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ARTIGO ORIGINAL

Propofol Administration in the Induction Phase of General Anesthesia in Portugal

Administração de Propofol na Indução da Anestesia Geral em Portugal

Ana Ferreira[1,2*], Joaquim Mendes[1], Catarina Nunes[2,3], Pedro Amorim[2]

Afiliações
[1] LAETA/INEGI, Faculdade de Engenharia, Universidade do Porto, Portugal.
[2] Centro de Investigação Clínica em Anestesiologia, Serviço de Anestesiologia, centro Hospitalar do Porto, Portugal.
[3] Departamento de Ciências e Tecnologia, Universidade Aberta, Delegação do Porto, Portugal.

Keywords
Anesthesia, General; Anesthesiologists; Anesthetics, Intravenous; Portugal; Propofol; Surveys and Questionnaires
Palavras-chave
Anestesia Geral; Anestésicos Intravenosos; Anestesiologistas; Inquéritos e Questionários; Portugal; Propofol

ABSTRACT

Introduction: Administering propofol intravenously adequately during induction of general anesthesia implies a good knowledge of pharmacokinetics and pharmacodynamics, a good understanding of how anesthesia alters consciousness and the ability to correctly interpret vital signs monitoring. The purpose of this study was to assess the usual practice of anesthesiologists in Portugal regarding the administration of propofol during the induction of general anesthesia.

Methods: A transversal observational analytical and descriptive study, conducted through a questionnaire sent by e-mail to all anesthesiologists of several Portuguese hospitals. The questionnaire presented a conventional scenario (male subject, 50 years, 60 kg, 160 cm, ASA I, submitted to general anesthesia with 1% propofol) and has 10 questions directed to the administration of propofol during induction phase of general anesthesia. A descriptive analysis of the data was performed through SPSS 23.0®.

Results: A total of 118 physicians responded to the survey, most of whom were experts for more than 5 years (56.9%). Based on the presented scenario, most anesthesiologists would administer a propofol dose of 60 mg at induction, at a rate greater than 1200 mL/hours, and would assess loss of consciousness by evaluating loss of the eyelid reflex, which, in BIS index, would be reflected in a 60 value. Most participants measure the patient's blood pressure every 5 minutes and have never used target-controlled infusion systems.

Discussion: The survey showed that there is a wide variety of methods to assess the loss of consciousness, a diversity in handling propofol in induction, a lack of experience in the use of target-controlled infusion systems and in the evaluation of the relationship between dose, velocity and concentration of propofol. In this work, some suggestions were also made for anesthesiologists to consider implementing in their clinical practices.

Conclusion: There seems to be a diversity in the amount and in the way propofol is used by the Portuguese anesthesiologists to induce general anesthesia.

RESUMO

Introdução: A administração adequada de propofol por via intravenosa durante a indução da anestesia geral implica um bom conhecimento da farmacocinética e da farmacodinâmica, um bom entendimento de como a anestesia altera a consciência e a habilidade de interpretar corretamente a monitorização dos sinais vitais. Este trabalho pretende avaliar a prática usual dos anestesiologistas em Portugal no que diz respeito à administração de propofol por via intravenosa durante a indução da anestesia geral.

Material e Métodos: Estudo observacional transversal, descritivo e analítico realizado através de um questionário enviado por correio eletrónico a todos os médicos internos e especialistas em Anestesiologia de vários hospitais portugueses. O questionário apresentava um cenário convencional (Sujeito do sexo masculino, 50 anos, 60 kg, 160 cm, ASA I, submetido a anestesia geral com propofol a 1%) e incluía 10 questões relacionadas com a administração de propofol durante a indução. Foi realizada análise descritiva dos dados obtidos através do programa SPSS 23.0®.

Resultados: Responderam ao inquérito 118 médicos, sendo que, a maioria eram especialistas há mais de 5 anos (56,9%). Baseados no cenário apresentado, a maioria dos anestesiologistas administraria uma dose de 60 mg de propofol na indução, a uma velocidade superior a 1200 mL/horas, avaliariam a perda de consciência através da perda do reflexo palpebral, o que se refletiria num índica BIS de 60. A maioria dos participantes medem a pressão arterial do doente a cada 5 minutos e nunca utilizaram sistemas de infusão alvo-controlada.

