# A Comparative Study of Non-Lipid Nanoemulsion of Propofol with Solutol and Propofol Emulsion with Lecithin

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**Summary:** Rodrigues TA, Alexandrino RA, Kanczuk ME, Gozzani JL, Mathias LAST – A Comparative Study of Non-Lipid Nanoemulsion of Propofol with Solutol and Propofol Emulsion with Lecithin.

**Background and Objectives:** Some formulations have been proposed to reduce the adverse reactions due to the lipid emulsion containing soybean oil used as propofol carrier. This study for endoscopy sedation was aimed at evaluating and comparing the safety, effectiveness and adverse effects of the use of propofol nanoemulsion compared to propofol currently commercialized.

**Method:** In this prospective study, 150 patients were submitted to upper digestive endoscopy. These patients were allocated into two groups: the control group (CONT Group; n = 75) and the nanoemulsion group (NE Group; n = 75). HR, SBP, DBP, $SpO_2$ and BIS (which is considered to be appropriate between 65 and 75 during procedure) were monitored. Gender, age, weight, height, BMI, ASA physical status, times and doses were analyzed, as well as adverse effects (phlogistic signs and pain on injection, apnea, nausea/vomiting) and alterations in monitoring variables. A p-value < 0.05 was considered significant.

**Results:** The groups had similar results concerning anthropometric data and physical status. None of the patients developed apnea or presented phlogistic signs in the injection site. The incidence of pain on injection in the CONT Group was 82.7% and 53.3% in the NE Group (p < 0.001), and the incidence of nausea and vomiting was 10.7% in the CONT Group and 2.7% in the NE Group (p > 0.05). The times, induction doses and the SBP and DBP values at the end of examination and at the moment of discharge from the PACU were lower in the NE Group (p < 0.05).

**Conclusions:** Lipid propofol and propofol nanoemulsion were equivalent concerning effectiveness, safety and adverse effects in the doses used. There was a lower incidence of pain on injection in the nanoemulsion formulation.

**Keywords:** Conscious Sedation; Endoscopy; Propofol.



## INTRODUCTION

Currently, commercial propofol consists of 1% and 2% solutions formulated in 10% soybean oil emulsions. Despite the success of this formulation, there are some drawbacks to the lipid emulsion containing soybean oil, such as pain on injection, solution instability, need for antimicrobial agents to prevent bacterial contamination, and the hyperlipidemia that may occur in continuous infusions [1-4]. International efforts have been invested to alter propofol carrier and reduce the side effects due to the lipid emulsion of soybean oil. Such efforts include, for example, solutions with low quantity of soybean oil, by associating short-and medium-chain fatty acids, albumin emulsions, propofol–cyclodextrin formulations and propofol aqueous solutions as a prodrug, associated to phosphate radicals [5,6]. However, all these carriers have their drawbacks or adverse effects. Fospropofol, for instance, has a longer onset and recovery duration, apart from the unreported side effects due to the use of conventional propofol, such as perineal pain and paresthesia [6].

The development of nanoemulsions led to improvements related to emulsion stability, due to the increase of the medication service life and to the reduction of the risk of separating oil from water. In addition, nanoemulsions have a wide antimicrobial activity, which can eliminate the need for adding agents such as EDTA (ethylenediaminetetraacetic acid), metabisulphite and benzoic acid [7]. In search of safer formulations, scientists started to use polyethylene glycol 660 hydroxystearate (Solutol® HS15 - BASF, Ludwigshafen, Germany) as a propofol carrier. Solutol is a water-soluble nonionic solubilizer developed for use in parenteral formulations with lipophilic agents and vitamins [8].

This study was aimed at performing a comparative evaluation of effectiveness, safety and adverse effects between the traditional propofol formulation used in soybean lecithin and the nanoemulsion formulation with solutol in endoscopy procedures.

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## METHOD

A prospective, open, random and comparative study was conducted with 150 patients submitted to upper digestive endoscopy. The study was approved by the Institution's Research Ethics Committee. After having signed the Informed Consent Form, patients were randomly distributed into two groups: the control group (CONT, n = 75), in which lipid emulsion propofol was used, and the nanoemulsion group (NE, n = 75), in which propofol nanoemulsion was used.

