Rev Bras Anestesiol. 2016;66(3):225–230

REVISTA BRASILEIRA DE ANESTESIOLOGIA
Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

SCIENTIFIC ARTICLE

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

José Carlos Rittes[a], **Guilherme Cagno**[a], **Marcelo Vaz Perez**[a,b], **Ligia Andrade da Silva Telles Mathias**[a,b,*]

[a] *Irmandade da Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil*
[b] *Faculdade de Ciências Médicas, Santa Casa de Misericórdia de São Paulo, São Paulo, SP, Brazil*

Received 28 May 2012; accepted 20 March 2013
Available online 17 April 2015

KEYWORDS
Propofol/pharmacology;
Propofol/pharmacokinetics;
Emulsions;
Nanostructures;
General anesthesia

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.

* Corresponding author.
E-mail: rtimao@uol.com.br (L.A.S.T. Mathias).

http://dx.doi.org/10.1016/j.bjane.2013.03.026

PALAVRAS-CHAVE
Propofol/farmacologia;
Propofol/farmacocinética;
Emulsões;
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.

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.[1] 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.[2] 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.[3]

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.[4,5]

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.[6,7]

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,[8] which reported incidence of pain in about 80% of patients who received propofol in lipid formulation.[9,10] 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