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## SCIENTIFIC ARTICLE

# Comparative evaluation of propofol in nanoemulsion with solutol and soy lecithin for general anesthesia



José Carlos Rittes<sup>a</sup>, Guilherme Cagno<sup>a</sup>, Marcelo Vaz Perez<sup>a,b</sup>,  
Ligia Andrade da Silva Telles Mathias<sup>a,b,\*</sup>

<sup>a</sup> Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil

<sup>b</sup> Faculdade de Ciências Médicas, Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil

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### Abstract

**Introduction:** The vehicle for propofol in 1 and 2% solutions is soybean oil emulsion 10%, which may cause pain on injection, instability of the solution and bacterial contamination. Formulations have been proposed aiming to change the vehicle and reduce these adverse reactions.

**Objectives:** To compare the incidence of pain caused by the injection of propofol, with a hypothesis of reduction associated with nanoemulsion and the occurrence of local and systemic adverse effects with both formulations.

**Method:** After approval by the CEP, patients undergoing gynecological procedures were included in this prospective study: control ( $n=25$ ) and nanoemulsion ( $n=25$ ) groups. Heart rate, non-invasive blood pressure and peripheral oxygen saturation were monitored. Demographics and physical condition were analyzed; surgical time and total volume used of propofol; local or systemic adverse effects; changes in variables monitored. A value of  $p < 0.05$  was considered significant.

**Results:** There was no difference between groups regarding demographic data, surgical times, total volume of propofol used, arm withdrawal, pain during injection and variables monitored. There was a statistically significant difference in pain intensity at the time of induction of anesthesia, with less pain intensity in the nanoemulsion group.

**Conclusions:** Both lipid and nanoemulsion formulations of propofol elicited pain on intravenous injection; however, the nanoemulsion solution elicited a less intense pain. Lipid and nanoemulsion propofol formulations showed neither hemodynamic changes nor adverse effects of clinical relevance.

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\* Corresponding author.

E-mail: [rtimao@uol.com.br](mailto:rtimao@uol.com.br) (L.A.S.T. Mathias).

**PALAVRAS-CHAVE**

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Nanoestruturas;  
Anestesia geral

**Avaliação comparativa do propofol em nanoemulsão com solutol e com lecitina de soja para anestesia geral****Resumo**

**Introdução:** O veículo do propofol em soluções a 1 e 2% é a emulsão de óleo de soja a 10%, que pode provocar dor à injeção, instabilidade da solução e contaminação bacteriana. Formulações foram propostas com o objetivo de alterar o veículo e reduzir essas reações adversas.

**Objetivos:** Comparar a incidência de dor à injeção do propofol com a hipótese de redução associada à nanoemulsão e a ocorrência de efeitos adversos locais e sistêmicos com as duas formulações.

**Método:** Após aprovação pelo Conselho de Ética em Pesquisa, foram incluídos neste estudo prospectivo pacientes submetidas a procedimentos cirúrgicos ginecológicos: grupos controle ( $n = 25$ ) e nanoemulsão ( $n = 25$ ). Foram monitorados frequência cardíaca, pressão arterial não invasiva e saturação periférica de oxigênio. Foram analisados dados demográficos e estado físico; tempo cirúrgico e volume total usado de propofol; efeitos adversos locais ou sistêmicos; alterações nas variáveis de monitoramento. Considerou-se significativo valor de  $p < 0,05$ .

**Resultados:** Não houve diferença entre os grupos em relação a: dados demográficos, tempos cirúrgicos, volume total usado de propofol, retirada do braço, presença de dor durante a injeção e variáveis de monitoramento. Verificou-se diferença estatística significativa na intensidade da dor no momento da indução da anestesia, com menor intensidade no grupo nanoemulsão.

**Conclusões:** Ambas as formulações de propofol, lipídica e em nanoemulsão, elicitaram dor à injeção venosa, porém a solução de nanoemulsão promoveu dor em menor intensidade. O propofol lipídico e o propofol em nanoemulsão não apresentaram alterações hemodinâmicas e efeitos adversos de relevância clínica.

