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ORIGINAL INVESTIGATION

Comparison of arterial hypotension incidence during general anesthesia induction — target-controlled infusion vs. bolus injection of propofol: a randomized clinical trial☆

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Abstract

Background: The incidence of arterial hypotension during induction of general anesthesia is influenced by the method of propofol administration, but there is a dearth of randomized clinical trials comparing bolus injection and target-controlled infusion in relation to arterial hypotension. This study seeks to compare the incidence of arterial hypotension between these two methods of propofol administration.

Methods: This prospective, randomized, single-center, non-blinded study included 60 patients (aged 35 to 55 years), classified as ASA physical status I or II, who were undergoing non-cardiac surgeries. They were randomly allocated using a computer to two groups based on the method of propofol administration during the induction of general anesthesia: the Target Group, receiving target-controlled infusion at 4 μg.mL^{-1}, and the Bolus Group, receiving a bolus infusion of 2 mg.kg^{-1}. Both groups also received midazolam 2 mg, fentanyl 3 μg.kg^{-1}, and rocuronium 0.6 mg.kg^{-1}. Over the first 10 minutes of anesthesia induction, Mean Arterial Pressure (MAP), Heart Rate (HR), level of Consciousness (qCON), and Suppression Rate (SR) were recorded every 2 minutes.

Results: Twenty-seven patients remained in the TCI group, while 28 were in the Bolus group. Repeated measure analysis using mixed-effects models could not reject the null hypothesis for the effect of group-time interactions in MAP (p = 0.85), HR (p = 0.49), SR (p = 0.44), or qCON (p = 0.72). The difference in means for qCON (60.2 for TCI, 50.5 for bolus, $p < 0.001$), MAP (90.3 for TCI, 86.2 for bolus, $p < 0.006$), HR (76.2 for TCI, 76.9 for bolus, p = 0.93), and SR (0.01 for

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TCI, 5.5 for bolus, $p < 0.001$), irrespective of time (whole period means), revealed some significant differences.
Conclusion: Patients who received propofol bolus injection exhibited a lower mean arterial pressure, a greater variation in the level of consciousness, and a higher suppression rate compared to those who received it as a target-controlled infusion. However, the interaction effect between groups and time remains inconclusive.

Introduction

Arterial hypotension occurring during general anesthesia significantly increases mortality and contributes to organ dysfunction during the perioperative period.[1-4] The duration and severity of hypotension are closely linked to the type and extent of organ dysfunction.[1-5] Maheshwari et al[6] revealed that nearly one-third of intraoperative hypotension episodes occur during the time between anesthesia induction and the start of surgery.

Intraoperative hypotension can have various causes, with some anesthetic agents, such as propofol, playing a significant role in inducing hemodynamic changes. Propofol, a commonly used hypnotic agent, is known to be associated with arterial hypotension and a reduction in Systemic Vascular Resistance (SVR).[7,8]

Propofol can be administered during the induction of general anesthesia using different methods, including bolus injection, Manually Controlled Infusion (MCI), or Target-Controlled Infusion (TCI), all based on pharmacokinetic models. Bolus injection is thought to produce more pronounced hemodynamic effects due to the rapid increase in plasma concentration.[9] Conversely, TCI ensures a gradual and consistent attainment of the therapeutic target. Despite a multitude of studies[3,9-11] comparing different propofol administration techniques, the existing evidence is characterized either by its low quality or by conflicting results.

The primary goal of this study is to assess the influence of the propofol infusion protocol (TCI or Bolus) on Mean Arterial Pressure. Secondary outcomes encompass the effects on Heart Rate (HR), level of Consciousness (qCON), and Suppression Rate (SR) when comparing these two administration methods.

Methods

This prospective, randomized, single-center, non-blinded study was carried out at the Hospital Universitário de Brasília from March 2022 to September 2022. Ethical approval for the study was obtained from the Research Ethics Committee of Faculdade de Medicina da Universidade de Brasília in July 2019 (approval number: CEP 3.468.330). It was also registered with the Brazilian Registry of Clinical Trials (REBEC RBR-69px3cj). The complete anonymized dataset (https://doi.org/10.7910/DVN/QOGOYX) and data analysis (https://rpubs.com/gabrielmng/AnaGGVNov23c) are publicly available.