The calculus of the sample was based on previous studies, which showed difference over the incidence of pain on injection of different propofol formulations, varying from 27% [9] to 49% [10]. The minimum size of the sample calculated was of 69 patients per group, so as to detect relevant difference over pain incidence (27%), according to the analysis based on the following parameters: type I error ($\alpha = 0.05$) and type II error ($\beta = 0.95$). We decided to organize two groups of 75 patients each, since we foresaw that there would be drop-outs.

The patients participating in the study were submitted to upper digestive endoscopy procedures. They were elective patients, from both genders, ages between 18 and 65 years, body mass index (BMI) $\geq 18.5$ e $< 30.0$ kg.m$^{-2}$ and ASA I and II physical status (according to the classification of the American Society of Anesthesiologists).

Exclusion criteria were: patients with treated or non-treated skin diseases, which prevented from evaluating the injection site; pregnant women; atopy and/or allergy antecedents; psychoactive agent use and history of nausea and vomiting after anesthetic procedures.

In the examination room physicians monitored the heart rate (HR), the electrocardiogram trace (ECG); the noninvasive systolic (SBP) and diastolic blood pressure (DBP); the peripheral hemoglobin saturation ($SpO_2$); and the bispectral index (BIS). All endoscopy procedures occurred with BIS score between 65 and 75, which is an appropriate sedation condition [11].

All patients received oral anesthetics with 10% lidocaine spray by the endoscopy staff, and then the dose of 1 mg.kg$^{-1}$ propofol was injected for 10 seconds. Limit weight for men and women was 100 kg.

Induction time was defined as the interval between the end of the propofol injection and the achievement of the BIS score below 75. In case the indexes were not achieved in the first minute, one third of the initial dose would be administered in bolus every minute. Induction dose was considered to be the sum of all the doses used during induction and the maintenance dose was considered to be the sum of the doses necessary to maintain the BIS score between 65 and 75 during examination.

The variables analyzed were:

- age, gender, weight, height, BMI and ASA physical status;
- adverse effects on the injection site (phlogistic signs at the puncture site and pain on injection: pain is evaluated as present or absent as the interval in seconds between the propofol injection and the beginning of sedation is very short, which impedes the evaluation in scales);
- systemic adverse effects (occurrence of apnea, nausea and vomiting after procedure and others. These are evaluated until the discharge from the post-anesthesia unit care (PACU)
- induction and maintenance times and doses; awakening time (from the moment of the last additional dose until the moment when the patient starts to respond to the physician's commands); and the time spent in the PACU (PACU discharge criteria: score of the modified Aldrette-Kroulik scale greater than or equal to nine);
- HR, SBP, DBP and $SpO_2$ (are analyzed in four moments: before the beginning of procedure, at the end of induction; at the end of examination and at the moment of discharge from PACU).

The statistical analysis was performed by the software SigmaStat 3.5. The t-test and the Mann-Whitney test were used to compare the quantitative variables between the groups, according to the sample distribution. The variable data with normal distribution are shown as the mean (standard deviation) and those with other types of distribution are shown as the median and the interquartile range [p25 – p75]. For the categorical variables, the z test was used. A p-value $< 0.05$ was considered significant. The MiniTab software was used for the graphs.

## RESULTS

The sample showed similar results concerning the age, gender, weight, height, BMI and ASA physical status variables and there was no statistical difference between the groups ($p > 0.05$) (Table I).

**Table I** – Demographic Data According to the Group

| Variables | CONT Group (n = 75) | NE Group (n = 75) | p |
|---|---|---|---|
| Age (years) | 43 (33-53) | 46 (39-54) | p = 0.357* |
| Gender | | | |
| Male | 39 (52%) | 44 (58.7%) | p = 0.511+ |
| Female | 36 (48%) | 31 (41.3%) | |
| Weight (kg) mean ± SD | 65.9 ± 10.6 | 67.4 ± 12.6 | p = 0.427** |
| Height (m) Median (p25-p75) | 1.65 (1.6-1.7) | 1.65 (1.6-1.7) | p = 0.493* |
| BMI (kg.m$^{-2}$) Median ± SD | 24.4 ± 2.9 | 24.5 ± 3.3 | p = 0.821** |
| Physical status | | | |
| ASA I | 50 (66.7%) | 45 (60%) | p = 0.498 |
| ASA II | 25 (33.3%) | 30 (40%) | |

CONT Group: control group; NE Group: nanoemulsion group; BMI: body mass index; p = significance of the statistical test used; * Mann-Whitney test; ** t test; + z test.