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**Introduction**

After many years of research for new intravenous drugs for use in anesthesia, the pharmaceutical industry has seen in propofol (ICI 35868) a potential anesthetic agent. During the study preclinical phase, the formulation with Cremophor EL, commonly used in the pharmaceutical industry, has been proposed.<sup>1</sup> Due to the frequent occurrence of hypersensitivity reactions and injection pain, Cremophor EL formulation was abandoned and the search for a viable formulation was initiated with the use of lipid emulsions. Lipid emulsions determine an increase in onset time, decrease in potency, and increase in awakening time relative to the initial formulation in Cremophor EL.<sup>2</sup> In an attempt to improve the limitations of propofol lipid emulsion, injection pain, and potential bacterial growth, formulations have been made with greater concentration of propofol; less than 10% oil; phospholipids modifications within the emulsion (containing different fatty acids) and emulsion droplets with proteins.<sup>3</sup>

Nanoemulsions have been associated with improvement in formulation stability, which increases the useful life of propofol, reduces the amount of free propofol and therefore may decrease the incidence of injection pain, in addition to a wide antimicrobial spectrum.<sup>4,5</sup>

In search for nanoemulsions with more safety features and lower risk of anaphylaxis, polyethylene glycol-660-hidroxiesterato (Solutol® HS15 – BASF, Ludwigshafen, Germany) was developed, a water-soluble nonionic solubilizer for parenteral use with lipophilic drugs and vitamins.

It contains about 70% of lipophilic molecules and 30% of hydrophilic molecules, so it is stable and has been used in parenteral solutions.<sup>6,7</sup>

Thus, taking into consideration that propofol is the intravenous anesthetic most commonly used in general anesthesia worldwide, its use still has limitations due to adverse effects, and there are few studies comparing conventional propofol with propofol nanoemulsion. We conducted a comparative evaluation between propofol formulations traditionally used (soy lecithin and nanoemulsion with solutol) in gynecological procedures. The objective of this study was to compare the incidence of propofol injection pain, with a hypothesis of reduction associated with nanoemulsion, and the occurrence of local and systemic adverse effects with both formulations.

**Methods**

After approval by the institutional Research Ethics Committee, a prospective, open, randomized and comparative study was initiated, which included 50 patients undergoing gynecological procedures in the Department of Obstetrics and Gynecology.

The sample size calculation was based on a previous study,<sup>8</sup> which reported incidence of pain in about 80% of patients who received propofol in lipid formulation.<sup>9,10</sup> To achieve a 50% reduction in the incidence of pain, the sample minimum size was calculated at 46 patients for chi-square test, with a degree of freedom equal to one (Table 1), test

**Table 1** Study population demographic data.

	$G_{\text{CONT}}$	$G_{\text{NE}}$	$p$
	$n = 23$	$n = 25$	
<i>Age (years)</i>			
Mean $\pm$ SD	44.0 $\pm$ 12.3	41.3 $\pm$ 12.2	0.4448 <sup>a</sup>
Minimum–maximum	20–69	19–72	
<i>Weight (kg)</i>			
Mean $\pm$ SD	60.1 $\pm$ 6.1	61.3 $\pm$ 7.2	0.4194 <sup>a</sup>
Minimum–maximum	49–73	48–75	
<i>Height (m)</i>			
Mean $\pm$ SD	1.59 $\pm$ 0.07	1.59 $\pm$ 0.07	0.9712 <sup>a</sup>
Minimum–maximum	1.45–1.75	1.42–1.72	
<i>BMI (<math>\text{kg m}^{-2}</math>)</i>			
Mean $\pm$ SD	23.9 $\pm$ 2.2	24.2 $\pm$ 3.1	0.369 <sup>a</sup>
Minimum–maximum	18.9–27.8	18.7–29.8	
<i>Physical status</i>			
ASA I	15 (65.2%)	15 (60%)	0,7761 <sup>b</sup>
ASA II	8 (34.8%)	10 (40%)	

$G_{\text{CONT}}$ , control group;  $G_{\text{NE}}$ , nanoemulsion group; BMI, body mass index;  $p$ , significance of the statistical test used.