This study enrolled patients aged 35 to 55 years with ASA (American Society of Anesthesiologists) physical status I or II, who were scheduled for elective non-cardiac surgeries under general anesthesia. All participants provided informed written consent and willingly participated in the research. Patients with heart conditions other than chronic arterial hypertension, those requiring combined anesthesia, rapid sequence induction, awake intubation, or intubation under conscious sedation were excluded from the study. Exclusion criteria encompassed protocol deviations, such as variations in dosages or medication injections due to complications during anesthesia induction, as well as data loss.

Patients were divided into two groups using a carefully planned randomization process. Initially, one author prepared 30 identical sealed opaque envelopes for each protocol. These envelopes were then shuffled randomly. A computer was employed to generate a list of 60 numbers, which was organized by a pseudo-random function seeded with the current time in milliseconds by a second author. Subsequently, a third author received these envelopes and sequentially wrote a number on the top of each envelope based on the list generated by the computer. Once the inclusion criteria were satisfied for a patient, the envelope with the lowest available number was selected. The envelope was then handed over to the anesthesiologist responsible for conducting the study protocol. One group of patients received propofol via target-controlled infusion (Target Group) during the induction of anesthesia, while the other group received bolus administration (Bolus Group). The anesthesiologist meticulously recorded study data using electronic records.

Upon entering the operating room, patients were subjected to monitoring, including ECG, pulse oximetry (SpO_2), noninvasive blood pressure (NIBP), and a level of consciousness monitor (CONOX®). After the initial blood pressure measurement, patients received 2 mg of intravenous (IV) midazolam for anxiolysis. Pre-oxygenation was initiated with 100% oxygen at a rate of 5 liters per minute using a face mask. Blood pressure was re-evaluated after 5 minutes, and the resulting Mean Arterial Pressure (MAP) was regarded as the baseline measurement (designated as minute zero or t0).

The Target Group received target-controlled infusion (TCI) of propofol at 4 $\mu g.mL^{-1}$, commencing 2 minutes after an IV bolus of fentanyl (3 $\mu g.kg^{-1}$) at t0, followed by bolus administration of rocuronium (0.6 $mg.kg^{-1}$) after the loss of the eyelash reflex. The plasma concentration was adjusted to a level 30% above the effect-site concentration at which loss of consciousness occurred.

Patients in the Bolus Group had general anesthesia induced with an IV bolus of fentanyl (3 $\mu g.kg^{-1}$) at t0, propofol (2 $mg.kg^{-1}$) at t2, and rocuronium (0.6 $mg.kg^{-1}$) after

the loss of the eyelash reflex. Propofol was infused in about 15 seconds.

Following apnea, face mask ventilation was initiated in volume-controlled ventilation (VCV) mode with a tidal volume (VT) of 6—7 mL.kg^{-1}, no Positive End-Expiratory Pressure (PEEP), and 100% oxygen. Tracheal intubation was performed by direct laryngoscopy 2 minutes after rocuronium administration, and mechanical ventilation began in VCV mode with a VT of 6—7 mL.kg^{-1} (based on ideal weight) and PEEP set at 5 cm H_2O. In the Bolus Group, propofol infusion was initiated after intubation with a target of 1 μg. mL^{-1}, adjusted to maintain the qCON between 40 and 60.

Starting from the initiation of anesthetic induction (t0), measurements for MAP, heart rate (HR), level of consciousness (qCON), and suppression rate (SR) were recorded every 2 minutes until the 10th minute (t10). After intubation, patients were maintained without painful stimuli until t10 to prevent measurement bias. Figure 1 shows the study protocol design.

The sample size calculation was conducted using GPower® software. It considered a mean blood pressure variation of -16.11% in the Target group and -23.08% in the Bolus Group, based on data from a pilot study. The significance level (alpha) was set at 5%, and the study aimed for 80% power. An effect size of 0.82, estimated through the Glass delta method, was used in the calculation. The allocation ratio between the two groups was equal, at 1:1. Based on these parameters, the estimated sample size was 60 patients, allowing for the possibility of up to four patients being lost from each group.

