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ORIGINAL RESEARCH **GERIATRIC ANESTHESIA**

Post-induction hypotension following entropy guided equipotent doses of propofol and thiopental in elderly surgical patients

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ABSTRACT

Background & Objective: Geriatric patients with reduced vascular auto regulation ability are susceptible to blood pressure fluctuations after anesthesia induction and specifically may suffer from hypotension, showing heightened sensitivity to anesthetics. It is unclear which induction agent, thiopental or propofol, is preferable with regard to hemodynamic stability after anesthesia induction. EEG "entropy" may help titrate induction doses and thus reduce their adverse effects in this category of patients. We conducted this research to compare the two drugs, using entropy to guide the induction dose, regarding hemodynamic stability.

Methodology: Sixty patients, over 65 years old, were randomly divided into two groups based on the anesthetic induction agent: Group P (propofol) and Group T (thiopental). Arterial blood pressure (ABP), heart rate (HR), induction doses, and postoperative Troponin I levels denoting myocardial injury secondary to hypotension were measured.

Results: Group P had more post-induction hypotension and less HR changes than Group T ($P < 0.001$). Induction doses in both groups were less than the conventional range. Troponin I levels in both groups were similar and statistically insignificant.

Conclusion: Induction technique with thiopental guided with entropy provided greater hemodynamic stability, with reduced fall in systolic, diastolic and mean arterial pressure in elderly surgical patients compared to those who were administered propofol guided with entropy.

Trial Registry: PACTR202406560110826.

Abbreviations: EEG - Electroencephalography; EMG - electromyography; PIH - post-induction hypotension; SE- state entropy; RE - response entropy;

Keywords: Propofol; Thiopental; Post-induction hypotension; Entropy; Elderly.

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1. INTRODUCTION

Hemodynamic alteration during anesthesia induction is common, with about one-third of hypotension incidents occurring before skin incision.[1] Worldwide post-induction hypotension (PIH) rates are around 10.3%, and can be as high as 66.96%.[2] PIH is defined as arterial hypotension within the first 20 min after anesthesia induction or until the surgical incision starts.[3] PIH impacts patient outcomes,[4] and is correlated with the induction drug's plasma concentration, age, dose, infusion rate, and cardiac output. Common induction anesthetics include propofol, thiopental, ketamine, and etomidate.[5]

Advances in healthcare have improved life expectancy and quality of life for the elderly,[6] who account for 40% of surgeries annually.[7] Older adults, with diminished vascular auto-regulation, are at higher risk for PIH due to blood pressure changes and increased sensitivity to anesthetics like thiopental, propofol, and midazolam. Despite the need for reduced induction doses in the elderly, it is unclear whether thiopental or propofol is preferable.

Futier et al. found that individualized management targeting systolic blood pressure within 10% of baseline significantly reduced postoperative organ dysfunction in patients with an average age of 70.[9] Cerebral monitoring with processed electroencephalography (EEG) (GE entropy) can help tailor anesthetic doses to patient's response, reducing adverse effects like hypotension. GE entropy produces state entropy (SE) and response entropy (RE)[10] values from EEG and electromyography (EMG) signals, aiding in the clinical management of anesthetized patients. SE and RE values near 40 indicate a low probability of consciousness. SE is less comprehensive than RE which involves uncovered perception of pain as well.[11]

1.2. Objective of study

The primary outcome was the incidence of post induction hypotension (PIH) till 30 minutes post entropy guided induction of general anesthesia with propofol and thiopental. And the secondary outcomes were the total consumption of propofol and thiopental until defined entropy hypnosis level was obtained and assessment of high-sensitive troponin I levels 6 hours post-operatively denoting myocardial injury secondary to hypotension.

2. METHODOLOGY

The study was a randomized prospective comparative study conducted from September 2022 to September 2023 at Ain Shams University Hospitals. It was approved by the research ethics committee at the faculty of medicine, Ain Shams University (FMASU 2022 / 2023) and registered with Pan African Clinical Trial Registry, identifier: PACTR202406560110826.