Autor Correspondente/Corresponding Author*:
Ana Leitão Ferreira
Morada: Centro de Investigação Clínica em Anestesiologia, Serviço de Anestesiologia, Centro Hospitalar do Porto, Largo Professor Abel Salazar, 4099-001 Porto, Portugal.
E-mail: ana.leitao.ferreira@gmail.com

Discussão: Os resultados do inquérito mostraram que existe uma grande variedade de métodos para avaliar a perda de consciência, uma diversidade no manuseamento e doses de propofol na indução, uma falta de experiência no uso de sistemas de infusão alvo-controlada e na avaliação da relação entre a dose, a velocidade e a concentração de propofol. Neste trabalho apresentaram-se também algumas sugestões para os anestesiologistas ponderarem implementar nas suas práticas clínicas. **Conclusão:** Parece haver uma diversidade na quantidade e na forma como os anestesiologistas portugueses utilizam o propofol na indução da anestesia geral.

INTRODUCTION

According to the Central Administration of the Health System in Portugal (ACSS), more than 600 000 patients have been submitted to a surgery in 2016.[1] As the population is ageing, and more people have access to medical services, it is expected that this number will increase in the future. In 2015, there were 1280 anesthesiologists and about 300 interns working at the public hospital in Portugal.[2]

In its core, general anesthesia can be divided into induction, maintenance, and recovery. Regarding induction, it is a crucial stage, since one seeks to stabilize the patient for the remainder of the surgery. A proper induction of general anesthesia can prevent or reduce two main serious problems: awareness and overdosing. Awareness is characterized by the patient being awake during surgery. Awareness events are reported to occur in about 2 out of 1000 surgeries with general anesthesia in the United States of America.[3] This occurrence can create deep psychological consequences in the patient and can also generate heart conditions, such as ischemia and infarction or adverse reactions to different combinations of drugs. A long post operatory recovery is also associated with this intraoperative awakening. Overdosing may be the consequence of an overshooting, which is a phenomenon that occurs due to another relevant characteristic known as hysteresis.[4] Hysteresis is the time delay between the peak of plasma concentration and the peak of the effect-site concentration. This leads to a continuous increase of the effect-site concentration even after the infusion is stopped. The difference between the maximum value of effect-site concentration and the effective loss of consciousness (LOC) effect-site concentration is then described as overshoot. The magnitude of the overshoot and hysteresis depend on the pharmacokinetic model. Propofol is the most commonly used intravenous anesthetic agent for induction of general anaesthesia.[5] During induction with propofol, the moment at which the patient loses consciousness is of extreme importance to determine the concentration required for a particular individual and it is critical to the accurate tuning of the depth of anesthesia. In fact, there are currently no effective and automatic mechanism for the determination of LOC. Consequently, the existence of these uncertainties leads to mistakes or accidents that may endanger human lives. Precise and timed monitoring of the patient's response to the anesthetic drugs is therefore a crucial task to help clinicians to titrate anesthesia to match individual patient needs.

The purpose of this work is to assess the usual practice of anesthesiologists in Portugal regarding the administration of propofol during the induction of general anesthesia.

MATERIAL AND METHODS

Transversal observational analytical and descriptive study directed at internal doctors with specific training and specialists in Anesthesiology working in the main public hospitals in Portugal, from December 2014 to April 2015.

A questionnaire was designed with the help of an experienced anesthesiologist to guarantee a proper context and to avoid bias. The questionnaire, comprising 10 questions about the administration of propofol in the induction phase of general anesthesia, was implemented using Google Drive and was sent by the Secretariat of the Anesthesiology Service of the Centro Hospitalar do Porto to the department directors that forwarded to all their anesthesiologists. The questionnaire was then sent to the following Hospitals: Centro Hospitalar do Porto, Centro Hospitalar de São João, Centro Hospitalar de Gaia-Espinho, Centro Hospitalar de Trás-os-Montes e Alto Douro, Centro Hospitalar e Universitário de Coimbra, and Centro Hospitalar de Lisboa Central. The questionnaire was intended to take about five minutes to respond. It was anonymous and was used for research purposes only. There was no way to identify the clinician's department which responded. The questionnaire was not a test, because there were no correct or incorrect answers. Before the questions, the anesthesiologists were presented with a scenario for them to consider and analyze. The scenario was as follows: "A male patient (50 years, 60 kg, 160 cm, ASA physical state I) without premedication, undergoing general anesthesia and tracheal intubation for laparotomy procedure in order to perform a cholecystectomy. Three minutes before induction, 0.15 mg of fentanyl was administered. General anesthesia was induced with 1% propofol by a 20 cc syringe. The anesthesiologist was at the bedside pre-oxygenating, monitoring and instructing the nurse who administer the drugs through an intravenous line inserted in the back of the patient's hand. ASA and BIS were the standard monitoring."

