Sedation Quality with Two Different Formulations of Propofol Given by TCI in Ambulatory Surgery

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Abstract

Objectives: The objectives are to compare the incidence, severity and duration of pain during i.v. injection of two formulations of propofol for sedation in ambulatory surgery.

Methods: In this randomized, double blind study, propofol was infused using a Target Controlled Infusion to attain a drug plasma concentration of 1 mg/ml in one minute. Patients were asked about location, timing, intensity and duration of pain. Upon waking, patients were asked about their degree of satisfaction and their recall of pain.

Results: Pain was reported by 50% of patients upon i.v. injection. The incidence, intensity and duration of pain could be significantly reduced in the LCT/MCT-propofol group when is used in sedation. No statistically significant differences were seen in any of the hemodynamic criteria or in the depth of anesthesia. The degree of satisfaction was in general very good.

Conclusions: We conclude that LCT/MCT-propofol is associated with reduced incidence, intensity or duration of pain of injection during TCI sedation in ambulatory surgery.

Keywords: LCT/MCT-propofol, LCT-propofol, ambulatory surgery, sedation, injection pain.

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Introduction

Propofol has become the most widely used intravenous (i.v.) anesthetic due to its favorable pharmacodynamic and pharmacokinetic characteristics (rapid recovery and a reduced incidence of post operative nausea and vomiting) [1]. Despite its numerous advantages, propofol has adverse side effects including injection pain, hypertriglyceridemia in prolonged administration schedules and a propensity for bacterial contamination. Thus pain during i.v. administration has been reported in 60% to 70% of cases [2, 3]. A number of factors may account for the appearance of pain including the injection site, the caliber of the blood vessel, the velocity of administration, the concentration, osmolality and pH of the preparation, the concentration of drug in the aqueous phase of the emulsion [4] and the solvent used in the pharmaceutical preparation [5].

In recent years, a number of attempts have been made to improve the formulation of propofol, in order to reduce these side effects. LCT/MCT (long-chain triglyceride/ medium-chain triglyceride) -propofol is a new formulation of propofol that has recently been introduced into the market. A number of clinical studies have found that the new formulation is associated with reduced incidence and intensity of pain during i.v. injection [2,5,6] and reduced hypertriglyceridemia was found with long-term administrations [7,8]. However, to date, all comparative studies of pain due to i.v. injection have been carried out in patients to whom propofol was administered for general anesthesia, not in sedation.

The objectives of the present study were to compare the incidence, severity and duration of pain during i.v. injection of both formulations of propofol for sedation in ambulatory surgery and to characterize the pharmacological effect of the two formulations and to compare the degree of patient satisfaction during recovering consciousness.

Methods

Following approval by the Ethics and Clinical Research Committee of the Galdakao Hospital (Vizcaya, Spain) and having obtained written informed consent of patients, we performed a double blind study of 130 patients, ASA I–III, age 18–65 years, who were being operated in the outpatient surgery program. In order to randomly select patients, we used two equally sized computer-generated lists of the patients who had been randomly assigned by the software to sedation with propofol in the form of LCTpropofol or LCT/MCT-propofol, after spinal anesthesia with 5% prilocaine. Patients who presented with neurological, hepatic or advanced renal disease were excluded from the study. Other excluded patients included those who were positive for pregnancy test or were breast-feeding, those who presented a history of drug or alcohol abuse, allergy to egg or soya oil, those who required i.v. lidocaine as a support drug and those who had morbid obesity.

Patients had an intravenous cannula 18G inserted on the dorsum of the hand and a Ringer Lactate solution was infused at 200 ml/h. They had no premedication. In the operating room, standard routine monitoring was performed: non-invasive arterial blood pressure (BP), continuous electrocardiogram (ECG) with heart rate (HR), pulse oximetry measured using a Vitara PM8060 monitor incorporated into a JULIAN Drager ventilator and measurement of the bispectral index (BIS, Aspect Medical System) in order to measure BIS values during the operation.

Following regional anesthesia and the stabilizing of regional block, sedation was performed with propofol using a Target Controlled Infusion (TCI) system, in order to achieve a plasma concentration of 1mg/ml in 1 minute. Propofol was administered using an infusion pump (ASENA-PK, TCI_TIVA MIII, Alaris) without addition of local anesthetic. No other sedative or narcotic agents were administered prior to or after the regional block. Half of patients received LCT-propofol according to the randomization tables and the remainder were administered LCT/MCT-propofol. Numbered propofol syringes were filled by an anesthesiology nurse and administered to the corresponding patient according to the numbered patient list, thus ensuring that both researchers and patients were blind with regard to the preparation that was being used. Once infusion began, patients were asked if they perceived any kind of pain at the injection site or in any region of the arm. They were asked to describe the pain and its intensity using a simple descriptive scale " Keele Scale"9 over a period of 5 minutes. Even if pain was not initially perceived, we continued to ask the patient about its presence over a five minute period. The level of sedation with propofol was maintained throughout the surgical intervention and was to be suspended only in the event of peripheral oxygen saturation falling below 90% despite oxygen therapy.

