

# Prevention of Pain on Propofol Injection: A Comparative, Randomized, Double Blind Study between Lignocaine, Pethidine, Dexamethasone and Placebo

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## Abstract

**Background:** Propofol is wonderful drug for short duration procedures. However, pain on injection of propofol, which has been reported to occur in 28-90% of patients, is a major drawback to its use. Different methods have been used to decrease this pain but intravenous lignocaine is most commonly used pretreatment.

**Methods :** A comparative, randomized, double blind study was undertaken to compare the efficacy of three drugs for prevention of pain on propofol injection on induction of anaesthesia 100 female patients of ASA status 1 and 2 posted for intracavitary radiotherapy were allocated randomly in four groups of 25 each, using computer-generated table of random numbers. Venous occlusion was made with tourniquet for one minute. The study drug intravenous lignocaine 1% 2ml (group 1), pethidine 25mg in 2 ml (group 2), dexamethasone 4mg in 2ml (group 3), or normal saline 2ml (group 4) was administered over 10 seconds according to random number. There after occlusion was released and intravenous propofol was given. After the first 25% of propofol given, patients were asked for intensity of pain she experienced.

**Results:** Lignocaine, pethidine and dexamethasone significantly reduces the pain on propofol injection in comparison to placebo ( $p < 0.002$ ), but there was no significant difference in pain score among groups 1, 2, 3 ( $p > 0.28$ ). There was no significant difference in recall of pain among groups 1, 2, and 3 ( $p > 0.43$ ). Although there was significant difference between placebo group and other three groups ( $p < 0.009$ ).

**Conclusion:** It was concluded that lignocaine, pethidine and dexamethasone significantly reduces the pain induced by propofol injection pain as compared to placebo but there is no difference in efficacy for prevention of pain among these three groups.

## INTRODUCTION

Propofol is frequently used intravenous anaesthetic induction agent, especially for brief cases, day care surgery or when a laryngeal mask airway is to be used.

Pain on injection with propofol is a common problem and can be very distressing to the patient. Incidence of pain varies between 28% and 90 % ( Stark RD et al 1955 & Mangar D et al 1992) in adults and 28% -85% in children (Valtonen M et al 1988 & 1989) .The younger the child, the higher is the incidence and severity of propofol injection pain (Cameron E et al 1992). This could be due to small veins in hand. 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 such as local anaesthetics and opiates.

Pain on injection of propofol can be immediate or delayed. Immediate pain probably results from a direct irritant effect whereas delayed pain probably results from an indirect effect via the kinin cascade. Delayed pain has latency of between 10 and 20 s (Briggs LP et al 1981). The sensation produced is usually described as tingling, cold, or numbing or, at its worst, a severe burning pain proximal to the site of injection. This sensation tends to occur within 10-20 s of injection and lasts only for the duration of injection. Despite this discomfort, the incidence of venous sequelae, such as

phlebitis, is less than 1 % (Mattila MAK et al 1985).

Different methods have been used to decrease this discomfort, including cooling, adding lignocaine, applying nitroglycerine ointment to the venepuncture site, injecting cold saline prior to the injection of propofol, and diluting the propofol with 5% dextrose or intralipid. Intravenous lignocaine is the most commonly used pretreatment, but has a failure rate of 13% to 32% (Scott RPF et al 1988 & Kingsy 1992 et al). Pethidine is synthetic opioid analgesic with proven local anaesthetic effects (Power I et al 1991 & Famewo et al 1985). Dexamethasone is a steroid it also used for postoperative vomiting and pain after pediatric tonsillectomy (Mokhtar E et al 2003). We had done a double-blind comparison of lignocaine, pethidine, Dexamethasone and placebo drugs on the incidence and severity of pain on injection with propofol.

## METHODS

The study was conducted at Institute Rotary Cancer Hospital, AIIMS, New Delhi, by the department of Anaesthesiology. Local ethics clearance and informed consent from 100 female patients of ASA physical status 1 and 2, aged 30-70 yrs with carcinoma cervix scheduled for ICRT (intra cavitary radio therapy) were taken for the study. Patients with history of allergy to propofol, lignocaine or pethidine, anticipated difficult venous access and patients with conduction cardiac defects were excluded from the study.

Patients were randomly assigned in to four groups of 25 each using a computer- generated table of random numbers.

Group 1 - patients receiving 1% 2ml lignocaine.

Group 2 - patients receiving 25 mg pethidine in 2ml normal saline.

Group 3 - patients receiving 4 mg Dexamethasone in 2ml normal saline.