Sixty patients, above 65 years old, of either sex and ASA physical status I-III were scheduled for any kind of surgery requiring general anesthesia except cardiac surgery. Patients were randomized into two equal groups by a computer-generated random numbers table, each consisting of thirty patients and received one of this following:

Group P: Patients received propofol 0.8-1 mg/kg as the intravenous anesthetic agent for induction.

Group T: Patients received thiopental 2 mg/kg as the intravenous anesthetic agent for induction.

Patients with known history of allergy to propofol or thiopental, patients diagnosed Alzheimer disease, dementia, and previous cerebrovascular accident, history of cardiac disease, including ischemic heart disease, heart failure, and/or valvular heart disease with established myocardial function impairment, ASA IV, long term use of drugs affecting central nervous system, were excluded.

The sample size was calculated using NCSS PASS 11.0 and based on a study carried out by Steib and colleagues [34], who mentioned that propofol significantly reduced the diastolic blood pressure at 1, 3 and 5 min after induction compared to thiopental. Group sample sizes of 30 patients in Group T (Thiopental group) and 30 patients in Group P (Propofol group) achieve 95% power to detect a difference of -16.0 between the null hypothesis that both group means are 58.0 and the alternative hypothesis that the mean of group 2 is 74.0 with estimated group standard deviations of 5.0 and 3.0 and with a significance level (alpha) of 0.05000 using a two-sided two-sample t-test. Sample size was inflated by 20% to compensate for attrition problems in prospective studies.

2.1. Study interventions and outcomes

Pre-anesthetic evaluation of every participant was done, including airway assessment, clinical history, general and systemic examination, routine biochemical investigations, chest X-ray, electrocardiography, and any previous anesthetic exposure and drug sensitivity. All patients provided fully informed consent. The procedure to be performed was explained in detail to the patients.

On the morning of this intervention, patients were randomly distributed and assigned to two groups guided by their anesthetic induction agent; Group P and Group T. The patients were admitted to the operating room where standard ASA monitoring and entropy sensors

Table 1: Baseline characteristics of the studied groups

Variables		Thiopental Group (n = 30)	Propofol Group (n = 30)	P-value
Age (y)	Mean ± SD	70.9 ± 3.1	71.3 ± 3.5	^0.666
	Range	65.0–77.0	65.0–78.0	
Sex	Male	18 (60.0)	20 (66.7)	#0.592
	Female	12 (40.0)	10 (33.3)	
Weight (kg)	Mean ± SD	91.3 ± 5.4	90.2 ± 6.1	^0.480
	Range	79.8–102.1	80.0–106.1	
ASA	I	5 (16.7)	6 (20.0)	30.857
	II	13 (43.3)	14 (46.7)	
	III	12 (40.0)	10 (33.3)	

Data presented as mean ± SD or n (%): ASA - American Society of Anesthesiologists; ^: Independent t-test; #: Chi square test. n: number.

were attached. Intravenous line (IV) was inserted using an 18G cannula. A high-sensitive troponin I sample was withdrawn from all patients before induction.

Premedication with midazolam 1 mg and fentanyl 1 µg/kg IV were given. All patients who were allowed to breathe 100% oxygen for 3 min before induction of anesthesia, EEG entropy monitor was connected. For Group P: propofol was given for IV induction in over a period up to 90 seconds, with titration to RE valued 40; this was confirmed clinically with loss of response to verbal commands. For Group T: thiopental was given for IV induction in over a period up to 90 sec, with titration to RE valued 40; this was confirmed clinically with loss of eyelash reflex.

The end point for induction of anesthesia was 40 being the RE value. Muscle relaxation was done by atracurium 0.5 mg/kg IV. Anesthesia was maintained with 100% oxygen mask-ventilation. Trachea was intubated with a cuffed endotracheal tube. Patients were not to be touched or otherwise disturbed for 5 min post intubation to discover this magnitude of RE-SE difference and the presence or absence of EMG during anesthesia without surgery, and to monitor magnitude of hypotension if it occurred. Inhalational anesthetic agents were initiated after 3 min of intubation. Monitoring and measuring SBP, DBP, MAP, RE and SE at baseline, and T1-T6 till up to 3 min post intubation were performed using M-entropy module (S5 Datex Ohmeda, Instrumentarium Corp., Helsonki, Finland). The findings which were recorded on a particularly prepared proforma for every patient were:

- T0 = Baseline (before fentanyl as a narcotic).
- T1 = Induction.
- T2 = 1 min post induction.
- T3 = 3 min post induction.
- T4 = immediately following using laryngoscope.
- T5 = 1 min post intubation.
- T6 = 3 min post intubation (inhalational anesthetic started at this point)

Total doses of propofol and thiopental given during induction of anesthesia were recorded. Anesthesia was maintained using sevoflurane and oxygen air mixture, and muscle relaxation was continued with atracurium. At the end of surgery, residual neuromuscular block was reversed with 2.5 mg of neostigmine and 1 mg of atropine IV, and repeated once if necessary.

High-sensitive troponin I was assessed for all patients 6 h postoperatively to assess the occurrence of myocardial injury secondary to hemodynamic instability. All patients in both groups were closely monitored with the incision of skin for detection of any possible complication. Hypotension (decrease in MAP of > 30% compared to immediate pre-induction values) was treated with boluses of ephedrine 6 mg every 3 min as needed. Bradycardia (HR < 50 beats/min) was treated with atropine 0.01 mg/kg IV in both groups.

The primary outcome was the incidence of PIH till 30 min post induction of anesthesia with entropy guided equipotent doses of propofol and thiopental. The secondary outcomes were the total consumption of propofol and thiopental until defined entropy hypnosis level was obtained and assessment of high-sensitive troponin I levels 6 hours post-operatively denoting myocardial injury.

2.2. Statistical Analysis:

The collected data was revised, coded and introduced to a PC using Statistical Package for Social Science (SPSS) program. Data was presented as mean and standard deviation (± SD) for quantitative parametric data;

Table 2: Comparative mean arterial pressure (MAP) in the studied groups

Time points	Measures	Thiopental Group (n = 30)	Propofol Group (n = 30)	^P-value	Relative effect Mean ± STE 95% CI
T0	Mean ± SD	91.7 ± 6.1	89.6 ± 7.3	0.230	2.1 ± 1.7
	Range	75.0–104.0	72.0–106.0		-1.4–5.6
T1	Mean ± SD	86.5 ± 5.8	83.0 ± 6.7	0.035*	3.5 ± 1.6
	Range	72.0–97.0	66.0–97.0		0.3–6.7
T2	Mean ± SD	79.0 ± 6.7	73.3 ± 7.0	0.002*	5.7 ± 1.8
	Range	63.0–91.0	55.0–88.0		2.1–9.2
T3	Mean ± SD	72.2 ± 7.1	64.4 ± 6.0	< 0.001*	7.7 ± 1.7
	Range	55.0–87.0	48.0–78.0		4.3–11.1
T4	Mean ± SD	73.3 ± 6.8	66.2 ± 6.1	< 0.001*	7.1 ± 1.7
	Range	57.0–87.0	50.0–80.0		3.8–10.5
T5	Mean ± SD	71.1 ± 7.2	63.4 ± 6.1	< 0.001*	7.8 ± 1.7
	Range	54.0–86.0	47.0–77.0		4.3–11.2
T6	Mean ± SD	69.1 ± 7.6	60.8 ± 6.1	< 0.001*	8.4 ± 1.8
	Range	51.0–85.0	45.0–75.0		4.8–11.9

*^Independent t-test. *Significant. Relative effect: STE: Standard error. CI: Confidence interval.*

median and range for quantitative nonparametric data, and as numbers and percentage for qualitative data. The suitable analysis was done according to the type of data obtained. $P < 0.05$ was considered significant.

3. RESULTS

Table 1 shows that there was no significant difference between these studied groups regarding age, sex, weight and ASA grade.

The mean dose of thiopental used was 228.5 ± 13.5 and the mean dose of propofol use was 78.7 ± 9.2 mg.

Table 2 shows MAP decreases in each group beginning from T1 until T6 with transient elevation at T4. MAP is significantly higher in Group T than in Group P at all times. The mean change of MAP was significantly less in Group T (-22.5 ± 6.6 mmHg) than in Group P (-28.8 ± 4.9 mmHg) The difference in the two groups was significant ($P < 0.001$).