The following data were collected: sex, age, height, weight, ASA, location of venipuncture, the existence of any degree of pain at the injection site or in any region of the arm, the degree of pain (mild, moderate or intense) and its duration. BP, HR and BIS data were also obtained at five distinct moments: basal, upon reaching 1 mg/ml propofol and at 5, 10 and 15 minutes afterward.

Patients were asked in the Post Anesthesia Recovery Room about their degree of satisfaction and their recollection of pain, if experienced, using a Likert Scale10. The following variables were analyzed and compared between both groups: the presence of pain during i.v. injection and its localization (site of injection and/or vessel trajectory); the intensity of pain; the intensity of pain as a function of gender; the duration of pain; pharmacological effect variables (BP, HR, BIS), patient satisfaction after waking and recollection of pain.

Statistical analysis

The size of the sample was calculated using the statistical program GPOWER. Calculations were performed on the basis of the intensity of pain during i.v. injection. Subsequently, and with the same program, the randomization of patients was achieved. We calculated means, standard deviations (s.d.) and percentages for the descriptive analysis of the studied sample. In order to examine associations between variables, we used the Chi-squared and Student t tests when the distribution was normal, and the Wilcoxon test for non-normal distributions. Data were considered to be statistically significant when the p value was less than 0.05. Statistical calculations were carried out using the SAS system, version 9.1.

Results

All of the 130 patients who were enrolled completed this study. No patient was excluded from the study for reasons of oxygen desaturation. Both groups were demographically similar, with no significant differences between them (Table 1). The mean age of patients was 46±13 years, with 66.9% of the population being male.

65 (50%) of all patients reported experiencing pain upon i.v. injection of propofol. There were statistical differences in presence of pain between the study groups (p=0.02) (Table 1). Pain was lower in the LCT/MCT-propofol group. We also found that LCT/MCT-propofol group had pain mostly limited to the injection site, whereas with LCT-propofol, a higher percentage of patients felt pain in the vessel trajectory or in both locations (site of injection and vessel trajectory). These differences were statistically significant (p=0.002).

Regarding pain intensity, no significant differences were found between both formulations (p=0.06) (Table 1). We found differences by gender. Analyzing the association between degree of pain and gender, we found differences in the men group (p=0.008), but no in women group (p=0.06) (Table 2). The mean duration of pain was significantly less in the LCT/MCT-propofol group compared to the LCT-propofol group, measured to be 52.5±94.0 seconds and 112.8±117.5 seconds respectively; (p=0.003) (Table 1).

Table 1 Demographic characteristics, as well as the degree, localization and duration of pain in the patients treated with LCT-propofol or LCT/MCT-propofol.

	LCT- propofol N=65 (%)	LCT/MCTp propofol N=65 (%)	p-value
GENDER			0.57
Male	42 (64.6)	45 (69.2)	
Female	23 (35.3)	20 (30.7)	
AGE*	48.2±12.1	44.4±14.7	0.15
Body Mass Index*	26.0±3.8	26.6±3.5	0.42
PRESENCE OF PAIN	39 (60)	26 (40)	0.02
DEGREE OF PAIN			0.06
Mild	17 (43.6)	19 (73.1)	
Moderate	14 (35.9)	5 (19.2)	
Intense	8 (20.5)	2 (7.7)	
LOCALIZATION OF PAIN			0.002
Injection site	10 (25.6)	20 (76.9)	
Vessel trajectory	15 (38.5)	4 (15.4)	
Both localizations	14 (35.9)	2 (7.7)	
DURATION OF PAIN	112.8±117.5	52.5±94.0	0.003

* mean ± s.d..

Table 1 Degree of pain in the two study groups according to genderwith LCT-propofol or LCT/MCT-propofol.

	MEN				WOMEN			
	LCT propofol N=42 (%)	LCT/MCT propofol N=45 (%)	TOTAL N=87 (%)	p-value	LCT propofol N=23 (%)	LCT/MCT propofol N=20 (%)	TOTAL N=43 (%)	p-value
				0.008				0.06
Nothing-mild	32	43	75		11	15	26	
	(76.8)	(95.8)	(86.2)		(47.8)	(75.0)	(60.5)	
Moderate–intense	10	2	12		12	5	17	
	(23.8)	(4.4)	(13.8)		(52.2)	(25.0)	(39.5)	
TOTAL	42	45			23	20		

No significant differences were found in the pharmacological effect of the formulations, as measured in terms of BP, HR and BIS parameters (Figs. 1,2,3).