**Table II –** Times and Doses Used for Each Group

| Variables | CONT Group | NE Group | p* |
|---|---|---|---|
| Times | | | |
| Induction (min) | 2 (1-2) | 1 (1-2) | **p = 0.023** |
| Maintenance (min) | 5 (4-6) | 6 (4-6.25) | p = 0.259 |
| Awakening (min) | 5 (3-6) | 5 (3-6) | p = 0.897 |
| PACU (min) | 10 (10-11) | 10 (10-10) | p = 0.297 |
| Doses | | | |
| Induction ($mg.kg^{-1}$) | 1.44 (1.24-1.67) | 1.27 (1.14-1.61) | **p = 0.039** |
| Maintenance ($mg.kg^{-1}$)** | 0.44 (0.35-0.56) | 0.50 (0.34-0.73) | p = 0.318 |

These data were presented as Medians (p25-p75) * Mann-Whitney test; CONT Group: control group; NE Group: nanoemulsion group; PACU: post-anesthesia Care Unit; ** Maintenance doses: n = 43 CONT group and n = 49 NE group.

**Table III –** Comparing the Monitoring Variables of the Two Groups

| Variables | CONT Group | NE Group | p* |
|---|---|---|---|
| HR (bpm) | | | |
| Beginning | 80 (71-90) | 80 (70-90) | p = 0.828 |
| End of Induction | 78 (71-87) | 83 (72-89) | p = 0.300 |
| End of Exam. | 80 (71-83) | 79 (70-82) | p = 0.304 |
| PACU Discharge | 71 (69-80) | 70 (66-76) | p = 0.244 |
| SBP (mm Hg) | | | |
| Beginning | 131 (125-138) | 133 (126-141) | p = 0.202 |
| End of Induction | 116 (102-121) | 117 (103-125) | p = 0.444 |
| End of Exam. | 120 (115-125) | 110 (105-121) | **p < 0.001** |
| PACU Discharge | 128 (125-131) | 112 (105-130) | **p < 0.001** |
| DBP (mm Hg) | | | |
| Beginning | 80 (69-88) | 78 (68-84) | p = 0.176 |
| End of Induction | 68 (60-72) | 66 (58-75) | p = 0.411 |
| End of Exam. | 70 (67-76) | 67 (61-70) | **p < 0.001** |
| PACU Discharge | 75 (70-78) | 69 (60-79) | **p < 0.001** |
| $SpO_2$ (%) | | | |
| Beginning | 98 (97-98) | 98 (98-98) | **p = 0.021** |
| End of Induction | 96 (95-96) | 96 (95-97) | p = 0.257 |
| End of Exam. | 96 (96-97) | 96 (96-97) | **p = 0.039** |
| PACU Discharge | 97 (96-97) | 96 (96-97) | p = 0.235 |

These data were presented as Medians (p25-p75) * Mann-Whitney test; CONT Group: control group; NE Group: nanoemulsion group; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; $SpO_2$: peripheral hemoglobin saturation; PACU: post-anesthesia care unit.

The incidence of pain on injection with propofol was 82.7% (62 patients) in the CONT group and 53.3% (40 patients) in the NE group. The difference between the groups (29.4%) was statistically significant (p < 0.001).

None of the patients showed flushing, edema, apnea or hypoxemia. In the CONT group, eight cases (10.7%) of nausea/vomiting were reported after examination, and two cases were reported in the NE group. There was no statistically significant difference between the two groups (p = 0.102). No other adverse effect was noticed.

In relation to the times and doses analyzed, researchers only verified a statistically significant difference between the time and induction dose of the patients from both groups, as shown in Table II.

