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PAIN INDUCED BY PROPOFOL-RANDOMISED DOUBLE BLIND STUDY

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ABSTRACT

Propofol is a commonly used intravenous anaesthetic agent to induce and maintain anaesthesia, especially for short cases, ambulatory surgery or when a laryngeal mask airway is to be used. Pain on injection with propofol is a common side effect and can be unacceptable to the patient. Incidence of pain varies between 28% to 90% in adults and 28% to 85% in childrens. The most frequently used method to reduce pain is the administration of lignocaine, either before propofol injection, with or without a tourniquet[25] or added to the propofol emulsion as a premixture. With this background, study was undertaken to compare the newly developed MCT/LCT propofol with standard LCT propofol and along with use of lignocaine in context of reducing pain on intravenous injection. 100 adults (20–40 yr), ASA risk I and II, of either sex scheduled for elective surgery under general anaesthesia were recruited for the randomised double blind comparative study. Subjects were divided into four groups of 25 receiving Premixed Inj. Propofol (LCT) (2.5 mg/kg) +2 mL of 0.9% NaCl at the rate of 1 mL/sec IV; Premixed Inj. Propofol (MCT/LCT) (2.5 mg/kg) + 2 mL of 0.9% NaCl at the rate of 1 mL/sec IV; Premixed Inj. Propofol (LCT) (2.5 mg/kg) + Inj. Lignocaine 40 mg at the rate of 1 mL/sec IV; Premixed Inj. Propofol (MCT/LCT) (2.5 mg/kg) + Inj. Lignocaine 40 mg at the rate of 1 mL/sec IV administered before surgery. The patients were previously explained about the study and the four point visual analogue scale, classifying the intensity of pain as none (negative response to questioning), mild (pain reported only in response to questioning without any behavioural signs), moderate (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning), Severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears). After the surgery, the injection site was checked for pain, edema, wheal and flare response. The observations made were tabulated and analysed using Chi-square test and Fisher´s exact test for categorical data. Parametric data was analysed using analysis of variance (ANOVA) and with t- test for analysis between individual groups. After analyzing the results of our study the following points are concluded 1) Propofol-MCT/LCT cause less pain and hemodynamic changes on IV injection than propofol-LCT. 2) Addition of lignocaine to propofol-LCT and propofol-MCT/LCT reduced the incidence and severity of pain and hemodynamic changes as compared to propofol- LCT alone. 3) The incidence and severity of pain and hemodynamic changes on injection of propofol MCT/LCT was not different from that caused by propofol LCT with pretreatment of lignocaine and propofol-MCT/LCT with pretreatment of lignocaine. 4) We did not find any advantage in using lignocaine with that for propofol-MCT/LCT in ensuring maximal patient comfort during induction of anaesthesia. It was concluded that addition of lignocaine to propofol-LCT and propofol-MCT/LCT reduced the incidence and severity of pain and hemodynamic changes as compared to propofol- LCT alone. Using propofol-MCT/LCT alone is equally benefited as using propofol-LCT premixed with lignocaine in reducing pain as compared to propofol-LCT alone.

Key Words: Four Point Visual Analogue Scale, Propofol-MCT/LCT, Lignocaine, Injection pain.

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INTRODUCTION

Propofol is a commonly used intravenous anaesthetic agent to induce and maintain anaesthesia, especially for short cases, ambulatory surgery or when a laryngeal mask airway is to be used. Pain on injection with

propofol is a common side effect and can be unacceptable to the patient. Incidence of pain varies between 28% to 90% in adults and 28% to 85% in childrens [1]. The younger the child, the higher is the incidence and severity of propofol injection pain. This pain in children could be due to small veins in hand [2,3]. Many factors appear to affect the incidence of pain, which includes site of injection, size of vein, speed of injection, buffering effect of blood, temperature of propofol and concomitant use of drugs [4].

Pain on injection of propofol can be immediate or delayed. Immediate pain probably results from a direct irritant effect of free propofol whereas delayed pain probably results from an indirect effect via the kinin cascade. Delayed pain has latency of between 10 s and 20 s.The sensation produced is usually described as tingling, cold, numbing or, at its worst, a severe burning pain proximal to the site of injection. This sensation tends to occur within 10 s to 20 s of injection and lasts only for the duration of injection. Despite this discomfort, the incidence of venous sequel, such as phlebitis, is less than 1% [5].