The complete survey is presented in Annex A.

The answers were collected and organized in Statistical Package for the Social Sciences (SPSS 23.0®) software for subsequent analysis. Descriptive statistics, namely frequencies, were used to describe the basic characteristics of the answers. Non-parametric tests were used during analyses, since the data was not normally distributed. Spearman correlation coefficient was used to analyze the correlation between the

answers given by the anesthesiologists (variables). The Chi-square of independence was used to test for a statistically significant relationship between the variables. The statistical significance was considered for p-value < 0.05.

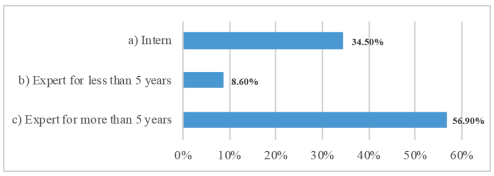
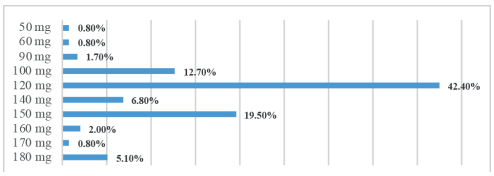
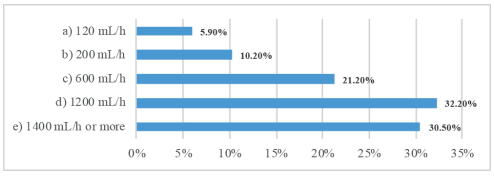
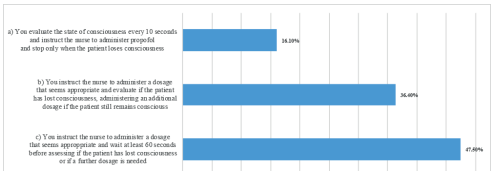
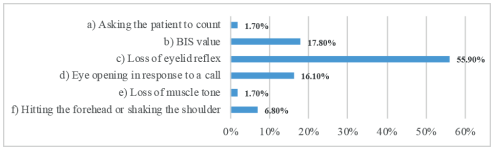
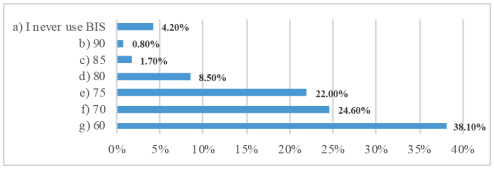
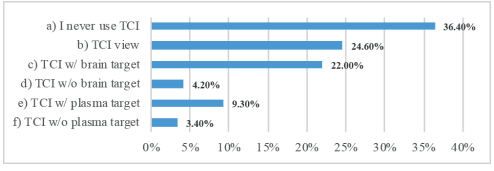
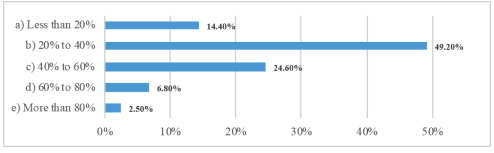
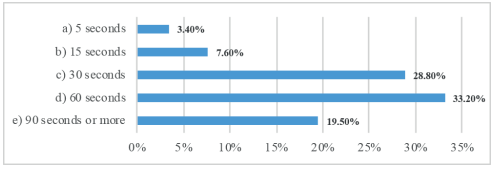
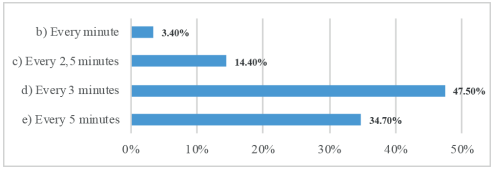
Results are presented in frequency tables, bar graphs or pie charts, in the next section.

RESULTS

One-hundred ten (110) physicians answered to the questionnaire: about 63 experts in anesthesiology for over 5 years, 38 interns and 9 experts for less than 5 years.