<sup>a</sup> Unpaired  $t$ -test.

<sup>b</sup>  $\chi^2$  test.

power of 80%, and significance level of 5%. It was decided to use 50 patients to compensate for possible losses.

Patients undergoing gynecological laparoscopic procedures and breast surgery, aged  $\geq 18$  years, ASA physical status I and II (according to the American Society of Anesthesiologists classification), BMI  $> 18.5$  and  $< 30.0 \text{ kg m}^{-2}$  were included in the study. Exclusion criteria were patients with history of dyslipidemia and post-anesthesia nausea and vomiting, atopy, use of psychoactive drugs, and pregnancy.

After obtaining written informed consent, patients were numbered and distributed according to the list of random numbers, at a ratio of 1:1, into two groups: control group (Cont) with 25 patients who received propofol with lecithin soy; nanoemulsion group (NE) with 25 patients who received propofol nanoemulsion.

Propofol concentration was 1% in both the conventional soy lecithin and nanoemulsion.

A blind study was not possible because the drugs used in the study had different organoleptic properties (propofol in nanoemulsion is transparent and stable at room temperature, while propofol in soybean lecithin is milky and requires cold storage).

Both groups received identical care and attention, as well as monitoring and anesthetic technique, except for the drug used. The patients received no premedication.

In the operating room, venous access was established in preferred upper limb by a 20G Teflon device, and hydration was started with lactated Ringer solution. Subsequently, patients were monitored with heart rate (HR), electrocardiogram (ECG), noninvasive systolic blood pressure (SBP) and diastolic blood pressure (DBP), peripheral oxygen saturation ( $\text{SpO}_2$ ), and bispectral index (BIS).

Initial oxygenation was performed with 100%  $\text{O}_2$  via face mask and at that time intravenous induction was initiated with sequential administration of the following

drugs: remifentanyl, propofol or propofol nanoemulsion, and atracurium. The doses used for induction of anesthesia were left to the clinical anesthesiologist discretion, without protocol interference. The hemodynamic changes caused by formulations at doses commonly used in clinical practice were recorded.

Induction time was considered from the end of drug injection until BIS values fall below 60.

After tracheal intubation, patients were maintained on mechanical ventilation in semi-closed loop system, with  $2 \text{ L min}^{-1}$  flow and ventilated with a mixture of oxygen/nitrous oxide (50:50), with adjusted ventilatory parameters from current volume (CV) =  $8\text{--}10 \text{ mL kg}^{-1}$ , end-expiratory pressure of zero, and respiratory rate (RR) to maintain ( $P_{\text{ET}}\text{CO}_2$ ) between 28 and 35 mmHg with  $\text{SpO}_2$  above 95%.

Anesthesia was maintained with remifentanyl, propofol or propofol nanoemulsion modified with an infusion pump speed, if necessary, to maintain BIS values between 40 and 60. After the end of anesthesia, the patients were taken to the post-anesthesia care unit and discharged to the ward with Aldrete-Kroulik modified index  $\geq 8$ .

The analyzed variables were:

- Age, weight, height, body mass index (BMI), and ASA physical status;
- Surgical time and total volume used of propofol and propofol nanoemulsion;
- Adverse effects at the injection site:
  - Injection pain.

During injection of propofol, the attempt to withdraw the arm was assessed (yes/no) and the patient was asked to evaluate the injection pain, according to the verbal pain scale of four terms (absent, mild, moderate, and severe).

Twelve hours after the puncture, the patient was asked if she felt pain during injection. If so, the degree of pain was evaluated using the verbal scale of four terms (absent, mild, moderate, and severe).

- Adverse effects:
  - Signs of infection at the puncture site;
  - Nausea and vomiting after the procedure (assessed up to discharge from post-anesthesia care unit);
  - Heart rate, systolic blood pressure, diastolic blood pressure, and peripheral oxygen saturation (every 10 min);
- Time and doses of induction and maintenance.