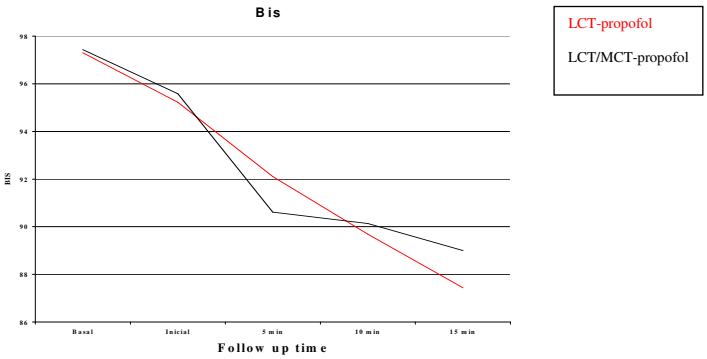

Figure 1 Changes in BIS values in the two groups during the course of the study.

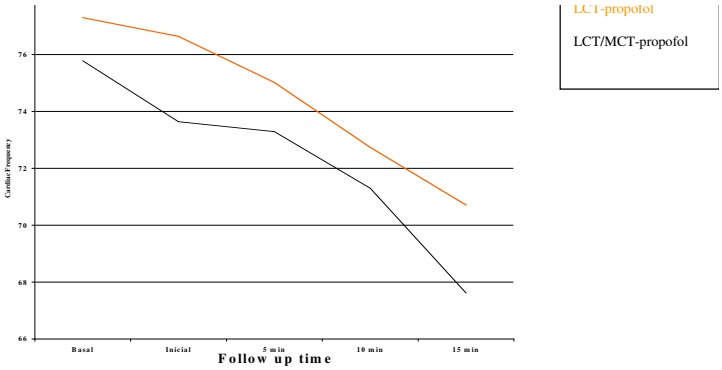

Figure 2 Changes in heart rate in the two groups during the course of the study.

The degree of satisfaction reported by all patients when asked about the sedation experience was excellent (62%), good (31%), poor (4%) and not good (3%) (Table 3). In the 4 patients who reported satisfaction as "not good", the intensity of pain was moderate (2 cases) and intense (2 cases). Moreover, in these cases, the duration of pain was very long, lasting over 300 seconds in 3 of the cases. However, pharmaceutical formulation was not associated with pain, since 2 belonged to the LCT-propofol group and 2 to the LCT/MCT-propofol group.

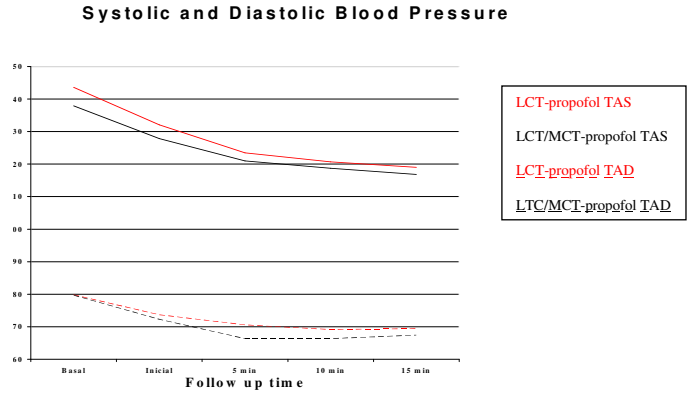

Figure 3 Intraoperative changes in systolic and diastolic blood pressure.

Table 3 Patient satisfaction using a Likert scale.

SATISFACTION SCALE	PATIENTS (%) n = 130
Strongly Agree (Excellent)	81 (62)
Agree (Good)	40 (31)
Neither Agree Nor Disagree (Poor)	5 (4)
Disagree (Not Good)	4 (3)

Discussion

Propofol is a lipid soluble i.v. anesthetic that is widely used in the clinical setting as a hypnotic to achieve general anesthesia as well as sedation [11]. It is formulated in a fat emulsion, which contains almost exclusively long chain triglycerides. This formulation induces pain during i.v. injection, with a reported incidence in 64–67% of patients [2,3].

