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PREVENTION OF PAIN ON PROPOFOL INJECTION;

A COMPARATIVE, RANDOMIZED, DOUBLE BLIND STUDY BETWEEN LIGNOCAINE, KETAMINE, 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. **Period:..... 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 patients of ASA status 1 and 2 posted for General Surgery 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 (group1), Ketamine 10mg (group2), 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 they experienced. **Results:** Lignocaine, Ketamine and Dexamethasone significantly reduces the pain on propofol injection in comparison to placebo, but there was no significant difference in pain score among groups 1, 2, 3. There was no significant difference in recall of pain among groups 1, 2, and 3. Although there was significant difference between placebo group and other three groups. **Conclusion:** It was concluded that Lignocaine, Ketamine 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

Key words: Propofol, pain, intravenous injection.

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%[1,2] in adults and 28% -85% in children[3,4]. The younger the child, the higher is the incidence and severity of propofol injection pain[5]. 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 20s[6]. 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

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injection and lasts only for the duration of injection. Despite this discomfort, the incidence of venous sequelae, such as phlebitis, is less than 1%[7].

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%[8,9]. Pethidine is synthetic opioid analgesic with proven local anaesthetic effects[10,11]. Dexamethasone is a steroid it also used for postoperative vomiting and pain after pediatric tonsillectomy[12]. 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 Madina Teaching Hospital, University Medical & Dental College, Faisalabad by the department of Anesthesiology. Local ethics clearance and informed consent from 100 patients of ASA physical status 1 and 2, aged 30-70 years undergoing general surgery were taken for the study. Patients with history of allergy to propofol, lignocaine or ketamine 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 10 mg ketamine.
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 anesthesia 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 they 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 with drawl or tears).

There after, the induction of anesthesia was continued with the remainder of the calculated propofol dose and for analgesia Nelbuphnine was given to all patients.

Anesthesia was maintained with isoflurane 0.5-2% and nitrous oxide 60% in oxygen, with controlled 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 and1-recall of pain present.

Ordinal Regression was used for significant difference among groups for pain score.

Statistical package SAS 9.0 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 and weight

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

The table-IV shows the comparisons between four different pain reducing groups. The group 1 has 2 time less pain as compare to group 2 but the difference is non-significant (odd ratio = 2.0061 , p-value = 0.1939)

The group 1 has 1.4 time less pain as compare to group 3 but difference is statistically non-significant (odd ratio = 1.4059, p-value = 0.5250)

The group 1 has 7.3 time less pain as compare to group 4 and the difference is statistically significant (odd ratio = 7.2556, p-value = 0.0006).

Similarly table-IV shows that the difference between group 2 and group 3 is non-significant while the group 2 and 4, group 3 and 4 has significant difference.

There was no significant difference in recall of pain among groups 1, 2, and3. Although there was significant difference in recall of pain between group 4 (placebo) and other three groups. None of patients had any side effects like erythema, itching, bradycardia, and arrhythmias.

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

Table-I. Demographic data

Variables	Group-1 (N=25)	Group-2 (N=25)	Group-3 (N=25)	Group-I4(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

Table-II. 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	

Table-III. Incidence of pain as recalled in the recovery room										
		Group-1		Group-2		Group-3		Group-4		Total No. of Patients
		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										

Table-IV. Pair wise comparison of groups.							
Label	**Estimate**	**Standard Error**	**Alpha**	**Confidence Limits**		**Chi-Square**	**Pr> Chisq**
LogOR12 Exp (LogOR12)	0.6962 2.0061	0.5359 1.0751	0.05 0.05	-0.3542 0.7018	1.7465 5.7347	1.69	0.1939
LogOr13 Exp(LogOR13)	0.3433 1.4095	0.5401 0.7613	0.05 0.05	-0.7153 0.4891	1.4018 4.0624	0.40	0.5250
LogOR14 Exp(LogOR14)	1.9818 7.2556	0.5756 4.1763	0.05 0.05	0.8536 2.3482	3.1099 22.4190	11.85	0.0006
LogOR23 Exp(LogOR23)	-0.3529 0.7026	0.5089 0.3576	0.05 0.05	-1.3504 0.2591	0.6446 1.9052	0.48	0.4880
LogOR24 Exp(LogOR24)	1.2856 3.6168	0.5341 1.9118	0.05 0.05	0.2387 1.2696	2.3324 10.3031	5.79	0.0161

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 intema[13]. Scott et al[14]. speculated that the injection pain is caused by activation of the kallikrein-kinin system either by propofol or the lipid solvent, there by 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[15]. 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)[16]. 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[17]. Our study has also showed similar results. The analgesic effect of lignocaine may occur because of a local anesthetic effect or an inhibitory effect on the enzymatic cascade which leads to release of kinine[14]. Different concentrations of lignocaine were used in different studies like P. Lee et al used 4 ml of 1% (40 mg) and 2 ml of 2% (40 mg) lignocaine to find out satisfactory results. Sharon et al used 1ml of 0.5% (5 mg) lidocaine, 1% (10 mg) lidocaine and 2% (20 mg) 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% (20 mg) and 60% patients had no pain on propofol injection, which was statistically significant when compared to placebo group.

Similarly Ketamine is a non barbiturate intravenous anaesthetic agent. Ketamine has multiple effects throughout CNS including blocking polysynaptic reflexes in the spinal cord and inhibiting excitatory neuromuscular effects in selected areas of brain.Ketamine has been demonstrated to be N–Methyl–D–Aspartate receptor antagonist. 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[18] compared the analgesic effect of fentanyl, morphine, and lidocaine in the peripheral veins and found that lidocaine 60 mg 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 10 mg Ketamine, 40% patients had no pain on propofol injection, in contrast to 24% in group 4 group. We used low doses of Ketamine like 10 mg this could be the reason that we did not met with problem of hallucinations etc.

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 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[19] and after pediatric tonsillectomy[12]. 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, Ketamine, 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, Ketamne, and dexamethasone.

Other methods that can be used are dilution of Propofol by 5 % dextrose,keeping Propofol in refrigefrator at 4-5^{O} C,Remifentanil if available 0.5 microgram\kg bolus 60 sec. before injection of propofol.Prior administration of Thiopental 0.5 mg\kg or Butorphanol 2 mg before administration of Propofol can reduce the incidence and severity of pain[20].

In conclusion data analysis showed that lidocaine 20mg, Ketamine 10 mg and Dexamethasone 4 mg 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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