Statistical analysis was performed with the aid of the software SPSS (Statistical Package for Social Sciences) for Windows 10. Student's *t*-test or the Mann-Whitney test was used to compare quantitative variables between groups, according to sample distribution. A *p*-value < 0.05 was considered statistically significant.

### Results

From the initial sample of 50 patients, 48 were included in the present study: 23 in control group (*G*<sub>CONT</sub>) and 25 in nanoemulsion group (*G*<sub>NE</sub>). Two patients were excluded for *G*<sub>CONT</sub> due to surgical complications.

There was no difference between groups regarding age, gender, weight, height, BMI, and ASA variables. There was no statistically significant difference between groups (*p* > 0.05) (Table 2). Surgical procedure times were similar in both groups: 3.02 h for *G*<sub>CONT</sub> and 2.50 h for *G*<sub>NE</sub> (*p* = 0.4893).

There was no significant difference between groups regarding arm withdrawal during the injection of propofol and presence of pain during injection, but there was a statistically significant difference in pain severity (*p* = 0.01) (Table 2).

The mean total volume used of propofol (*G*<sub>CONT</sub>) was 96.70 ± 26.09 mL and propofol nanoemulsion (*G*<sub>NE</sub>) was 82.93 ± 37.77 mL. There was no statistically significant difference between the two groups (*p* = 0.1521).

There was no significant difference in prevalence and severity of pain at the injection site, assessed at 12 hours

**Table 2** Distribution of patients regarding arm withdrawal during propofol injection, presence and severity of pain during injection, assessed at the time of induction of anesthesia.

<i>G</i> <sub>CONT</sub>	<i>G</i> <sub>NE</sub>		Test		
<i>Arm withdrawal during injection</i>					
No	17	73.9%	23	92%	$\chi^2 = 2.82$ <i>p</i> = 0.09
Yes	6	26.1%	2	8%	
<i>Pain during injection</i>					
No	5	21.7%	12	48%	$\chi^2 = 3.61$ <i>p</i> = 0.07
Yes	18	78.3%	13	52%	
<i>Severity of pain during injection</i>					
Absent	5	21.7%	12	48%	$\chi^2 = 6.56$ <i>p</i> = 0.01
Mild	6	26.1%	8	32%	
Moderate	7	30.4%	5	20%	
Severe	5	21.7%	0	0%	

**Table 3** Evaluation of pain and other adverse events in the ward, 12 h after anesthesia.

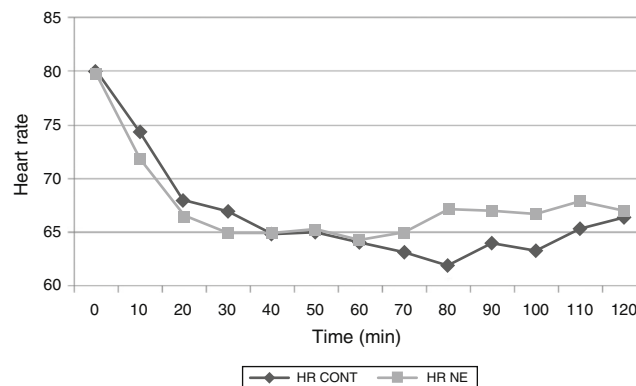
	<i>G</i> <sub>CONT</sub> ( <i>n</i> = 23)		<i>G</i> <sub>NE</sub> ( <i>n</i> = 25)		Test
<i>Pain during injection</i>					
No	10	43.5%	16	64%	$\chi^2 = 1.29$ <i>p</i> = 0.2561
Yes	13	56.5%	9	36%	
<i>Severity of pain during injection</i>					
Absent	10	43.5%	16	64%	$\chi^2 = 2.51$ <i>p</i> = 0.6110
Mild	8	34.8%	6	24%	
Moderate	3	13.0%	2	8%	
Severe	2	8.7%	1	4%	
<i>Inflammatory signs</i>					
Absent	23	100%	25	100%	
<i>Postoperative nausea and vomiting</i>					
No	20	87%	23	92%	$\chi^2 = 0.01$ <i>p</i> = 0.9215
Yes	3	13%	2	8%	

after venipuncture, in the ward (56.5% in *G*<sub>CONT</sub> and 36.0% in *G*<sub>NE</sub>). It was mild in both *G*<sub>CONT</sub> and *G*<sub>NE</sub>, 34% and 24.0%, respectively. No patient showed signs of inflammation (Table 3).