Group 4 - patients receiving 2 ml normal saline.

All patients were premedicated with oral Diazepam 5mg on night before surgery. On arrival in the operation theater, a 20 G cannula was placed without the use of local anaesthesia in the largest vein on the dorsum of the hand and attached to an infusion of acetated ringers solution. Personnel not involved in the study prepared identical syringes.

Venous occlusion was made by manually compressing the forearm with a rubber tourniquet for one minute. Study drug was injected over 10 seconds and there after the occlusion

was released and propofol 2.5mg/kg was delivered through this intravenous cannula.

During the 10 seconds after the first 25% of calculated propofol was given, the patients were instructed to inform the researcher, who was unaware of group assignments, of the intensity of pain she experienced.

The intensity of pain was graded using a verbal rating scale.

0-None (negative response to questioning)

1-Mild pain (pain reported only in response to questioning without any behavioral signs)

2-Moderate pain (pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning)

3-Severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears)

There after, the induction of anaesthesia was continued with the remainder of the calculated propofol dose and for analgesia fentanyl was given to all patients. Anaesthesia was maintained with isoflurane 0.5-2% and nitrous oxide 60% in oxygen, with spontaneous ventilation. Intra muscular injection of diclofenac sodium 75mg was given just after induction for post procedure pain. All patient were observed for 2-hrs in recovery room. Patients were asked to recall if there was pain during injection of propofol in the recovery room and incidence of pain was graded as 0-No recall of pain & 1-Recall of pain present.

For continuous variables one-way ANOVA test was used. Chi square test was used for significant difference among groups for pain score and recall of pain.

Statistical package SAS 8.0 for statistical analysis.

P value <0.05 has been considered as statistically significant

## RESULTS

One hundred patients were enrolled in this study; there were 25 patients in each treatment group. Groups were similar in respect to age (p-0.143) and weight (p-0.648) (Table 1)

Base line values of HR, SBP, DBP, SPO2 are comparable in all the groups. None of the patients showed significant change in hemodynamic variables after giving test drug and after propofol.

**Figure 1**

Table 1: Demographic Data

Variables	Group-1 n=25	Group-2 n=25	Group-3 n=25	Group-4 n=25
AGE	53.32±12.46	53.20±9.56	50.72±7.63	53.71±10.62
WEIGHT	50.08±19.66	47.04±9.89	49.04±10.35	50.20±9.44

Data represented as mean ± SD  
n- Number of patients

There was no significant difference in pain score among groups 1, 2, and 3 (p= 0.28)

Although there was significant difference between groups 4 (placebo) and other three groups (p=0.002). The overall incidence of pain during injection of propofol in the various groups was shown in Table 2. The incidence of pain in group 4 was 76% as compared to 40%, 60% and 52% in the groups 1, 2, 3 respectively. There was no significant difference in incidence of severe pain among groups 1, 2, and 3 (p=0.60 when group 1 compared with group 2 and 3, p=0.47 when group 2 compared with group 3) although there was significant difference between placebo and other 3 groups (p=0.02).

**Figure 2**

Table 2: Assessment of pain during injection of propofol

		GROUP-1		GROUP-2		GROUP-3		GROUP-4	
		number	%	number	%	number	%	Number	%
PAIN SCORE	0	15	60	10	40	12	48	6	24
	1	6	24	7	28	8	32	5	20
	2	1	4	7	28	4	16	3	12
	3	3	12	1	4	1	4	11	44
TOTAL		25		25		25		25	

There was no significant difference in recall of pain among groups 1, 2, and 3 (p=0.43) Table 3. Although there was significant difference in recall of pain between group 4 (placebo) and other three groups. (p=0.009). None of patients had any side effects like erythema, itching, bradycardia, and arrhythmias.

**Figure 3**

Table 3: Incidence of pain as Recalled in the Recovery Room

		GROUP								Total No. of Patients
		1		2		3		4		
		n	%	n	%	n	%	n	%	
RECALL OF PAIN	0	21	84	19	76	21	84	13	52	75
	1	4	16	6	24	4	16	12	48	25
TOTAL		25		25		25		25		100

n=Number of patients

## DISCUSSION

The use of propofol as intravenous anaesthetic agent has increased rapidly because of the high quality of anaesthesia and rapid recovery. However, pain on injection of propofol, which has been reported to occur in 30-90% of patients, is a major drawback to its use. Various methods of minimizing pain have been proposed. Based on proposed mechanism and factor associated with propofol injection pain, several methods for prevention of pain have been tried with varying degrees of success.

