data (unknown concomitant use of other sedatives, n = 29; weight, n = 20), and (iii) sedation outside the ED (n = 14). We defined elderly as aged 65 years or over.[1] We considered the patients 18–64 years as non-elderly and those 65 years and older as elderly.

MEASUREMENTS

OUR PRIMARY AIM compared the incidence of thiopental-related AEs in elderly with non-elderly patients. The JPSTAR collects reports for the following AEs: cardiac arrest, hypoxic ischemic brain injury, apnea (requiring an intervention, such as repositioning, jaw thrust, or bag-valve-mask ventilation), glossoptosis, hypoxia (saturation of peripheral oxygen [SpO_2] <90%), laryngeal spasm, hypersalivation, hypertension (systolic pressure > 180 mmHg), hypotension (systolic pressure < 90 mmHg), tachycardia (heart rate > 120 bpm), bradycardia (heart rate < 60 bpm), other dysrhythmias, agitation, prolonged sedation, nightmares, and local anesthetic toxicity.[7] Secondary aims were comparative procedure success and initial and total doses of thiopental (mg/kg).

Statistical analyses

We used median and interquartile range summary statistics for continuous measures and number and percentage (%) for categories to describe patient characteristics. We described the dose of thiopental (mg/kg) using mean and standard deviation. We used the chi-square test to compare categories and Mann–Whitney U test to compare continuous measures. We used a 5% two-tailed type I error rate to determine statistical significance. We adjusted for sex, body mass index, American Society of Anesthesiologists (ASA) physical status classification, supplemental oxygen use, analgesic use, and multiple administrations of thiopental, based on clinical plausibility and *a priori* knowledge.[16] AEs and procedure success were tested using logistic regression models, adjusting for the covariates listed previously.[16]

We used the EZR graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria version 4.0.3) for statistical analyses.[17]

RESULTS

THERE WERE 1,341 patients in the registry between May 2017 and August 2021. We included 311 patients (23.1%) who received thiopental (elderly, n = 222; non-elderly, n = 89) in the analysis (Fig. 1). The frequency of thiopental use for PSA varied among hospitals from 0% to 56.7%. Four (out of ten hospitals) had at least one adult patient who received thiopental for PSA. Other sedatives such as midazolam, propofol, and ketamine were frequently used for PSA in those hospitals where thiopental was not routinely used. The median age of the non-elderly group was 57 years (interquartile range, 46–61 years) and 74 years (interquartile range, 70–79 years) for the elderly group. The proportion of a high ASA score (≥3) was similar between the two groups (26.9% versus 26.5%, P = 0.94). Cardioversion was the most common indication for PSA for both groups (96.6% versus 95.9%, P = 0.66; Table 1).

Table 2 shows the primary outcome. The overall AE incidence was similar between groups (13.4% versus 20.7%, adjusted odds ratio 1.75, 95% confidence interval [CI] 0.85–3.58; P = 0.13). The incidence of hypoxia (SpO_2 < 90%) was significantly higher in the elderly group than in the non-elderly group (23/222, 10.3% versus 2/89, 2.2%; adjusted odds ratio 5.63, 95% CI 1.27–25.0; P = 0.023). The

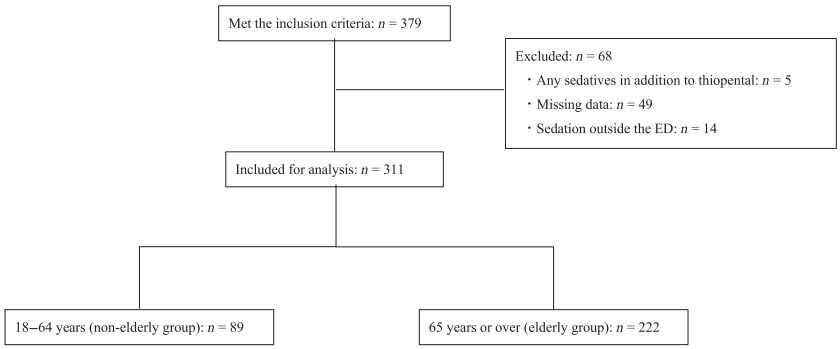


Fig. 1. Study participant flow. ED, emergency department.