Results

Sixty patients were initially randomized, with 30 assigned to the Target Group and 30 to the Bolus Group. However, five patients had to be excluded from the statistical analysis due to protocol deviations. These deviations included two cases of intubation complications and one case of altered blood pressure in the Target Group, as well as one case of data loss and one case involving unforeseen medication in the Bolus Group (Fig. 2). Detailed patient characteristics can be found in Table 1.

We employed Mixed Effects Models to assess the outcomes of MAP, HR, qCON, and SR within patients, treating patient ID as a random effect. We considered time, group allocation, and the interaction between time and group allocation as fixed effects in our analysis. The primary focus was on group-time interaction, which reflects the longitudinal impact of the interventions.

Additionally, we conducted an analysis of the outcome means, irrespective of time, between the two groups. This analysis revealed significant differences in means for qCON (60.2 for TCI, 50.5 for Bolus, $p < 0.001$), MAP (90.3 for TCI, 86.2 for Bolus, $p < 0.006$), HR (76.2 for TCI, 76.9 for Bolus, $p = 0.93$), and SR (0.01 for TCI, 5.5 for Bolus, $p < 0.001$). Figure 3 illustrates the longitudinal variation of these outcomes between the two groups.

Discussion

The results revealed that the group receiving bolus administration had a lower Mean Arterial Pressure, decreased qCON values, and a reduced SR when looking at the entire ten-minute measurement period compared to the TCI group. However, our mixed-effect analysis could not dismiss the null hypothesis for the group-time interaction, possibly due to the small sample size, which represents the primary limitation of this study.

Propofol is a commonly used hypnotic agent thanks to its swift onset of action, short context-sensitive half-time, and antiemetic properties. However, it is also associated with lowering blood pressure and systemic vascular resistance. These hemodynamic effects of propofol stem from its direct

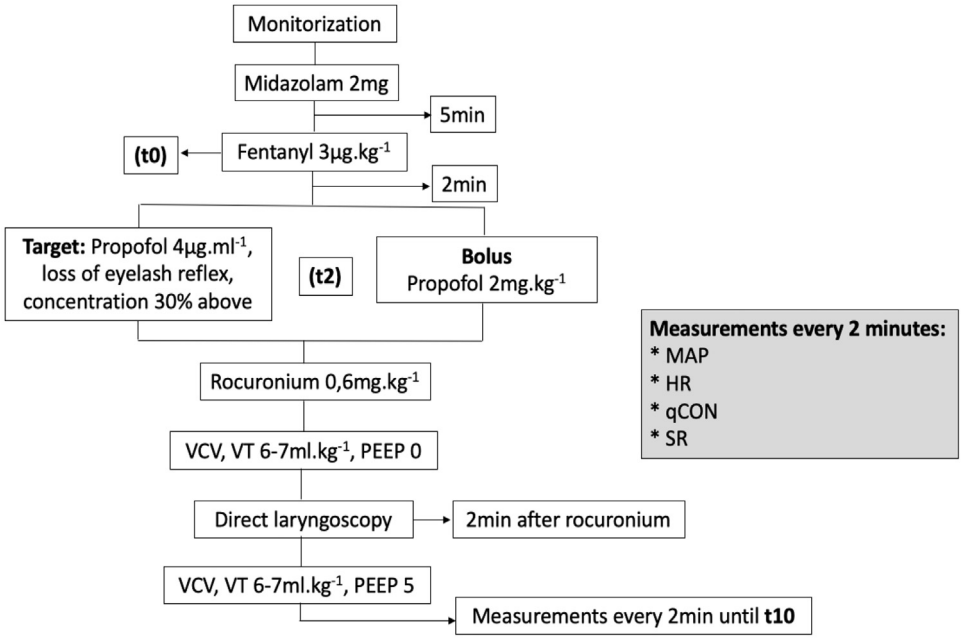

Figure 1 Study protocol design.