The most frequently used method to reduce pain is the administration of lignocaine, either before propofol injection, with or without a tourniquet [6] or added to the propofol emulsion as a premixture [7-9]. The mechanism of pain relief can be two fold; first by reduction of propofol in the aqueous phase and second by lignocaine acting as a stabiliser in the kinin cascade.

It has been studied that pain on injection is due to the amount of free propofol in the aqueous phase of the emulsion. In 1997, Doenicke et al. advocated a reformulated lipid emulsion of propofol to alleviate pain on injection. This reformulation of propofol contains both medium chain triglycerides (MCT) and long chain triglycerides (LCT) in equal proportions in contrast to usual LCT formulation. The amount of free propofol in a MCT/LCT emulsion is assumed to be less compared with propofol LCT thus causing less pain on injection [10-14]. This new formulation of propofol has similar pharmacokinetics and efficacy as propofol.

With this background, study was undertaken to compare the newly developed MCT/LCT propofol with standard LCT propofol and along with use of lignocaine in context of reducing pain on intravenous injection.

METHODS

100 adults (20–40 yr), ASA risk I and II, of either sex scheduled for elective surgery under general anaesthesia were recruited for the randomised double blind comparative study. The study protocol was approved from the institutional ethical committee and written informed consent was obtained from all the patients. Both the patients and the investigator were unaware of the type of study drug given.

Patients with allergic to propofol, history of chronic pain or daily intake of analgesics, patients with neurological or psychological disease, history of intake of non-steroidal anti-inflammatory drugs or steroids within 24 h before surgery were excluded from the study.

The patients were assigned into either of following four groups with each group including 25 patients. Propofol injections stored at 4-6 degree Celsius were used in all patients, maintaining the cold chain while using the drug.

a) Group A

Premixed Inj.Propofol (LCT) (2.5 mg/kg) + 2 mL of 0.9% NaCl at the rate of 1 mL/sec IV.

b) Group B

Premixed Inj.Propofol (MCT/LCT) (2.5 mg/kg) + 2 mL of 0.9% NaCl at the rate of 1 mL/sec IV.

c) Group C

Premixed Inj. Propofol (LCT) (2.5 mg/kg) + Inj. Lignocaine 40 mg at the rate of 1 mL/sec IV.

d) Group D

Premixed Inj.Propofol (MCT/LCT) (2.5 mg/kg) + Inj.Lignocaine 40 mg at the rate of 1 mL/sec IV.

After arrival in operating room, routine monitoring was applied and 18 G intravenous cannula was inserted into a suitable vein on the dorsum of non-dominant hand, and flushed with 10 mL of normal saline over 5 seconds to confirm that patient does not have any pain before the study of drug to be injected. The patients were given premedication in the form of Inj.Glycopyrrolate (4 ug/kg) and Inj.Ondansetron (150 ug/kg) intravenously followed by flush of 5 mL of normal saline without giving any sedative or analgesics as premedication. The patients were previously explained about the study and the four point visual analogue scale, classifying the intensity of pain as none (negative response to questioning), mild (pain reported only in response to questioning without any behavioural signs), moderate (pain reported in response to questioning and accompanied by a behavioural sign or pain reported spontaneously without questioning), Severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).

The patients were then pre-oxygenated via a face mask with fresh gas flow of 8 L / min oxygen for 5 min. Anaesthesia was induced with 2.5 mg/kg propofol at 1 mL/sec without a flowing intravenous fluid during and following the propofol injection. After giving approximately 2 mL of propofol preparation, the patient was immediately asked for pain on injection. After the assessment of pain, the induction of anaesthesia was continued as per routine practice. After the surgery, the injection site was checked for pain, edema, wheal and flare response. The observations made were tabulated and analysed using Chi-square test and Fisher´s exact test for categorical data. Parametric data was analysed using analysis of variance (ANOVA) and with t- test for analysis between individual groups

RESULTS

a) Group A

Premixed Inj. Propofol (LCT) (2.5 mg/kg) +2 mL of 0.9% NaCl at the rate of 1 mL/sec IV

b) Group B

Premixed Inj. Propofol (MCT/LCT) (2.5 mg/kg) + 2 mL of 0.9% NaCl at the rate of 1 mL/sec IV.

c) Group C

Premixed Inj. Propofol (LCT) (2.5 mg/kg) + Inj. Lignocaine 40 mg at the rate of 1 mL/sec IV.

d) Group D

Premixed Inj. Propofol (MCT/LCT) (2.5 mg/kg) + Inj. Lignocaine 40 mg at the rate of 1 mL/sec IV.