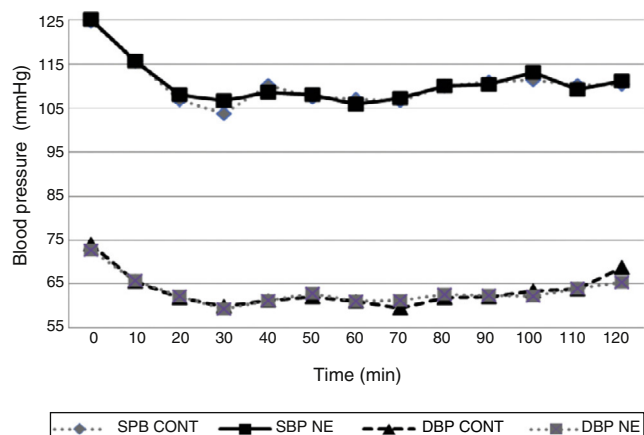
Five patients (3 in *G*<sub>CONT</sub> and 2 in *G*<sub>NE</sub>) had postoperative nausea and vomiting ( $\chi^2 - p = 0.9215$ ) (Table 3). Five patients (2 in *G*<sub>CONT</sub> and 3 in *G*<sub>NE</sub>) had systemic adverse events ( $\chi^2 - p = 0.9215$ ): two patients in each group had mild skin rash and one patient in *G*<sub>NE</sub> had moderate bronchospasm and wheezing. There was no significant difference between groups regarding HR, SBP, DBP, and SpO<sub>2</sub> at all assessed times (unpaired *t*-test - *p* > 0.05) (Figs. 1 and 2).

### Discussion

Although the success of propofol is indisputable, an ideal formulation which eliminates the adverse reactions resulting from lipid formulations is investigated until the present day. There are few studies comparing the propofol nanoemulsion and classical lipid formulations,<sup>7,8</sup> which led to the present study in which 48 patients undergoing gynecological procedures were evaluated in order to identify specific clinical features, such as propofol injection pain and presence of



**Figure 1** Heart rate evolution in both groups.



**Figure 2** Systolic and diastolic blood pressure evolution in both groups.

local and systemic adverse events associated with the use of propofol nanoemulsion. They were compared with those related to the administration of propofol in lipid emulsion (conventional propofol).

Although several preparations of propofol were tested, a preparation that reduces the incidence of pain after injection has not been found yet. Because it belongs to a group of phenols with chemical stability and low toxicity, but with the potential to cause skin, endothelium, and mucous membranes irritation, it is expected but not desired that propofol injection causes pain. In this study, the incidence of propofol injection pain assessed at the injection time was lower in nanoemulsion group ( $G_{NE}$ ) than in control group, without statistical significance ( $G_{NE} = 56.0\%$  versus  $G_{CONT} = 78.3\%$ ). Regarding arm withdrawal frequency during propofol injection, there was no statistical difference ( $G_{NE} = 8.0\%$  versus  $G_{CONT} = 26.1\%$ ). Regarding injection pain severity, mild, moderate, and severe pain were more frequent in  $G_{CONT}$ ,  $p = 0.01$ . However, in both assessments, pain incidence and arm withdrawal frequency at propofol injection time, the differences were clinically significant and  $p$ -values (0.07 and 0.09) suggest that, if the sample were larger, statistical difference would have been found.

In the same study, the incidence of propofol injection pain assessed 12 h after puncture was lower in nanoemulsion group than in the control group, without statistical significance ( $G_{NE} = 36.0\%$  versus  $G_{CONT} = 56.5\%$ ), as well as injection pain severity.