Table 3 shows that HR increased in Group T from T1 to T6, these elevations were mainly in T1 to T3. While in Group P HR decreased from T1 till T6, with transient elevation at T4, these reductions were mainly in T1 to T3. HR was significantly higher in the Group T compared to the Group P beginning from T1 to T6.

HR change was significantly increased in Group T (11.2 ± 4.0) than in Group P (-15.0–-1.0). The difference in the two groups was significant ($P < 0.001$).

Thiopental caused hemodynamic stability not requiring any rescue medication in 29/30 patients while ephedrine as a rescue medication was used to maintain hemodynamic stability in 11/30 of patients in the Group P. Hypotension was significantly less frequent in Group T than in Group P. High-sensitive troponin I levels were negative in both groups.

4. DISCUSSION

Our study aimed to compare the hemodynamic response of thiopental vs. propofol for intravenous (IV) induction of anesthesia in elderly patients using entropy monitoring. This observational randomized prospective study showed that thiopental administration in elderly surgical patients was associated with less drop in MAP and HR values compared to propofol. Entropy-guided equipotent doses provided greater hemodynamic stability (reduced fall of SBP, DBP, and MAP) for both drugs by reducing doses in this age group. High-sensitive troponin I levels, indicating myocardial injury secondary to hypotension, were negative in both groups. Previous studies indicated varying impacts of propofol and thiopental on blood pressure in elderly patients, showing more pronounced hemodynamic changes due to age-related physiological alterations.

The entropy monitor provided comprehensive status on muscle relaxation, pain relief, and anesthesia depth. The exact induction dose of propofol and thiopental for stable hemodynamics in elderly patients is not agreed upon.

Table 3: Comparative heart rates in the studied groups

Time points	Measures	Thiopental Group (n = 30)	Propofol Group (n = 30)	^P-value	Relative effect Mean ± SE 95% CI
T0	Mean ± SD	77.8 ± 5.6	76.7 ± 3.9	0.382	1.1 ± 1.2
	Range	69.0–89.0	71.0–84.0		-1.4–3.6
T1	Mean ± SD	80.2 ± 5.7	75.1 ± 4.1	< 0.001*	5.1 ± 1.3
	Range	71.0–90.0	69.0–83.0		2.5–7.7
T2	Mean ± SD	84.1 ± 6.1	72.4 ± 4.6	< 0.001*	11.7 ± 1.4
	Range	73.0–94.0	66.0–82.0		8.9–14.5
T3	Mean ± SD	87.6 ± 6.5	70.0 ± 5.5	< 0.001*	17.6 ± 1.6
	Range	77.0–100.0	61.0–81.0		14.5–20.7
T4	Mean ± SD	89.0 ± 6.9	71.7 ± 5.6	< 0.001*	17.3 ± 1.6
	Range	78.0–102.0	62.0–83.0		14.1–20.5
T5	Mean ± SD	88.0 ± 6.6	69.3 ± 5.6	< 0.001*	18.7 ± 1.6
	Range	77.0–101.0	60.0–81.0		15.5–21.9
T6	Mean ± SD	88.4 ± 6.7	69.1 ± 5.9	< 0.001*	19.4 ± 1.6
	Range	78.0–101.0	59.0–81.0		16.1–22.6

*^Independent t-test. *Significant. SE: Standard error. CI: Confidence interval.*

Previous studies showed various dose ranges in this age group. For propofol different authors suggested different doses; e.g., 1-1.5 mg/kg,[14] 1.27 mg/kg,[7] and 1 mg/kg).[15] FDA recommended induction dose range in age > 55 y; for thiopental less than 1.5 mg/kg.[16] In our study we utilized propofol at a dose of 0.8–1 mg/kg, similar to a study by Brown,[17] and thiopental in a dose of 2.5 mg/kg similar to a study by Sørensen et al.[8] The entropy monitor helped tailor the induction dose to each patient's response, making doses and resulting PIH comparable in both groups.

In our study, no significant differences were found between groups regarding age, sex, weight, and ASA grade, consistent with Nega et al. findings,[1] which associated PIH with age > 60 y, ASA II-III.