The distribution of the answers to all questions, based on the scenario presented in the Material and Methods section, is presented in Table 1. In question 1 was asked what the dose of propofol would be administered for induction by the anesthesiologist, given the scenario presented, and the majority participants (42.4%) answered that they would administer 120 mg of propofol. With regard to the dose chosen in question 1, the participant was asked to choose the infusion velocity of propofol from the following options: 120 mL/h, 200 mL/h, 600 mL/h, 1200 mL/h or 1400 mL/h or more. Only 19 anesthesiologists (16.1%) chose a rate of infusion below 200 mL/h, which can be considered a slow infusion. Regarding the question on the anesthesiologist's protocol while performing induction, the answer "Instructing the nurse to administer a dosage that seemed appropriate and evaluate if the patient had lost consciousness, and administering an additional dosage if the patient still remained consciousness" was the most selected by

Table 1. Distribution of the answers to all questions in the questionnaire

Distribution of the answers to questionnaire questions	
1. What is your experience as an anesthesiologist?	**2. What dosage of propofol would you administer for induction?**
	
3. In your clinical practice, for the chosen dosage, how fast would the administration of propofol (1% by a 20 cc syringe administered by a nurse) typically be performed?	**4. When performing the induction, with an administration of propofol with the dosage and speed set, how would you proceed?**
	
5. During the induction of anesthesia with propofol, which method would you use to assess loss of consciousness?	**6. When you monitor the patient with BIS and the index would start to decrease during induction as a result of propofol administration, what would be the value below which you can tell when patients, on average, lose consciousness?**
	
7. When you use propofol TCI with the Schnider model, how would you perform induction, in most cases?	**8. Overshooting occurs during induction, when you stop administering propofol. Considering the scenario presented, what would be the magnitude of the overshoot?**
	
9. How long after the injection will the concentration of propofol in the brain achieve its maximum?	**10. During the administration of anesthesia and using a non-invasive method, how often would you measure blood pressure for an ASA I, 50 years old, 60 kg and 160 cm patient?**
	

the participants (n=56). Thirty-six per cent of the participants answered that they would instruct the nurse to administer a dosage that seemed appropriate and would wait at least 60 seconds before assessing if the patient had lost consciousness or if a further dosage was needed. And, 19 anesthesiologists would prefer to evaluate the state of consciousness every 10 seconds and would instruct the nurse to administrate propofol and stop only when patient loses consciousness. When asked which method they would use to assess loss of consciousness during induction of propofol, most anesthesiologists (53.4%) would assess loss of consciousness by evaluating loss of eyelid reflex. Twenty-three participants (19.5%) would assess LOC by relying on the BIS value, and 14 (11.9%) would observe the absence of eye opening or movement in response to call. Twelve anesthesiologists (10.2%) would consider the absence of any movement when hitting the forehead or shaking the patient's shoulder as the most important method to evaluating LOC, and only three (2.5%) would ask the patient to count (up to ten or twenty, for example), and would consider that LOC occurs when the patient stops counting or stops having a reaction (no movement) in response to a pinch in the shoulder. The participants could write their responses in an empty box in the event they would use other approach than the one selected in the previous question. Eight (8) participants (n=8) would also rely on the BIS value, 3 on the loss of eyelid reflex and 5 or on the absence of movement to evaluate loss of consciousness during induction with propofol. Regarding the question: "Which is the value below which you can tell when a patient loses consciousness, on average, when monitoring with BIS?", the majority of the anesthesiologists (38.2%) would consider a value of 60 in BIS for LOC. When asked about the use of propofol TCI of propofol with the Schnider's model,[6] 24.6% would use it only on TCI-View mode and 39% would use pre-determined TCI mode. About thirty-six per cent (36.4%) of the participants never used TCI systems. Considering the scenario presented, the dosage and the rate of administration selected in the previous answers, anesthesiologists were asked about the estimated magnitude of the overshoot when propofol administration was stopped, and, most participants (n=87) referred to 20% to 60%. For a patient with the characteristics described in the scenario presented, question 9 asked: "How long after the end of the bolus of propofol will the patient achieve its maximum brain concentration (when performing the induction with 3µg/kg of fentanyl and a propofol bolus of 100 mg administered over 30 seconds)?". Most anesthesiologists referred 60 seconds (39%) or 30 seconds (28.8%). Regarding the last question, participants were asked how often they would measure the blood pressure (using a non-invasive method) during the anesthetic procedure. Most anesthesiologists (47.5%) would measure blood pressure every 5 minutes, 34.7% would measure it every 3 minutes, 14.4% every 2.5 minutes, and 43.4% would continuously measure it. We considered 9 different variables, corresponding to the last 9 questions of the questionnaire, which can be measured accordingly to different types such as: scale, ordinal or nominal - experience as anesthesiologist (nominal), dose (scale), velocity (ordinal), procedure (nominal), LOC assessment (nominal), BIS value at LOC (ordinal), TCI (nominal), overshoot (nominal), time to maximum brain concentration (ordinal) and time measuring blood pressure (nominal). According to the Spearman rank correlation coefficient analysis, our results showed a significant association between the velocity of propofol chosen by the participants for administering propofol and the method they used to determine LOC. We also found a significant correlation between time measuring blood pressure and the experience as anesthesiologist. Table 2 shows the results for the Pearson Chi-Square test considering the categorical (nominal and ordinal) variables. The following variables have a statistically significant relationship: infusion velocity and LOC assessment (p=0.018); infusion velocity and BIS value at LOC (p=0.033); infusion velocity and time to maximum brain concentration (p=0.016);BIS value at LOC and time to maximum brain concentration (p=0.034); and, time to maximum brain concentration and time measuring blood pressure (p=0.020). The results of the Kruskal-Wallis 1-way ANOVA test show no relations between the dose (scale variable) and the other variables (p>0.05).