Data related to the monitoring variables are shown on Table III. Researchers found a statistically significant alteration concerning SBP and DBP between the two groups at the end of examination and at the moment of discharge from PACU (p < 0.001 for both variables in the two moments) (Figure 1), and also concerning $SpO_2$ in the beginning and at the end of examination (p = 0.021; 0.039), although the medians are the same.

## DISCUSSION

This study evaluated 150 patients submitted to upper digestive endoscopy in order to understand the clinical characteristics associated to the use of propofol nanoemulsion, compared with the lipid emulsion propofol. It is worth mentioning that there are few studies about clinical use of formulations of propofol nanoemulsion [12].

In this study the incidence of pain on injection with propofol nanoemulsion was lower than the incidence of pain with the use of conventional propofol, with statistical relevance (53.3% *vs.* 82.7%). In a study with rats receiving intraperitoneal infusion of acetic acid (control group) or lipid propofol and non-lipid nanoemulsion carriers (similar to those used in this research), the aim was to evaluate the occurrence of pain by means of the number of abdominal distresses of the animal. The acetic acid and the lipid propofol caused 46.0 ± 2.0 and 12.5 ± 0.6 distresses in the 20 minutes following the intraperitoneal injection, respectively. Abdominal distress after the administration of propofol nanoemulsion was not observed, which indicates that the animals had less pain on injection with such solution [12].

In a study conducted in India, the incidence of pain due to the use of non-lipid formulation of propofol (Cleofol®; Themis Medicare, Mumbai, India) was greater than the incidence due to the use of propofol emulsion containing medium-chain triglyceride (Propofol-Lipuro®; B Braun, Melsungen, Germany) [10]. A possible explanation for the difference found in this study and in the Indian publication may be the concentration of free propofol in the non-lipid formulations used (Cleofol® with a higher concentration of propofol in the aqueous phase than the nanoemulsion formulation). Another fact to be mentioned is that the propofol in lipid solution used in this research was different from the one used in the mentioned publication (Propofol-Lipuro®, mixture of 50% medium-chain triglyceride with 50% long-chain triglyceride, compared with propofol containing long-chain triglyceride emulsion - Propovan®, Cristália Produtos Químicos Farmacêuticos, Itapira - SP, Brazil).

Literature data show that the formulations containing medium-chain triglyceride emulsion have less concentration of free propofol. Consequently, there is lower incidence of pain associated to its use [9,13-15].

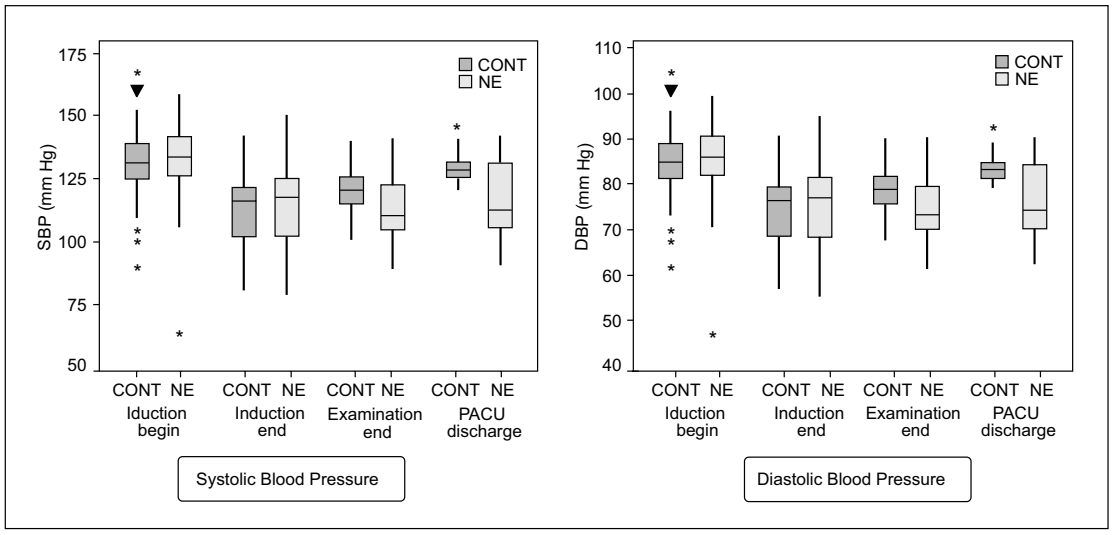


**Figure 1** – Comparing SBP and DBP in the CONT and NE Groups.
*Cases over 90% (p90) or less than 10% (p10); CONT Group: control group; NE Group: nanoemulsion group; SBP: systolic blood pressure; DBP: diastolic blood pressure; PACU: post-anesthesia care unit.