As per table no 2 and graph 1patients in Group A had significant incidence of pain compared to patients in Group B, C and D. In Group A the incidence of pain was100% compared to 44% in Group B (X^2=19.44, p<0.0001) whereas in Group C incidence of pain was 20% compared to Group A (X^2=33.333, p<0.0001) and in Group D the incidence of pain is 28% as compared to group A(X^2=28.1, p<0.0001). There was no significant difference in incidence of pain between Group B and C (X^2=3.309, p=0.0689), Group C and D (X^2=0.439, p=0.5078), Group B and D (X^2=1.389, p=0.2386).

As per table no 3 and graph 2 there was significant difference in severity of pain between groups A and B (p = < 0.0001) between groups A and C (p = < 0.0001) and between groups A and D (p = < 0.0001). There was no difference in severity of pain between groups B, C and D (p = > 0.50).

From Table 4 and graph 3 it can be seen that there was significant difference in between groups A and B (t = 7.18; p = < 0.0001) between groups A and C (t = 8.87; p = < 0.0001) and between groups A and D (t = 8.4379; p = < 0.0001) for mean difference in pulse rate at 0 minute and 1 minute. There was no significant difference in between groups B, C and D (t = 1.63; p = 0.60) for mean difference in pulse rate at 0 minute and 1 minute.

From Table 5 and graph 4 it can be seen that there was significant difference in between groups A and B (t = 3.35; p = 0.001) between groups A and C (t = 4.72; p = < 0.0001) and between groups A and D (t = 4.4206; p = < 0.0001) for mean difference in systolic blood pressure at 0 minute and 1 minute. There was no significant difference in between groups B, C and D (t = 1.50; p = 0.37) for mean difference in systolic blood pressure at 0 minute and 1 minute.

Table 1. Demography

Parameters		Group A	Group B	Group C	Group D	p-Value
Age (Yrs) (Mean ± SD)		31.76 ± 9.06	34.72 ± 10.10	35.24 ± 7.30	30.80 ± 7.51	>0.001
Sex	Male	17 (68%)	14 (56%)	18 (72%)	13 (52%)	>0.001
	Female	8 (32%)	11 (44%)	7 (28%)	12 (48%)	
ASA Grade	I	15 (60%)	14 (56%)	12 (48%)	16 (64%)	>0.001
	II	10 (40%)	11 (44%)	13 (52%)	9 (36%)	

The Table 1 shows that both the groups were comparable with respect to age, sex distribution and ASA physical status (p > 0.001).

Table 2. Incidence of pain

Pain/No pain	Group			
	A (n=25)	B (n=25)	C (n=25)	D (n=25)
No Pain	0	14 (56%)	20 (80%)	18 (72%)
Pain	25 (100%)	11 (44%)	5 (20%)	7 (28%)

Table 3. Severity of pain

Pain Score	Group			
	A (n=25)	B (n=25)	C (n=25)	D (n=25)
0 = no pain or discomfort	0	14(56%)	20(80%)	18(72%)
1=mild pain	2(8%)	10(40%)	5(20%)	7(28%)
2= moderately painful	8(32%)	1(4%)	0	0
3=severely painful	15(60%)	0	0	0

HEMODYNAMIC CHANGES

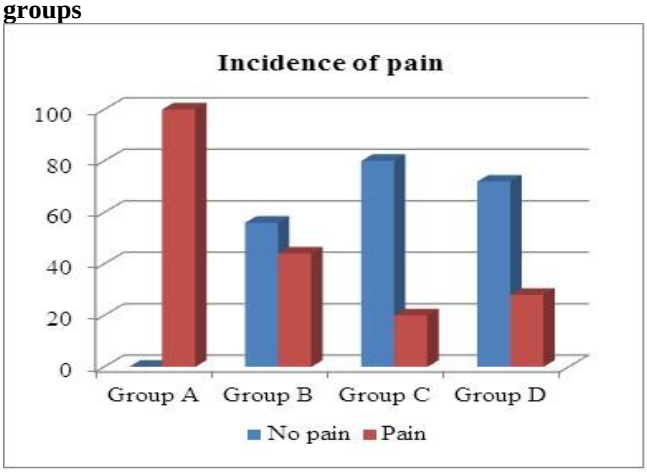
Table 4. Comparison of difference in pulse rate at 0 minute and 1 minute