Table 1. Patient characteristics

Variables, *n* (%)	Non-elderly group (*n* = 89)	Elderly group, (*n* = 222)	*P* value
Age (years), median (IQR)	57 (46–61)	74 (70–79)	<0.001
Sex (male)	50 (56.1)	117 (52.7)	0.57
BMI (IQR)	23.0 (21.8–26.0)	23.7 (21.1–25.3)	0.36
ASA class			0.016
1	8 (8.9)	4 (1.8)	
2	57 (64.0)	159 (71.6)	
3	24 (26.9)	56 (25.2)	
4	0 (0)	3 (1.3)	
Indication			0.66
Cardioversion	86 (96.6)	213 (95.9)	
Dislocation reduction	2 (2.2)	8 (3.6)	
Others	1 (1.1)	1 (0.4)	
Supplemental oxygen during PSA	37 (41.5)	88 (39.6)	0.75
Analgesic use	1 (1.1)	3 (1.3)	0.29

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IQR, interquartile range; PSA, procedural sedation and analgesia.

incidence of interventions for AEs was similar (Table 3). Patients who required a repeat administration of thiopental in the overall incidence of AEs were 9/46 (19.5%) in the elderly and 3/12 (25%) in the non-elderly groups.

The procedure success rates were the same in both groups at 98.1%. The initial dose of thiopental was significantly lower in the elderly than in the non-elderly group (1.95 mg/kg versus 2.21 mg/kg, mean difference −0.25, 95% CI −0.41 to −0.086; $P = 0.011$) as was the total dose of thiopental (2.33 mg/kg versus 2.93 mg/kg, mean difference −0.60, 95% CI −0.89 to −0.30; $P < 0.001$; Table 4). Figure 2 shows the initial and total doses of thiopental by age groups. The initial dose of thiopental peaked at the 50–64 age group and gradually decreased, while the total dose of thiopental decreased with increasing age.

DISCUSSION

WE OBSERVED A similar incidence of thiopental-related AEs for the patients in the elderly and non-elderly groups who underwent PSA. While hypoxia was significantly more frequent in the elderly group, neither apnea nor interventions for AEs significantly differed between the groups. The most common indication for PSA was cardioversion. As far as we know, this is the first study that characterized thiopental-related AE during PSA in elderly patients and compared the incidence of AEs between elderly patients and non-elderly patients who received thiopental for PSA.

In both elderly and non-elderly patients, the most common type of AE was respiratory. In one randomized

Table 2. Adverse event incidence

Variables	Non-elderly group (n = 89), n (%)	Elderly group (n = 222), n (%)	AOR (95% CI)	P-value
All adverse events	12 (13.4)	46 (20.7)	1.75 (0.85 to 3.58)	0.13
Cardiac arrest	0	0	N/A	N/A
Hypoxic ischemic brain injury	0	0	N/A	N/A
Apnea	9 (10.1)	21 (9.4)	0.93 (0.39 to 2.18)	0.86
Glossoptosis	2 (2.2)	6 (2.7)	1.19 (0.22 to 6.31)	0.84
Hypoxia	2 (2.2)	23 (10.3)	5.63 (1.27 to 25.0)	0.023
Hypotension	1 (1.1)	4 (1.8)	1.42 (0.14 to 13.60)	0.76
Bradycardia	0	1 (0.4)	N/A	N/A
Others	1 (1.1)	2 (0.9)	1.17 (0.098 to 13.80)	0.9

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable.

Table 3. Interventions for adverse events

Variables	Non-elderly group (n = 89), n (%)	Elderly group (n = 222), n (%)	AOR (95% CI)	P-value
Simple manual airway maneuvers (e.g., jaw thrust, head tilt/chin lift)	3 (3.3)	7 (3.1)	0.98 (0.23–4.11)	0.98
Advanced airway maneuvers	0	0	N/A	N/A
Bag-valve-mask ventilation	9 (10.1)	27 (12.1)	1.24 (0.54–2.86)	0.6
Fluid bolus	0	2 (0.9)	N/A	N/A
Vasopressor administration	0	0	N/A	N/A
Others[†]	2 (2.2)	15 (6.7)	3.78 (0.82 to 17.3)	0.08

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; N/A, not applicable.
[†]One patient received intravenous atropine for bradycardia in the elderly group. One patient was treated for mild asthma attack in the non-elderly group.

