Original Article

Comparison Of Prevention Of Pain Of Propofol Injection With Iv 2% Lignocaine By Different Method Of Intermittent Venous Occlusion Vs Iv 2% Lignocaine Without Venous Occlusion

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Abstract

Objective: To evaluate the efficacy of 60 mg diluted 2% intravenous (IV) lignocaine (60 mg in 4cc) by intermittent venous occlusion (occlusion time 15 sec/cc, 5 sec gap, 4 occlusion) vs without venous occlusion to prevent pain of propofol injection.

Background: Propofol is one of the most common anesthetic agents used because of its unique pharmacological properties. But, pain of Propofol injection is one of the most common and day to day problem faced by anesthetists. Even though various studies have been used to decreases pain of propofol injection, it has still remained as an unsolved problem. Previous studies with venous occlusion have been done which have not shown much relief. The cause may be due to inadequate time for lignocaine to act on the endothelium. This study highlights different methods of giving 60mg diluted IV 2% lignocaine (preservative free) to prevent the pain of propofol injection.

Method: 40 Patients with age range (18-65) years and classified ASA 1 and ASA 2 undergoing general anaesthesia for elective surgery were included in this study. Patients were randomized into 2 groups; GROUP A (n=20) received 60mg diluted IV 2% lignocaine (preservative free) by intermittent venous occlusion; i.e., 4cc (3cc of IV 2% lignocaine + 1 cc of normal saline) (occlusion time 15 seconds/cc; 5 seconds gap; 4 occlusions) and GROUP B (n=20) received 60 mg diluted IV 2% lignocaine (preservative free) without venous occlusion slowly over 30 seconds. The primary objective was to compare the prevention of pain of propofol injection by verbal rating score. The secondary objective was to study the change in pressor response on laryngoscopy.

Results: Patients receiving 60 mg diluted IV2% lignocaine (preservative free) by intermittent venous occlusion experienced significantly less pain after injecting propofol compared to patients receiving 60 mg diluted IV 2% lignocaine (preservative free) without venous occlusion. There was a significant difference in pressor response seen to laryngoscopy also. Group A patients had less pressor response seen in comparison to Group B.

Conclusion: Reduction of pain due to propofol injection with our method of intermittent venous occlusion i.e., occlusion time 15 seconds/cc; 5 seconds gap; 4 occlusions, shows better results as sufficient time is given for IV lignocaine to act on the endothelium. Pain of propofol injection can be reduced by just putting in some extra time and attention while giving a lignocaine before the drug.

Keywords: Pain of propofol injection, Verbal Rating Score, Analgesia, Pain with propofol, lignocaine, venous occlusion, intermittent venous occlusion

INTRODUCTION

Propofol is an IV induction agent that is used by anesthetists worldwide on a day to day basis. A major issue with propofol is pain during its IV administration. Over the years, various research modalities have been attempted to minimize pain but still it remains as an unsolved problem.

Current formulation of 1% (weight/volume) propofol is available in 10% soybean oil, 2.25% glycerol, and 1.2% purified egg phosphatide; also disodium edetate (0.005%) is added as a bacterial growth retardant. This formulation appears milky. Its pH is 7 and pKa in water is 11; it looks viscous apart from being milky. This formulation causes pain on injection in 28%–90% of patients. This pain of propofol injection is immediate as well as delayed by 10-20 seconds[1, 2].

Irritation of vascular endothelium causes an immediate pain where as delayed pain is due to the release of mediators such a kininogen from kinin cascade. The possible mechanism is stimulation of non-selective ligand gated cation channels like TRPA1 and TRPV2; they are known as sensors for pain, irritants, cold and stretch and release neuropeptides which in turn cause neurogenic inflammation and cause late pain[3].

Clinical strategies designed to alleviate this pain have been described in the literature including dilution of the propofol solution, injection of propofol in a large antecubital vein, application of topical nitroglycerin on the skin overlying the tip of the intravenous catheter. There are different drugs which have been studied for reducing pain of propofol injection like lignocaine, ondansetron, fentanyl, diclofenac, ketamine, tramadol, dexamethasone, etc. Various studies done for the same have been mentioned as follows:

Jalota et al. in 2011 hypothesized that use of antecubital vein reduces pain of propofol injection as due to larger diameter and a faster flow rate, the amount of time of contact between propofol and endothelium of the vein is reduced[4].

Derakshan et al. concluded that use of nitroglycerine also helps alleviate the pain of propofol injection as nitroglycerine releases NO which causes vasodilation and hence resulting in higher venous flow of the drug [5].

Kizilcik et al. concluded that an admixture of fentanyl with propofol is better in reducing pain of propofol injection compared to pretreatment with fentanyl or normal saline, the reason being reduction in pH of propofol[6].

Ambesh et al. used ondansetron in reducing pain of propofol injection as a result of its multifaceted actions as a Na^+ channel blocker, a 5-HT_3 receptor antagonist, and & μ opioid agonist, ondansetron may potentially be used to alleviate pain produced by a drug similar to propofol[7].