Pulse rate / minute	Group A	Group B	Group C	Group D
Average baseline pulse rate(0 minute)	81.16	77.2	79.6	78.44
Average pulse rate at 1 minute	89.84	78.68	79.92	79.16
Average of difference in pulse between 0 minute and 1 minute (Mean ±SD)	8.68 ± 4.21	1.48 ± 2.55	0.32 ± 1.68	0.72 ± 1.61

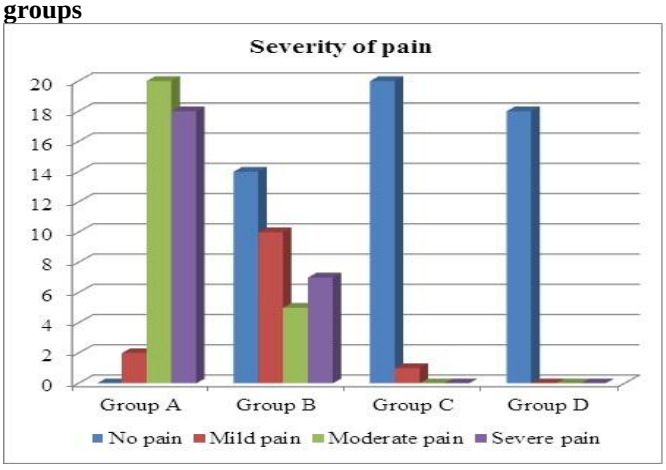
Table 5. Comparison of systolic blood pressure difference at 0 minute and 1 minute

Systolic blood pressure(mm of Hg)	Group A	Group B	Group C	Group D
Average baseline systolic BP at 0 minute	118.88	121.32	120.72	121.84
Average systolic BP at 1 minute	124.72	122.88	121.04	122.56
Average difference in systolic blood pressure between 0 minute and 1 minute (Mean ± SD)	5.84 ± 5.59	1.56 ± 3.28	0.32 ± 1.66	0.72 ± 1.48

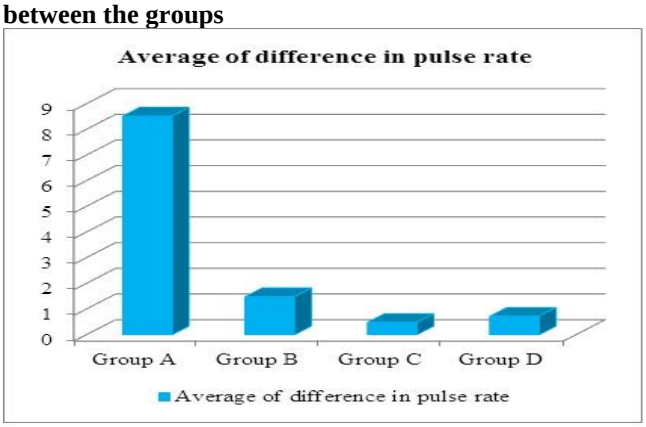
Graph 1. Comparison of incidence of pain between the groups



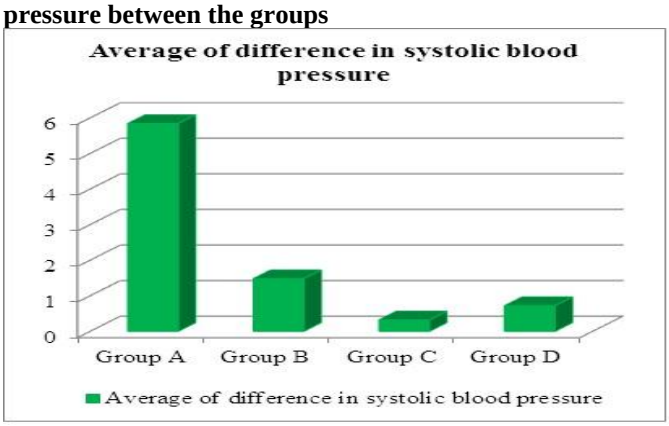
Graph 2. Comparison of severity of pain between the groups



Graph 3. Comparison of difference in pulse rate between the groups



Graph 4. Comparison of difference in systolic blood pressure between the groups



DISCUSSION

Propofol (2, 6 diisoporpylphenol) was formulated in 1982, in a concentration of 10 mg/mL in a fat emulsion consisting of soyabean oil (LCT-Long chain triglycerides). It is used to induce and maintain anaesthesia as well as for sedation of intensive care patients. The advantages include a good control of anaesthesia and very short sleep phase of approx 8 minutes after single injection. Like other phenols it causes irritation to the skin and to mucous membranes, as well as pain at the site of injection. Incidence of pain varies between 28% to 90% in adults and 28% to 85% in childrens [17]. Even when injected into large proximal veins; the probability of a painful reaction is still up to 30%. Propofol is highly lipophilic compound and is 97-