DISCUSSION

This study reports on the results from a survey developed to assess the usual practice of anesthesiologists in Portugal, concerning the administration of propofol, intravenously, for induction of general anesthesia. Participation in this study was not what would be desirable in terms of number of responses: only 8% of the Portuguese anesthesiologists responded. It was not clear whether the low adherence to the study was the result of demotivating professionals or the inefficiency of the medium chosen for dissemination of questionnaires; for example, some emails not active, incorrect, directly sent to spam or colleagues did not have an available email. The anesthetic induction dose of propofol in adult varies from 2.0 to 2.5 mg/kg with recommended maintenance infusion rates ranging from 0.05 to 0.2 mg/kg/min, depending on the depth of anesthesia that is required.[7] This means that, in the induction phase of the scenario presented in the questionnaire, in which a male patient weights 60 kg, the recommended dose of propofol should be between 120 and 150 mg. In clinical practice and according to results of our survey, most anesthesiologists would administer a dose that ranged between 100 and 150 mg. Apparently, our anesthesiologists are following the recommendations. When asked about the infusion rate for administering the dose of propofol in induction, only slightly above 50% of the anesthesiologists would choose 1200 mL/h

Table 2. *P*-values for the Pearson Chi-Square test relating the different questions of the survey

Questions about	Infusion Velocity	Procedure	LOC assessment	BIS value at LOC	TCI	Overshoot	Time to max. brain concentration	Time measuring blood pressure	Experience as anesthesiologist
Infusion Velocity	-	0.099	0.018*	0.033*	0.421	0.149	0.016*	0.123	0.195
Procedure	0.009	-	0.382	0.678	0.445	0.304	0.897	0.691	0.549
LOC assessment	0.018*	0.382	-	0.030	0.935	0.427	0.395	0.081	0.361
BIS value at LOC	0.033*	0.678	0.030	-	0.080	0.615	0.034*	0.368	0.677
TCI	0.421	0.445	0.935	0.08	-	0.684	0.432	0.362	0.085
Overshoot	0.149	0.304	0.427	0.615	0.684	-	0.634	0.710	0.496
Time to maximum brain concentration	0.016*	0.897	0.395	0.034*	0.432	0.634	-	0.020*	0.539
Time measuring blood pressure	0.123	0.691	0.081	0.368	0.362	0.71	0.020*	-	0.147
Experience as anesthesiologist	0.195	0.549	0.361	0.677	0.085	0.496	0.539	0.147	-