MAP decreased in both groups from T1 to T6 with a transient rise at T4, but was significantly higher in the thiopental group. Several studies confirmed thiopental's superiority over propofol in hemodynamic stability, and found a direct correlation between propofol induction dose and severe pre-incision hypotension (MAP ≤ 55 mmHg) in patients over 65.[7, 12, 20] Elderly patients have distinct pharmacokinetic properties, such as reduced elimination and prolonged half-life, exacerbated by altered pharmacodynamics and receptor affinity.[19] In addition, altered lipid and water distribution volumes in the elderly, results in lower distribution of the agents involved, and altered protein bonding causes an increase in circulating serum levels of agents normally bound to albumin.[20]

In this study, increased HR was observed in Group T from T1 to T6, while it decreased in Group P with a transient rise at T4. Kalluri and Mehandale used the change in perfusion index (PI) to explain the peripheral vasodilation (VD) and decrease in cardiac output (COP) that caused the hypotension following induction of anesthesia with propofol, thiopental and etomidate. [21] The ejection fraction and contractility didn't experience instability after induction with all three anesthetic induction agents while there was an ongoing and building up elevation in PI and hypotension from the time of induction, maximally with propofol. A marginal increase in HR was seen with thiopental, while propofol caused a steady fall, concluding that VD and reduced HR were responsible for the hypotension following the induction of anesthesia with these intravenous agents, being maximal with propofol, and providing no evidence of myocardial depression. In our study, Thiopental provided hemodynamic stability without rescue medication in 29/30 patients, while 11/30 propofol patients required ephedrine. Thiopental, unlike propofol, had less pronounced effects on systemic vascular resistance, which could explain this higher MAP with it. Another theory stated that propofol, as a highly lipophilic intravenous anesthetic agent, exerts its profound hypotensive effect primarily through its inhibitory action on the sympathetic nervous system,

temporally relative elevation of cardiac sympathovagal balance, potent vasodilatory properties, negative inotropic effects, and reducing preload and afterload.[22, 23, 24]

Contradicting findings have been reported by some researchers, where thiopental showed lower DBP and MAP than propofol in brain surgery, or in ECT. [15,25,26, 27]

In this study, thiopental induction dose in Group T was 228.5 ± 13.5 mg; while propofol dose in Group P was 78.7 ± 9.2 mg (less than the expected range). We revealed that when RE had a value of 40, the hypotension with thiopental was less than propofol during the period of induction and intubation, so titration guided by RE values avoided further hypotension. Similar findings were reported by various authors.[13, 28, 29, 30] Contrarily, Rao et al. found higher propofol doses were needed for entropy-guided induction.[31] Wesam et al. deemed entropy-guided induction unnecessary in geriatric patients.[32]

High-sensitive troponin I levels were negative in both groups, indicating no myocardial injury. Ruetzler et al. noted perioperative myocardial injury was restricted to patients with preexisting cardiovascular risk, not intraoperative hypotension.[33]

5. LIMITATIONS

Our conclusions are based on documented medication dosing in the elderly aged group which may contain inaccuracies in relation to actual practice. While we included fentanyl in our study, it is not clear how to interpret its concomitant dosing in relation to an expected propofol and thiopental dose range.

6. CONCLUSION

Our induction technique with entropy guided equipotent doses can be used to provide higher stability of the hemodynamics with both of the anesthetic induction drugs: propofol and thiopental, by dose reduction in the category of elderly surgical patients. Thiopental administration was associated with higher mean arterial pressure and heart rate values compared to propofol.

7. Future scope

Incorporation of entropy guidance into general anesthesia induction in elderly surgical patients can avoid the incidence of hemodynamic instability by tailoring a reduced induction anesthetic dose.

8. Data availability

The datasets produced and/or analyzed during the current study are available from the corresponding author on reasonable request.

9. Competing interests

The authors declare that there were no conflicts of interest.

10. Funding

The study was completed with the institutional resources, and no industry funding was involved.

11. Authors' contribution

All authors contributed intellectually to the manuscript and the manuscript has been read and approved by all the authors. All authors read and approved the final manuscript.

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