Koo et al.concluded that small doses of ketamine immediately before giving propofol reduces the pain of propofol by peripheral local anaesthetic action[8].

Ahmad et al. hypothesized that treatment with dexamethasone also helps in reduction of pain of propofol injection, possibly due to decreases in nitric oxide production[9].

Mohta et al. concluded that the reduction in pain of propofol injection can be achieved by diclofenac as well as ketorolac by inhibition of prostaglandin synthesis[10].

Kaya et al. concluded that treatment of lignocaine with venous occlusion was superior to without use of venous occlusion in reduction of pain of propofol injection due to its local anaesthetic action on endothelium[11].

Even though various studies and methods have been researched over the years, pain of propofol injection still remains as an unsolved problem. Previous studies with venous occlusion have been done which have not shown much relief. The cause may be due to inadequate time for lignocaine to act on the endothelium. So we thought of developing a technique of giving lignocaine where we can allow sufficient time for it to act on the endothelium.

In this study we have used different technique of dilution and venous occlusion to reduce pain due to IV propofol injection.

METHODOLOGY

After obtaining Ethics Committee approval (I.E.S.C,/59/2022) and CTRI no (CTRI/2022/07/044346), this prospective, randomized controlled trial was conducted in a tertiary care hospital over a period of six months. The study was done in accordance with the principles of the Declaration of Helsinki.

Patients with ASA grade I or II status, ages 18 to 65 years, hemodynamically stable, with availability of informed consent, undergoing general anaesthesia were selected. Exclusion criteria were patients below the age of 18 years or above the age of 65 years, ASA III or more, major neurological, cardiac, respiratory, metabolic, renal, hepatic diseases, known allergies to the study drugs or refusing to give consent.

These 40 patients were enrolled and randomized into two groups of 20 each using a computer-generated balanced allocation table. After attaching all standard monitors and securing a 20G IV cannula, pre-oxygenation was started and patients from both groups were given pre-medications (IV glycopyrollate 0.004mg/kg and IV Midazolam 0.2mg/kg, IV fentanyl 1.5mcg/kg). To avoid any confounding effect of IV diclofenac or IV dexamethasone, we did not use these drugs.

Patients in Group A were given 60 mg of IV 2% lignocaine (preservative free) and diluted till a volume of 4cc (3cc of IV 2% lignocaine + 1 cc of normal saline) via intermittent venous occlusion where each 1 cc of this volume was given slowly after occluding the vein at mid-arm level with a rubber catheter or by hand if circumference of forearm is sufficient for the same, for 15 seconds and releasing the occlusion for 5 seconds, i.e. 20 seconds for each cc and total time of 80 seconds used for total 4cc of volume.

Patients in Group B were given 60mg of IV 2% lignocaine (preservative free) and diluted till a volume of 4cc (3cc of IV 2% lignocaine + 1 cc of normal saline) without venous occlusion slowly over 30 seconds.

Both the groups will be given the induction dose of propofol (1-2 mg/kg) and pain of propofol injection will be assessed by Verbal Rating Score after initial 3-5 cc of propofol.

Verbal Rating Score

Pain Score	**Severity of Pain**
None	No pain
Mild	Pain reported in response to questioning only, Without any behavior signs.
Moderate	Pain reported in response to questioning and accompanied by a behavioral signs, or pain reported spontaneously without questioning.
Severe	Strong verbal response accompanied by facial grimacing, withdrawal of the hand, or tears.

Pressor response during laryngoscopy and hemodynamics till 20 minutes after intubation were also noted.

Considering the incidence of pain of propofol injection with lignocaine to be 21.17% from R. Ganta & J. P. H Fee study[12] and incidence of pain of propofol njection with lignocaine with venous occlusion to be 77.27% from Sedat Kaya study[13] at 5 % significance level and 89% power, the sample size required was calculated to be 24, 12 in each group with ratio being 1:1. The software used is WinPepi. But for better results, larger sample size of 40 was taken, with 20 in each group.

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The following statistical tests were applied for the **Statistical analysis**

1. The comparison of the variables which were quantitative and not normally distributed in nature were analysed using Mann-Whitney Test and variables which were quantitative and normally distributed in nature were analysed using independent t test.

2. The comparison of the variables which were qualitative in nature were analysed using Chi-Square test. If any cell had an expected value of less than 5 then Fisher's exact test was used.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, ver 25.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