A multitude of strategies have been tried to reduce this pain, although not eliminate it. The most widely used and efficacious method consists of adding lidocaine to propofol [12], although other methods such as the addition of opiates [3], metoclopramide or modification of the temperature of the product [12,13] have also been tried. Alternatively, the pharmaceutical formulation of the drug can also be modified. New generic formulations of propofol have appeared on the

market [14], as well as variations of the original drug with changes in its formulation in order to try to minimize the undesirable side effects such as pain during i.v. injection, hypertriglyceridemia in prolonged administration regimes and ease of bacterial contamination [6]. One of these new formulations is LCT/MCT-propofol. This emulsion contains triglycerides with an equal proportion of medium and long chains. Since its appearance on the market, a reduced incidence of pain has been reported with LCT/MCT-propofol in one study, 37% vs. 64%. [2]

The pain produced by propofol may be associated with the quantity of drug in the aqueous phase of the emulsion and that reduced pain is associated with a lower concentration of propofol in the total volume [4]. LCT-propofol presents a concentration of propofol in the aqueous phase of the emulsion of about 18.6±0.6 mg/ml, whereas LCT/MCT-propofol presents a concentration of 14±0.5 mg/ml. This reduced concentration may explain the reduction in the irritation of the vascular endothelium [6].

Previous studies were conducted with patients who had received general anesthesia [3,6,15]. Thus, pain was monitored over short time intervals, from the administration of the drug until the loss of consciousness. However, Song et al. documented pain experienced during i.v. injection in sedation cases [16]. We believe that sedation is the ideal framework for studies of i.v. pain, since the patient is awake and can provide more and better quality information.

The objective of the present study was to report pain during i.v. injection when using propofol for sedation, in order to adequately ask patients about the characteristics and duration of the associated pain. It is very important to specifically ask the patient, because much information can be lost if we rely only on spontaneous patient reporting. This has been demonstrated by other authors such as Ayuso et al [5], who estimated the incidence of pain during i.v. injection and found that only a third of patients spontaneously reported pain, with the remainder of patients reporting pain only when asked about it. It is also important to note that pain is not felt by all patients immediately upon beginning drug infusion. Rather, in some cases it appears later. These data could be lost if one does not continue to specifically ask the patient.

It should be noted that in the reported studies, propofol was administered manually [3,5,6,15]. Manual administration may result in a large variation in the velocity of infusion between patients and this raises the possibility a conditioning factor in the appearance of pain. In order to reduce this bias, we used an infusion pump (TCI system) to administer infusion of propofol equal velocity in all patients.

There were statistical differences in presence of pain between the groups, with the LCT/MCT formulation of propofol associated with a decreased incidence of pain during sedation administered by TCI system, compared with the LCT formulation. These results are similar to other authors present, when use propofol to induction of anesthesia [17].

Significant differences were observed in the localization of pain between groups. In the case of LCT/MCT-propofol, pain was restricted principally to the site of injection, whereas in the case of LCT-propofol, a broader localization was reported (Table 1). This difference may be due to the concentration of propofol in the aqueous phase of the emulsion. Thus, in patients who received LCT-propofol, pain was perceived over wider areas, perhaps due to the larger concentration of drug in the aqueous phase of the emulsion in comparison to LCT/MCT-propofol and this may underlie why pain is perceived farther away from the injection site.

An important parameter that we could measure because our patients were sedated was the duration of pain. We found that the duration of pain in patients administered LCTpropofol was almost double that of those who received LCT/MCT-propofol (112.8±117.5 sec vs. 52.5±94.0 sec respectively) with a significant difference ($p=0.003$). Significant differences were found in the severity of pain between treatment groups in men ($p=0.008$), however in women no significant differences ($p=0.06$) were found. There may have been too few women enrolled in the study to detect a statsitical difference in the incdence of pain.

We assessed the commonly-used BP, HR and BIS values as a measure of pharmacological effect [18,19,20]. The BP-systolic, BP-diastolic and HR values, as well as BIS values were found to be similar for the two formulations (Figs. 1,2,3). These data corroborate those of other studies that also reported an absence of pharmacodynamic differences [21,22].

The degree of patient satisfaction was overall quite good (Table 3). In four cases where satisfaction was not good this was due to moderate to intense pain. Also, in three of these cases, the patients experienced long-duration pain; 300 secs in three of the cases which is the maximum duration that we measured. When pain is moderate or intense and in addition of long duration, the benefit which sedation offers may be lost because the patient feels uncomfortable and does not attain the intended degree of comfort. If the patient experiences moderate-intense pain, it nay be advisable to employ a different sedative drug.

In conclusion, we monitored pain induced by i.v. injection for sedation, using the LCT/MCT- propofol and LCT-propofol, and we observed that LCT/MCT-propofol reduces the incidence, degree and duration of pain of injection when it is used for sedation by TCI. The degree of patient satisfaction with sedation was very good, except in cases in which pain was intense and prolonged over time.

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