In a study in which plasma bradykinin was introduced after venous injection with 0.9% sodium chloride, lipid emulsion propofol, propofol microemulsion and polyethylene glycol 660 hydroxystearate (Solutol® HS15), higher incidence of pain was associated to injection with microemulsion and with solutol (1.5 times greater than the 0.9% sodium chloride solution. However, these levels were not associated to the pain increase in these groups. Therefore, the authors suggested that pain produced after injection with propofol was not totally related to the release of bradykinin [16].

None of the patients presented flushing following injection, but that may occur from one to five percent of the cases [17]. This result can be explained by the fact that during the selection of patients those with history of atopia were excluded.

Apnea cases were not observed, which shows that the induction doses used were appropriate (median 1.44 $mg.kg^{-1}$ for the control group and 1.27 $mg.kg^{-1}$ for the nanoemulsion group). According to studies, the mean of propofol dose capable of causing apnea (1.82 $mg.kg^{-1}$) is greater than the dose mean injected in patients submitted to digestive endoscopies (1.25 $mg.kg^{-1}$) [18].

Unlike studies [19] with patients receiving lipid propofol for colonoscopy in which hypoxemia was observed in 30% of the ASA I patients and in 6% of the ASA II patients, in this research the peripheral hemoglobin saturations remained normal in all patients from both groups ($SpO_2$ greater than or equal to 93% in both medications used), and researchers did not find cases of hypoxemia. However, at the beginning and at the end of the procedure, a statistic difference was observed between the groups, with no clinical impairment. This difference may be due to a greater dispersion of a group in relation to the other, even if such distribution occurs between very close and normal values. Hypoxemia may have been avoided by providing supplemental oxygen (nasal catheter).

It is widely known that propofol has antiemetic property [1]. The mechanism which may explain such effect is the antidopaminergic activity with a depressor effect on the chemoreceptor trigger zone and vagal nucleus, the smaller release of glutamate and aspartate in the piriform cortex, and the reduction of serotonin in the area postrema. The antiemetic activity can be noticed in sub-hypnotic doses of the medication (10 mg in bolus) [20]. In this study, few cases of nausea/vomiting following examination were observed, and there was no statistical difference between the medications used, although the conducted procedure favored their appearance.

In relation to the procedure times and the medication doses, the CONT group presented higher times and induction doses, showing a significant statistical difference from the NE group. Literature data show little or no pharmacokinetic difference among different formulations of propofol [5], and, according to the present research, a one minute increase in the induction time and a 12% dose increase do not seem to have clinical relevance for healthy patients. The other times and doses were not statistically different between the groups.

The results concerning the cardiac frequency were also reported in a study involving rats receiving lipid propofol or propofol nanoemulsion. The results were similar between the analyzed groups [12].

In this study researchers only verified statistical difference between SBP and DBP values at the end of examination and at the moment of discharge from PACU. The NE group showed lower values. However, all patients remained hemodynamically stable, and the minimum values registered for patients classified into the ASA physical status were acceptable. A study about the use of propofol microemulsion in dogs also showed lower values of mean blood pressure from the fifth minute of the experiment, which is the moment near the

end of examination and awakening of the patients evaluated in the mentioned study [7]. In a study with rats [12], lower values of mean blood pressure occurred after one-hour infusion of propofol nanoemulsion.

The doses of lipid propofol and propofol nanoemulsion allowed an appropriate anesthetic plan to perform upper digestive endoscopy without cardiorespiratory alterations of clinical relevance. Therefore, they are equivalent in effectiveness, safety and adverse effects. It is important to mention a lower incidence of pain on injection with the nanoemulsion formulation, which may be a possible advantage of its clinical use in anesthesiology.

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