Propofol belong to group of phenol that can irritate the skin, mucous membrane, and venous intima (Ambesh SP et al 1999). Scott et al. speculated that the injection pain is caused by activation of the kallikrein-kinin system either by propofol or the lipid solvent, thereby generating kinins, probably bradykinin. Bradykinin, by producing local vasodilation and hyper permeability, may increase the contact between the aqueous phase propofol and the free nerve ending resulting in pain on injection (Coderre TJ et al 1993). This pain has a 10-20s delayed onset. But immediate pain may be caused by direct irritation of afferent nerve ending with in the veins.

Best way of measuring pain in the clinical setting is by verbal response or its derivatives, the visual analogue scale (VAS) (Ohnhaus EE et al 1975). The VAS appears to be sensitive to smaller changes in effect over time than are categorical measure. A four- point verbal categorical scoring system was chosen in this study rather than VAS as it was very simple to use by the patient and as appropriate hand eye coordination required for a VAS might not be present in all patients during the rapidly changing state of consciousness of anaesthesia induction.

The use of pretreatment to reduce the pain of injection of

propofol has become standard practice. The pain of injection at the induction of anaesthesia can cause agitation and hinder the smooth induction of anaesthesia and thus an effective method of prevention would be beneficial.

Several authors have found that lignocaine in propofol reduced the pain on injection (Gehan G et al 1991). Our study has also showed similar results. The analgesic effect of lignocaine may occur because of a local anaesthetic effect or an inhibitory effect on the enzymatic cascade which leads to release of kinine (Scott RP et al 1988). Different Concentrations of lignocaine were used in different studies like P. Lee et al used 4ml of 1% (40mg) and 2ml of 2% (40mg) lignocaine to find out satisfactory results. Sharon et al used 1ml of 0.5% (5mg) lidocaine, 1% (10mg) lidocaine and 2% (20mg) lidocaine mixed with 19 ml of propofol and they supported the use of 20 mg of lignocaine to minimize discomfort due to propofol injection. In our study concentration of lignocaine was 2 ml of 1% (20mg) and 60% patients had no pain on propofol injection, which was statistically significant when compared to placebo group.

Similarly Pethidine is a synthetic opioid with proven local anaesthetic effect Armstrong PJ et al 1993). Local anesthetic action is most likely due to its structural similarity to cocaine (Way EL et al 1946). It has been shown to produce sensory block both centrally and peripherally (Oldroyd GJ 1994). B. Lyons. et al found that pethidine (25 mg) appears to be a suitable drug to use prior to the injection of propofol. The very low incidence of moderate and severe pain (<10%) makes an attractive pretreatment to aid the smooth induction of anaesthesia with propofol. Similarly in our study the incidence of severe pain was 4%.

Wei Wu Panget et al compared the analgesic effect of fentanyl, morphine, and lidocaine in the peripheral veins and found that lidocaine 60mg or meperidine 40 mg effectively reduces the pain on propofol injection but 74% patients complained of skin erythema distal to tourniquet. Our findings resembles with this study. We used 25mg in 2ml solution, 40% patients had no pain on propofol injection, in contrast to 24% in group 4 group. None of patients complained of skin erythema after getting meperidine. We used low doses of pethidine like 25 mg this could be the reason that we did not met with this problem.

Injection of propofol without any drug (group 4) caused pain in 76% of patient, 44% complaining of severe pain. But in contrast incidence of pain in group 1, 2, and in 3 is, 40%,

60%, and 52% and percentage of patients having severe pain was 12%, 4%, 4% respectively.

Dexamethasone also has been used for postoperative pain and emesis after intrathecal neostigmine (Ping-Heng T et al 2001) and after pediatric tonsillectomy (Mokhtar E et al 2003). Anti nociceptive mechanism of corticosteroids is unknown. Dexamethasone inhibits the synthesis of prostaglandin. But no previous data was found to suggest its role on preventing the pain on propofol injection so we designed the study to compare lignocaine, pethidine, dexamethasone and placebo. In our study we used 4 mg of Dexamethasone in 2 ml of normal saline and it effectively reduced the pain on propofol injection i.e. 48% patient had no pain. There was no significant difference between lignocaine, pethidine, and dexamethasone.

In conclusion data analysis showed that lidocaine 20mg, pethidine 25mg and Dexamethasone 4mg significantly reduce the incidence of propofol injection pain more than placebo ( $p < 0.05$ ). There is no significant difference in pain score among groups 1, 2 and 3 ( $p > 0.05$ )

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