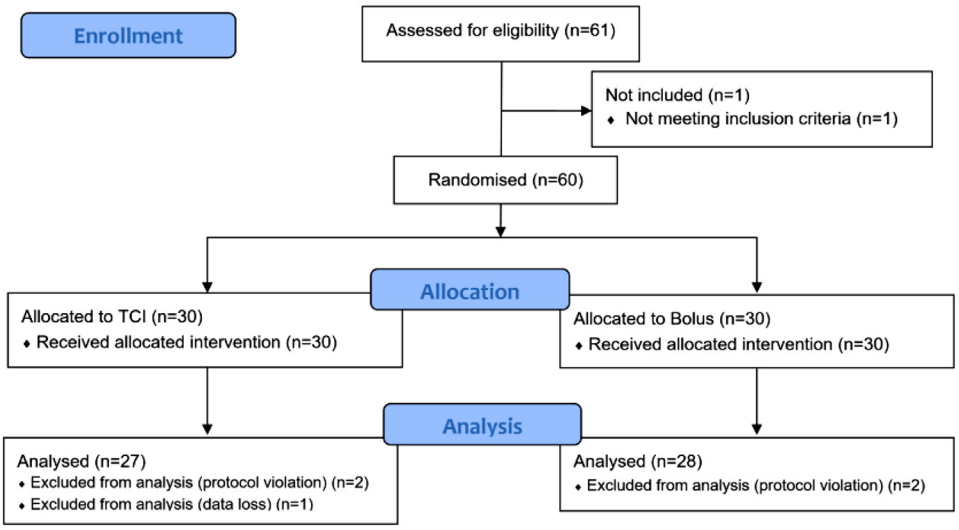

Figure 2 Study Flow Diagram.

Table 1 Characteristics and preoperative data of patients receiving TCI or bolus. Values are mean ± SD.

	Target Group (n = 27)	Bolus Group (n = 28)
Age (years)	44.8 ± 6.57	45.2 ± 6.23
Weight (kg)	68.6 ± 15.55	75.3 ± 7.01
Height (m)	1.64 ± 0.08	1.63 ± 0.12
Body Mass Index (kg.m^{-2})	25.3 ± 4.21	28.1 ± 7.38
Sex		
Female	17 (63%)	21 (75%)
Male	10 (37%)	7 (25%)
Physical status		
ASA I	11 (41%)	13 (46%)
ASA II	16 (59%)	15 (54%)
Procedures		
VLP cholecystectomy	7	9
ERCP	2	5
VLP hernioplasty	3	1
Septoplasty	1	2
Tympanomastoidectomy	2	1
Sinusectomy	3	0
Laryngeal microsurgery	2	1
Lumpectomy/Sectorectomy	2	1
Hysterectomy	1	1
Others	4	7
Comorbidities		
Apnea Syndrome	5	5
Type 2 Diabetes (NID)	1	4
Hypothyroidism	1	1
Asthma	2	0
Others	7	6

VLP, Videolaparoscopic; ERCP, Endoscopic Retrograde Cholangeopancreatography; NID, Non-Insulin Dependent.

impact on the peripheral vascular system, the myocardium, and its depression of the central nervous system, all contributing to a reduction in sympathetic tone.

This study specifically included patients classified as ASA I and II, aged between 35 and 55 years, without an in-depth evaluation of their cardiovascular capacity. The assumption here was that these patients would exhibit a similar hemodynamic response to propofol induction. It is important to note that the hemodynamic effects of propofol are dose dependent. Bolus administration can result in a higher plasma concentration within a shorter timeframe, potentially explaining the lower MAP observed in the bolus group.

The infusion pump used in this study operated based on the Marsh pharmacokinetic model, which solely takes