Only two studies were found in the literature that also compared the classical soy lecithin versus nanoemulsion formulations of propofol used in this study.<sup>7,8</sup> Sudo et al.<sup>7</sup> evaluated the incidence of pain in mice receiving intraperitoneal infusion of acetic acid and lipid vehicle of propofol and non-lipid nanoemulsion (same as that used in this study). Acetic acid and lipid vehicle of propofol caused pain after intraperitoneal injection. However, there was no pain after the administration of propofol nanoemulsion. In the study by Rodrigues et al.<sup>8</sup>, with patients undergoing sedation for endoscopy, the incidence of propofol nanoemulsion injection pain (same formulation used in this research) was lower than with the use of conventional propofol, with statistical significance (53.3% vs. 82.7%).

Other studies with different formulations showed different results, such as the research that found higher incidence of pain with the non-lipid formulation of propofol (Cleofol®; Themis Medicare, India) than with propofol emulsion with medium chain triglycerides (Propofol-Lipuro®, B Braun, Germany).<sup>9</sup> It is worth mentioning that the lipid emulsion propofol used in this study was different from that used in the cited publication. Previous studies have found that formulations with medium chain triglycerides have lower free fraction of propofol and hence tendency to a lower incidence of pain.<sup>10-14</sup>

Sim et al.,<sup>15</sup> in a study that comparatively assessed the level of plasma bradykinin after intravenous injection of 0.9% saline solution, lipid emulsion propofol, propofol microemulsion, and polyethylene glycol-660-hydroxiestearato (Solutol® HS15), showed higher levels with the injection of microemulsion and solutol not related to increased incidence of pain. Thus, the authors propose that the onset of pain after propofol injection is not entirely related to the bradykinin release.

The application of lidocaine, strategy widely used to reduce pain on injection of propofol, has been discussed. Sim et al.<sup>15</sup> reported that there was no change in free propofol concentration during the aqueous phase after lidocaine addition; while Yamakage et al.<sup>14</sup> reported that there was a change of pH and stability of the solution with the lidocaine addition, suggesting that lidocaine administered before propofol may inhibit transmission of pain through endothelial free nerve endings.

Although the assessment of surgical time and total volume used of propofol has not been part of the objectives of this study, these data were analyzed and are part of the results because statistically significant differences in any of them or both could create a bias in interpreting the results of adverse events.

There were no signs of inflammation at the injection site in any patient, which may occur in 1–5% of the cases.<sup>16</sup>

It has been widely reported in the literature that intravenous administration of propofol may lead to decreased blood pressure with little change in heart rate and rhythm,<sup>17-21</sup> which is confirmed in this study that found similar reduction of SBP and DBP values in both groups only at induction time, with posterior stability, with minimum tolerable values. Rodrigues et al.,<sup>8</sup> in humans, and Sudo et al.<sup>7</sup> in mice, both used lipid or nanoemulsion propofol and reported reduction in systolic and diastolic arterial pressures, with no difference between the analyzed groups. Heart rate also decreased at the time of induction in both groups, with subsequent stabilization, without reaching critical levels.

In the present study, few cases of nausea/vomiting were observed after surgery ( $G_{NE} = 8.0\%$  versus  $G_{CONT} = 13.0\%$ ), with no statistical difference between the drugs used, which confirms the literature reporting that propofol has antiemetic property, by antidopaminergic activity, with depressant effect on the chemoreceptor trigger zone and vagal nuclei, lower release of glutamate and aspartate in the olfactory cortex, and decreased serotonin in the area postrema.<sup>22</sup>

Both formulations of propofol, lipid and nanoemulsion, caused intravenous injection pain, but the nanoemulsion solution promoted less intense pain. Propofol in lipid



emulsion and propofol in nanoemulsion showed no hemodynamic changes and adverse effects of clinical relevance.

### Conflicts of interest

The authors declare no conflicts of interest.