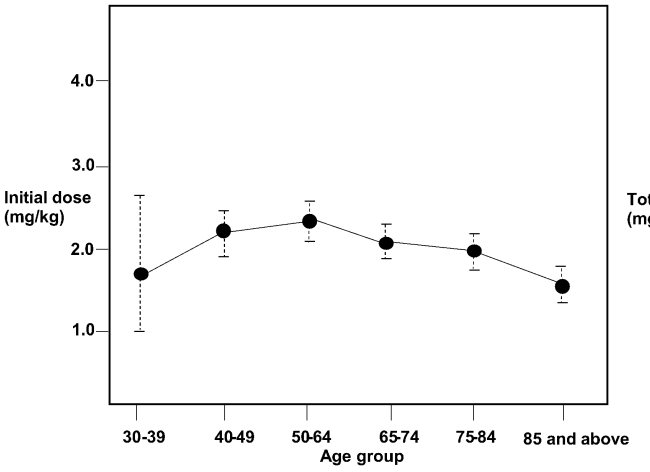
Table 4. Initial and total doses of thiopental (mg/kg)

	Non-elderly group (n = 89), mean (SD)	Elderly group (n = 222), mean (SD)	Mean difference (95% CI)	P-value
Initial dose	2.21 (0.82)	1.95 (0.59)	−0.25 (−0.41 to −0.086)	0.011
Total dose	2.93 (1.22)	2.33 (1.17)	−0.60 (−0.89 to −0.30)	<0.001

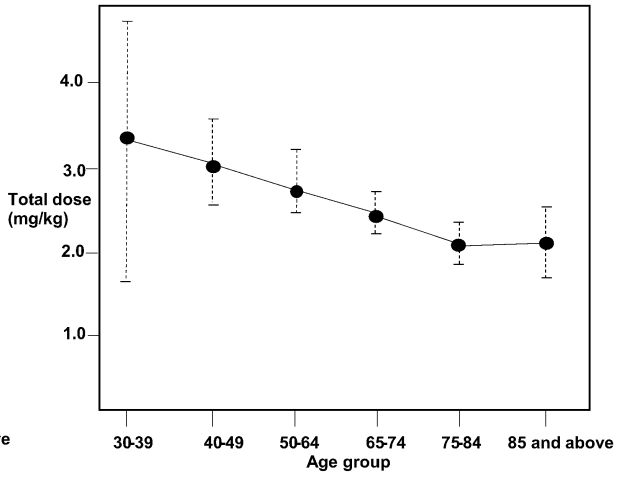
Abbreviations: CI, confidence interval; SD, standard deviation.

controlled trial with a thiopental/fentanyl (1 mg/kg, 1 μg/kg respectively) arm, hypoxia requiring intervention was the most common AE (8.6%).[12] In another randomized controlled trial with a thiopental/fentanyl (2 mg/kg, 2 μg/kg) arm, apnea was the most common (50%).[11] While these two trials looked at thiopental plus fentanyl, our results which looked at each individually similarly showed high rates of respiratory AE.

The overall incidence of AEs was 20.7% and 13.4% in the elderly and non-elderly groups. A Dutch study in which



Age group (years)	Patient number	Initial dose (mg/kg) Mean (95% CI)
30-39	5	1.84 (0.95 to 2.72)
40-49	26	2.20 (1.97 to 2.43)
50-64	58	2.23 (1.98 to 2.47)
65-74	114	2.02 (1.90 to 2.13)
75-84	81	1.94 (1.81 to 2.06)
85 and above	27	1.72 (1.55 to 1.88)



Age group (years)	Patient number	Initial dose (mg/kg) Mean (95% CI)
30-39	5	3.23 (1.60 to 4.85)
40-49	26	3.08 (2.63 to 3.52)
50-64	58	2.84 (2.50 to 3.18)
65-74	114	2.50 (2.24 to 2.75)
75-84	81	2.14 (1.96 to 2.31)
85 and above	27	2.20 (1.76 to 2.63)

Fig. 2. Initial and total doses of thiopental by age groups. The initial dose of thiopental peaked at the 50–64 age group and gradually decreased, while the total dose of thiopental decreased with increasing age. CI, confidence interval.

emergency physicians performed PSA in the ED had an overall AE incidence of 10.6% with hypoxia (4.0%) and apnea (2.9%) occurring as respiratory AEs.[9] AE rates in our study were higher than the Dutch study. The difference could explain several reasons. First, definition of AEs was different between the studies. The Dutch study defined AE as follows: apnea (>20 s), hypoxia (oxygen saturation < 90% for >60 s). Second, patients in our study were older and more patients had an ASA class of 3 or 4 than in the Dutch study.