98% is protein bound. Hence it is always formulated in a lipid emulsion. It is not hydrophilic and hence cannot and should not be formulated into an aqueous solution. The mass flux of a molecule at the interface of two immiscible solvents is governed by its lipophilicity. The more lipophilic molecule is, the more soluble it is in lipophilic organic phase. For the same reason, drug penetration into a biological membrane is also influenced by its lipophilicity.

Cause of Pain

In vitro investigations by Klement at the Dusseldorf University published the first paper examining pain on injection with propofol in respect of effects of concentration and diluent. They demonstrated that the high concentrations of free propofol in the aqueous phase are a decisive variable for associating pain with injection. The view has since then been shared by other eminent researchers including Doenicke, Rau, Babl et al.

The commercially available emulsion of propofol varies mainly in the composition of its inner phase, which may be pure soya oil (LCT) or an equal mixture of soya oil (LCT) and Medium Chain Triglycerides (MCT). The outer phase is water that is made isotonic with glycerol. The emulsifier is usually present as unilaminar layer on the boundary surfaces of the very fine oil globules, stabilizes the otherwise unstable system by reducing surface tension. In a system of this nature, the drug is distributed differently in the two phases of aqueous and oil. During injection, the outer phase (aqueous) comes into direct contact with the intima and concentration of an irritating agent in this phase is the element causing venous pain on administration.

The advantage of emulsions as drug carriers for lipophilic compounds is the reduction of side effect of pain. Despite the fact that drug released from oil droplets is quite rapid, due to partitioning effects, the reduction of free drug and delayed release are still sufficient to minimize pain.

The use of lignocaine to prevent propofol injection pain is the most extensively studied technique and is the most common method used in clinical practice. However, the availability of plain lignocaine without preservative is still lacking in many countries including Thailand. Moreover, the mixing of propofol emulsion with any other drug is not recommended by the manufactures because emulsions are thermodynamically unstable despite the use of stabilizing agent. The addition of lignocaine 20 mg or 40 mg to propofol 200 mg results in coalescence of oil droplets, which finally proceeds to a visible separate layer, indicating physicochemical incompatibility [19]. Importantly, the addition of lignocaine may destabilize the emulsion formulation of propofol with a subsequent risk of causing a pulmonary fat embolism. These methods also have the disadvantage of requiring additional manipulation, which may or may not alter pharmacokinetics and pharmacodynamics and makes delivery of anaesthesia less efficient. There is also the potential of introducing contaminants into the emulsion, because LCT fat emulsion can serve as excellent growth media. Propofol-LCT/MCT formulations have been reported to reduce injection pain [20-30].

The following parameters were observed in our study:

a) Incidence of pain
b) Severity of pain
c) Change in pulse rate after IV injection at 1 minute
d) Change in blood pressure after IV injection at 1 minute
e) Complications: Pain, edema, wheal and flare response at the sight of injection.

a) Demography

The number of patients in each group was 25. The mean age of patients was 31.77 ± 9.06 years in Group A, 34.72 ± 10.1years in Group B, 35.24 ± 7.30 years in Group C and 30.80 ± 7.51 years in Group D. The ratio of Male to Female was 17:8 in Group A, 14:11 in Group B, 18:7 in Group C and 13:12 in Group D. The ASA I patients in group A were 15, in group B were 14. In group C 12 and in group D 16, while ASA II patients in group A were 10, in group B were 11. In group C 13 and in group D 9. The groups were comparable with respect to age, sex distribution and ASA physical status ($p > 0.001$).

b) Incidence of pain

In our study it was found out that patients in Group A had significant incidence of pain compared to patients in Group B, C and D. In Group A the incidence of pain was100% compared to 44% in Group B (X^2=19.44, $p < 0.0001$) whereas in Group C incidence of pain was 20% and 28% in Group D compared to 100% in Group A (X^2=33.333, $p < 0.0001$). There was no significant difference in incidence of pain between Group B and C (X^2=3.309, p=0.0689), Group C and D (X^2=0.439, p=0.5078), Group B and D (X^2=1.389, p=0.2386).