### Acknowledgements

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### References

- Glen JB, Davies GE, Thomson DS, et al. An animal model for the investigation of adverse responses to i.v. anesthetic agents and their solvents. *Br J Anaesth*. 1979;51:819–27.
- Baker MT, Naguib M. Propofol: the challenges of formulation. *Anesthesiology*. 2005;103:860–76.
- Thompson KA, Goodale DB. The recent development of propofol (Diprivan). *Intensive Care Med*. 2000;26 Suppl. 4:S400–4.
- Date AA, Nagarsenker MS. Design and evaluation of microemulsions for improved parenteral delivery of propofol. *AAPS PharmSciTech*. 2008;9:138–45.
- Sneyd JR, Rigby-Jones AE. New drugs and technologies, intravenous anaesthesia is on the move (again). *Br J Anaesth*. 2010;105:246–54.
- Morey TE, Modell JH, Shekhawat D, et al. Anesthetic properties of a propofol microemulsion in dogs. *Anesth Analg*. 2006;103:882–7.
- Sudo RT, Bonfá L, Trachez MM, et al. Caracterização anestésica da nanoemulsão não lipídica de propofol. *Rev Bras Anesthesiol*. 2010;60:475–83.
- Rodrigues TA, Alexandrino RA, Kanczuk ME, et al. Avaliação comparativa entre propofol com dois veículos diferentes: em nanoemulsão com solutol e com lecitina de soja em pacientes submetidos a procedimentos endoscópicos. *Rev Bras Anesthesiol*. 2012;62:324–33.
- Dubey PK, Kumar A. Pain on injection of lipid-free propofol and propofol emulsion containing medium-chain triglyceride: a comparative study. *Anesth Analg*. 2005;101:1060–2.
- Larsen B, Beerhalter U, Biedler A, et al. Less pain on injection by a new formulation of propofol? A comparison with propofol LCT. *Anaesthesist*. 2001;50:842–5.
- Larsen R, Beerhalter U, Erdkönig R, et al. Injection pain from propofol-MCT-LCT in children. A comparison with propofol-LCT. *Anaesthesist*. 2001;50:676–8.
- Rau J, Roizen MF, Doenicke AW, et al. Propofol in an emulsion of long- and medium-chain triglycerides: the effect on pain. *Anesth Analg*. 2001;93:382–4.
- Sun NC, Wong AY, Irwin MG. A comparison of pain on intravenous injection between two preparations of propofol. *Anesth Analg*. 2005;101:675–8.
- Yamakage M, Iwasaki S, Satoh J, et al. Changes in concentrations of free propofol by modification of the solution. *Anesth Analg*. 2005;101:385–8.
- Sim JY, Lee SH, Park DY, et al. Pain on injection with microemulsion propofol. *Br J Clin Pharmacol*. 2009;67:316–25.
- Pederneiras SG, Duarte DF, Teixeira Filho N, et al. Uso do propofol em anestésias de curta duração: estudo comparativo com o tiopental. *Rev Bras Anesthesiol*. 1992;42:181–4.
- Claeys MA, Gepts E, Camus F. Haemodynamic changes during anaesthesia induced and maintained with propofol. *Br J Anaesth*. 1983;60:3–9.
- Grounds RM, Twigley AJ, Carli F, et al. The haemodynamic effects of intravenous induction. Comparison of the effects of thiopentone and propofol. *Anaesthesia*. 1985;40:735–40.
- Hug CC, McLeskey CH, Nahrwold NL, et al. Hemodynamic effects of propofol – data from 24,771 patients. *Anesth Analg*. 1993;76:S154.
- El-Beheiry H, Kim J, Milne B, et al. Prophylaxis against the systemic hypotension induced by propofol during rapid-sequence intubation. *Can J Anaesth*. 1995;42:875–8.
- Sato M, Tanaka M, Umehara S, et al. Baroreflex control of heart rate during and after propofol infusion in humans. *Br J Anaesth*. 2005;94:577–81.
- Kranke P, Eberhart LH. Postoperative nausea and vomiting: rational algorithms for prevention and treatment based on current evidence. *Anesthesiol Intensivmed Notfallmed Schmerzther*. 2009;44:286–94.