Hypoxia was significantly more common in the elderly than in the non-elderly group in our study. The supplemental oxygen use during PSA was only 39.6% in the elderly group. Importantly, supplemental oxygen use during propofol sedation is recommended in the clinical practice guideline.[18] Administration of supplemental oxygen prevents hypoxia and patients tolerate apnea due to preoxygenation. Both propofol and thiopental have rapid onsets of action and quick recovery.[19] Similar to propofol for PSA, routine supplemental oxygen may reduce the incidence of hypoxia for the elderly patients receiving thiopental. Notably, capnography is not routinely used in Japanese EDs,[20] thus transient apnea may be overlooked. The incidence of hypoxia could be explained by overlooked apnea; thus, routine use of capnography might need to be considered.

Elderly patients received lower initial and total thiopental doses than non-elderly patients (initial 1.95 mg/kg versus 2.21 mg/kg, $P = 0.011$; total: 2.33 mg/kg versus 2.93 mg/kg, $P < 0.001$). As elderly patients are more sensitive to sedatives than non-elderly patients, reduced sedative doses for PSA may be necessary.[21] Previous studies on PSA with propofol also showed that elderly patients required fewer initial and total doses of propofol than non-elderly patients for PSA.[22,23] Similar to propofol, the dose of thiopental likely needs to be reduced in the elderly patients.

Sedatives such as propofol, midazolam, and ketamine have been used in both mechanical ventilation management and PSA. These sedatives, particularly propofol, have been in serious short supply during the pandemic,[8] and might be prioritized for use in mechanical ventilation management. As such, propofol may not be available for PSA in some EDs. Continuous administration of thiopental is used only for selected cases such as status epilepticus[24] or refractory intracranial hypertension,[25] and is less likely to be in short supply. Thiopental for

PSA might be a good option when sedative supplies are low, such as during the COVID-19 pandemic.

We note several limitations. Treating physicians reported data into the registry that is open to reporting bias. To address this, each site investigator reviewed the nursing records to minimize bias. Second, the type of monitoring and timing of measurements depended on the physician who performed PSA. Japanese EDs do not routinely use capnography,[20] thus transient apnea may be overlooked. Likewise, the incidence of hypotension in our study was low but may be overlooked due to long noninvasive blood pressure measurement intervals. Third, our data consist of EDs in Japan and most PSA indications were for cardioversion in our study. A short-duration PSA such as cardioversion seldom requires repeating doses of sedatives. As thiopental has a longer context-sensitive half-time than propofol,[26] AEs might be different for long-duration PSAs such as shoulder reduction or endoscopy that often require a repeat administration of sedatives and concomitant use of analgesics. Fourth, our data did not include many patients with high body mass index, thus characteristics of AEs might be different for patients with obesity. Fifth, all of the hospitals in the registry are teaching hospitals that are located in Japan, thus the results might differ for nonteaching hospitals.

CONCLUSION

OVERALL, THE AE incidence in elderly and non-elderly patients receiving thiopental for PSA was similar. While the elderly patients received lower thiopental doses, hypoxic events were significantly more frequent in the elderly compared with the non-elderly patients. Supplemental oxygen and capnography during PSA may reduce the incidence of hypoxia.

ACKNOWLEDGEMENTS

WE THANK THE JPSTAR and all personnel at participating institutions who contributed the data.

DISCLOSURE

APPROVAL OF THE Research Protocol with Approval No. and Committee Name: Approval No. 18–68; the protocol was approved by the Institutional Review Board of Fukui Prefectural Hospital.

Informed Consent: The requirement for informed consent of the patients was waived.

Registry and the Registration No. of the Study/Trial: N/A.

Animal Studies: N/A.

Conflict of Interest: None declared.

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