*$p<0.05$

or more. An infusion of about 120 mg takes up to 40 seconds to be completed, which means that the infusion rate needed to be performed at, at least, 1000 mL/h. The determination of an adequate infusion rate and a proper dose of propofol proved already to restrict the overshoot during induction. Studies have shown that the expected doses for anesthesia onset are affected by changes in the injection rate.[8,9] Another study showed that the propofol dose is reduced by using slower infusion rates, while rapid infusion rates have resulted in greater decreases in heart rate and higher incidence of apnea.[10] A slow infusion rate results in a longer duration of induction but requires a lower dose of propofol, which decreases blood pressure and incidence of apnea.[11] As demonstrated by our group in a previous study,[12] the amount of propofol required to produce unconscious varies widely from patient to patient and was independent of age, gender, weight or height. It has been shown that there is no way to predict how much propofol an individual patient will need. We suggest that anesthesiologists replace the recommendation of administering a specific amount of propofol based on patient weight and age with a technique that enables individualization of a patient's needs, i.e. administering propofol slowly at induction. Regarding the monitoring of the patient during induction, approximately 50% of the participants would administer a dose of propofol that seems appropriate to the patient and evaluate if the patients have lost consciousness, administering an additional dosage if the patient remains conscious. In this matter, only 16% of the anesthesiologists would evaluate the state of consciousness every 10 seconds and would administer propofol until the patient loses consciousness, stopping the administration of propofol at this time. When asked which method the anesthesiologists would use to determine if the patient was unconscious during the administration of propofol, the responses vary widely: some anesthesiologists would rely on loss of eyelid reflex, others on BIS value, others on the observation of the absence of eye opening or movement in response to call, absence of any movement when hitting the forehead or shaking the patient's shoulder and some anesthesiologists would ask the patient to count. This shows the uncertainty regarding the method that should be used to ensure a correct assessment of the dose of propofol during induction of general anesthesia. We suggest that, in addition to slowly infusing propofol during induction, anesthesiologists should monitor the response of the patient to a stimulus, every 10 seconds, to precisely assess the moment of loss of consciousness, thus identifying the amount of propofol each patient needs. And then use that information to guide the infusion rate of propofol required to maintain an adequate level of anesthesia. The question now is on which method would be better for monitoring patient's responses every 10 seconds. To avoid complications, such as awareness[3,13] or excessive anesthesia, the anesthesiologists should be aware of situations that cause false BIS readings In our study, most anesthesiologists had the perception that the magnitude of the overshooting, in the scenario presented, was from 20% to 60%. According to the t-test for paired samples, there was a correlation between the velocity chosen in the administration of propofol and the magnitude of the overshooting. This means that the anesthesiologists were sensitive to the occurrence of this phenomenon at a pharmacodynamic level. The familiarity of this behavior is important since overdosing is associated with the increase of morbidity and mortality in 1 to 2 years of postoperative.[14] When this occurrence is combined with low brain activity (low BIS), the risk of mortality can increase.[15] This questionnaire suggests that Portuguese anesthesiologists are aware of overshooting risks, however, not applied to preventing measures to avoid it, because there is no developed objective method that permits the precise identification of the moment of loss of consciousness yet. The introduction of TCI systems has enabled relatively accurate dosing by continuous infusion, based on the pharmacokinetic models to titrate propofol

administration to achieve specific plasma or effect-site drug concentrations in an average patient.[16] Various plasma administration and effect-site targeting TCI systems are commercially available to administer hypnotics and opioids. Currently, TCI systems are approved and available in more than 90 countries.[17] More than 60 000 units have been sold and are being used to provide TCI propofol-based intravenous sedation and anesthesia for millions of patients around the world every year.[17] Although TCI is a part of established practice around the world, TCI devices have not yet received regulatory approval in the United States.[17] Results from our study showed that 36% of the Portuguese anesthesiologists never used TCI. This may be to the lack of knowledge on how to use these systems. The fact that most anesthesiologists that used TCI system had chosen the TCI view mode (the learning mode of the TCI that uses a constant infusion only with a theoretical reference) may be because they are not actually using the system to its purpose, which is to set a determined concentration of propofol and to maintain it during maintenance. In this manner, because anesthesiology is a pioneering specialty in the development and use of simulation tools, with positive results that impact clinical practice, an educational intervention should be adopted aiming at preparing not only students or residents of anesthesia but also specialized physicians. For example, to benefit from the usefulness of TCI systems, workshops could be provided by the brands, training sessions at anesthesiology service meetings could be given, specialized physicians could be updated by other experts with more experience, and, maybe anesthesiology services could be sensitized to the importance of these systems and contribute for the acquisition of such tools. As the main conclusion of this study, there appears to be a diversity in the amount and in the way propofol is used by the Portuguese anesthesiologists to induce general anesthesia. Our results showed that there are a wide variety of methods for evaluating the loss of consciousness, a diversity in handling propofol in induction, a lack of experience in using target-controlled infusion systems, and in assessing the relationship between dose, velocity, and concentration of propofol. There were also some recommendations in this study for anesthesiologists to consider implementing them in their clinical practices. We intend to forward the questionnaire to 40 international experts in the future to compare our results with other countries' results.

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Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).
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ORCID
Ana Ferreira https://orcid.org/0000-0003-2350-6947
Joaquim Mendes https://orcid.org/0000-0003-4254-1879
Catarina Nunes https://orcid.org/0000-0002-8357-0994
Pedro Amorim https://orcid.org/0000-0001-7466-4174

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