This shows that propofol-MCT/LCT causes less incidence of pain on injection than propofol-LCT. This result was comparable to the study done by Kinoshita et al. Rau et al. and Larsen et al [14,15]. In the present study we also studied that addition of lignocaine to propofol-LCT and propofol-MCT/LCT reduced the incidence of pain as compared to propofol- LCT alone. This result was comparable to the study done by Rhom KD et al [27]. The addition of lignocaine to propofol-MCT/LCT did not significantly reduce the incidence of pain on injection as compared to propofol-MCT/LCT alone or propofol-LCT premixed with lignocaine. These findings correlate with the study of Banjong Krobbuaban et al [16], Burimsittichai et al [12] and Nitin Sethi et al [23].

c) Severity of pain

In our study it was found out that there was significant difference in severity of pain between groups A and B (p = < 0.0001), between groups A and C (p = <

0.0001), and between groups A and D (p = < 0.0001). There was no difference in severity of pain between groups B, C and D (p = > 0.50).

This shows that propofol-MCT/LCT causes less severity of pain on injection than propofol-LCT. This result was comparable to the study done by Kinoshita et al., Rau et al. and Larsen et al. In the present study we also studied that addition of lignocaine to propofol-LCT and propofol-MCT/LCT reduced the severity of pain as compared to propofol- LCT alone. This result was comparable to the study done by Rhom KD et al. The addition of lignocaine to propofol-MCT/LCT did not significantly reduce the severity of pain on injection as compared to propofol-MCT/LCT alone or propofol-LCT premixed with lignocaine. These findings correlate with the study of Banjong Krobbuaban et al., Burimsittichai et al. and Nitin Sethi et al.

d) Change in pulse rate after IV injection at 1 minute

In our study we observed that there was significant difference in between groups A and B (t = 7.18; p = < 0.0001), between groups A and C (t = 8.87; p = < 0.0001) and between groups A and D (t = 8.4379; p = < 0.0001) for mean difference in pulse at 0 minute and 1 minute. There was no significant difference in between groups B, C and D (t = 1.63; p = 0.60) for mean difference in pulse at 0 minute and 1 minute.

This shows that propofol-MCT/LCT causes less change in pulse rate after IV injection than propofol-LCT. In the present study we also studied that addition of lignocaine to propofol-LCT and propofol-MCT/LCT reduced the change in pulse rate as compared to propofol- LCT alone. The addition of lignocaine to propofol-MCT/LCT did not significantly reduce the change in pulse rate on injection as compared to propofol-MCT/LCT alone or propofol-LCT premixed with lignocaine.

e) Change in blood pressure after IV injection at 1 minute

In our study we observed that there was significant difference in between groups A and B (t = 3.35; p = 0.001), between groups A and C (t = 4.72; p = < 0.0001) and between groups A and D (t = 4.4206; p = < 0.0001) for mean difference in systolic blood pressure at 0 minute and 1 minute. There was no significant difference in between groups B, C and D (t = 1.50; p = 0.37) for mean difference in systolic blood pressure at 0 minute and 1 minute.

This shows that propofol-MCT/LCT causes less change in systolic blood pressure after IV injection than propofol-LCT. In the present study we also studied that addition of lignocaine to propofol-LCT and propofol-MCT/LCT reduced the change in systolic blood pressure as compared to propofol- LCT alone. The addition of lignocaine to propofol-MCT/LCT did not significantly reduce the change in systolic blood pressure on injection as compared to propofol-MCT/LCT alone or propofol-LCT premixed with lignocaine.

f) Complications

None of the patients in different groups demonstrated any pain, edema, wheal and flare response at the sight of injection

After analyzing the results of our study the following points are concluded

1) Propofol-MCT/LCT cause less pain and hemodynamic changes on IV injection than propofol-LCT.

2) Addition of lignocaine to propofol-LCT and propofol-MCT/LCT reduced the incidence and severity of pain and hemodynamic changes as compared to propofol- LCT alone.

3) The incidence and severity of pain and hemodynamic changes on injection of propofol MCT/LCT was not different from that caused by propofol LCT with pretreatment of lignocaine and propofol-MCT/LCT with pretreatment of lignocaine.

4) We did not find any advantage in using lignocaine with that for propofol-MCT/LCT in ensuring maximal patient comfort during induction of anaesthesia.

5) Using propofol-MCT/LCT alone is equally benefited as using propofol-LCT premixed with lignocaine in reducing pain as compared to propofol-LCT alone.

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