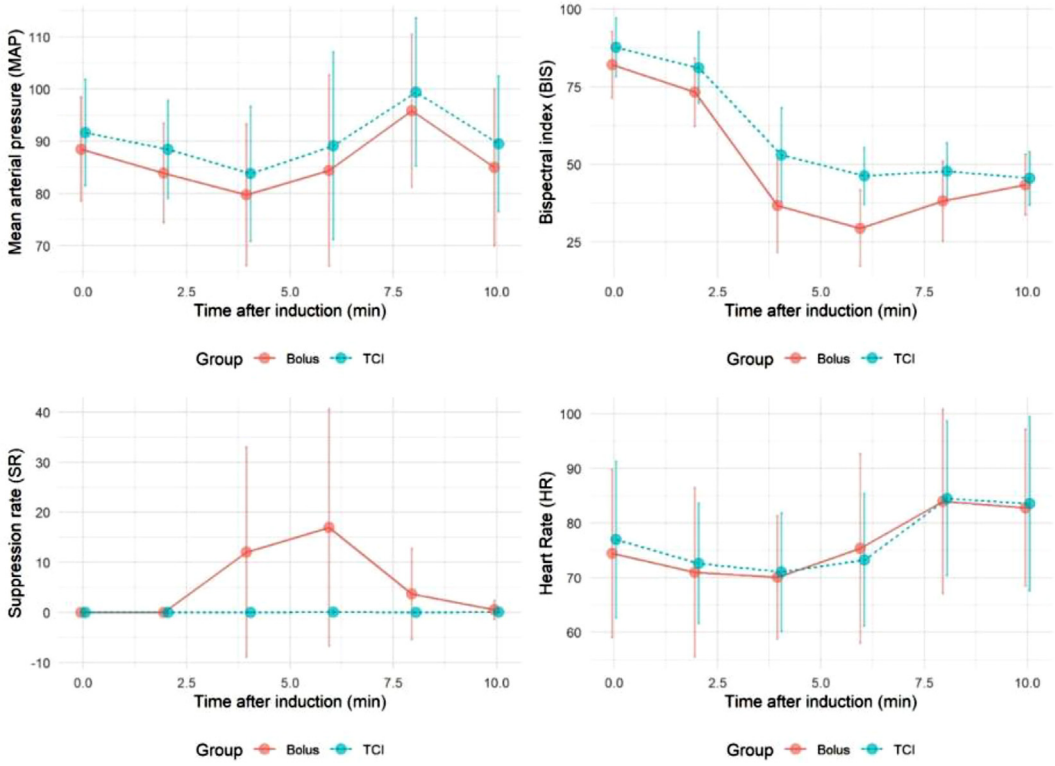

Figure 3 Outcomes longitudinal variation.

patient weight into account when determining compartment volume. However, the propofol dose was tailored for each patient to reach a sufficient concentration at the effector site for hypnosis induction. This approach in TCI, guided by a plasma target, offers a more stable drug administration profile, likely contributing to the fewer observed hemodynamic consequences in the TCI group.

The increased variation in the level of consciousness and suppression rate in the bolus group could be attributed to the relative overdose delivered during bolus induction. Administering a propofol bolus can lead to a plasma concentration significantly higher than necessary to induce hypnosis in an adult patient. Monitoring the level of consciousness during anesthesia induction remains crucial for patient safety and for mitigating postoperative morbidity.

Additionally, the propofol target in the TCI group was adjusted to 30% more than the expected for the loss of consciousness instead of being guided by qCON or Bispectral Index. This deviation may have contributed to a more substantial drop in MAP and qCON than usual. Future studies should consider setting the propofol target after induction based on qCON or the Bispectral Index.

Regarding group-time interaction, we were unable to reject the null hypothesis in relation to the outcomes, as shown in Table 2. Therefore, interpreting coefficients from this model would be misleading.

As limitations, this study could not compare the total dose used in both modes of administration as loss of consciousness propofol concentrations were not recorded. The fasting time was not standardized for all participants, which could raise concerns about their volume status. Also, the lack of information about diastolic function could significantly impact the results in a potential multivariate analysis.

Table 2 Hypothesis tests *p*-values for repeated measurements using mixed effect models.

Variable	*p*-value for Initial Group Difference	Group-Time Interaction *p*-value
Mean Arterial Pressure	0.236	0.859
Suppression Rate	0.042	0.446
qCON	0.001	0.726
Heart Rate	0.604	0.492

Conclusion

This study found that in adults aged 35 to 55 years-old, there was a lower mean arterial pressure, a greater variation in the level of consciousness, and a higher suppression rate in patients who received propofol bolus injection compared to those who received it as a target-controlled infusion, but the group-time effect interaction is still not clear.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgments

No competing interests were declared.

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