Participant Enrolment

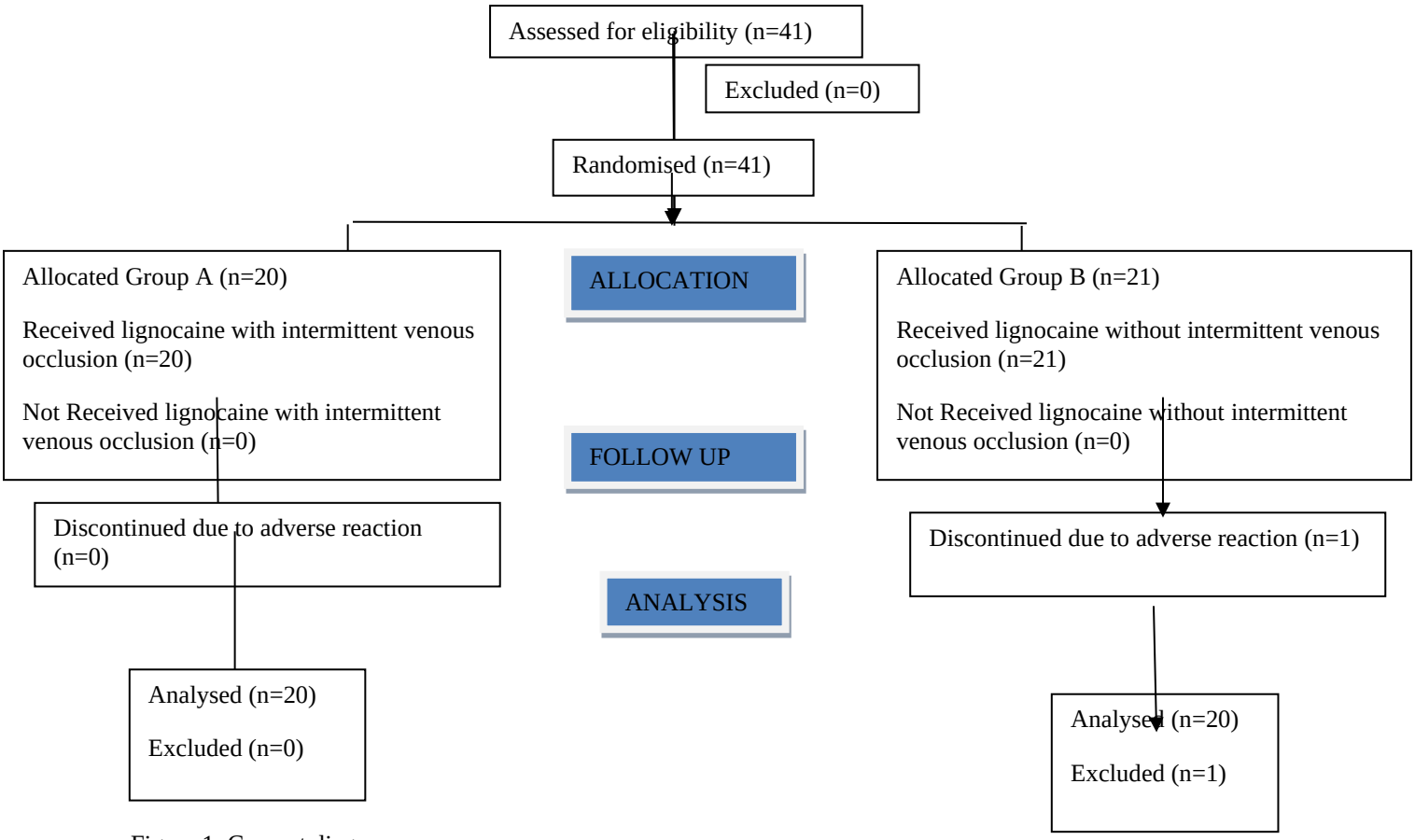

Figure 1: Consort diagram

RESULTS

Table 1: Comparison of demographic characteristics between Group A and Group B

	Group A(n=20)	Group B(n=20)	Total	P value
Age(years)				
18-30	5 (25%)	8 (40%)	13 (32.50%)	0.286*
31-40	4 (20%)	6 (30%)	10 (25%)	
41-50	5 (25%)	1 (5%)	6 (15%)	
51-60	6 (30%)	5 (25%)	11 (27.50%)	
Mean ± SD	42.6 ± 11.13	37.45 ± 15.2	40.02 ± 13.41	0.229‡
Median(25th-75th percentile)	43.5(36.5-51)	35(24.75-51.25)	40(27.75-51)	
Range	25-60	18-60	18-60	
Gender				
Female	9 (45%)	10 (50%)	19 (47.50%)	0.752†
Male	11 (55%)	10 (50%)	21 (52.50%)	

Total	20 (100%)	20 (100%)	40 (100%)	
Weight(kg)				
Mean ± SD	61.75 ± 10.67	61.9 ± 9.92	61.82 ± 10.17	0.964‡
Median(25th-75th percentile)	60(55-66.5)	65(56-68.5)	61(55-68.5)	
Range	45-86	35-76	35-86	

* Fisher's exact test; ‡ Independent t test, † Chi square test

Patients in both the groups did not show statistically significant differences in their age (P = 0.229), gender (P = 0.752), weight distribution (P = 0.964). It is shown in Table 1.

Table 2: -Comparison of verbal rating score between group A and B.

Verbal rating score	Group A(n=20)	Group B(n=20)	Total	P value
No pain	7 (35%)	0 (0%)	7 (17.50%)	<.001*
Mild pain	12 (60%)	2 (10%)	14 (35%)	
Moderate pain	1 (5%)	11 (55%)	12 (30%)	
Severe pain	0 (0%)	7 (35%)	7 (17.50%)	
Mean ± SD	0.7 ± 0.57	2.25 ± 0.64	1.48 ± 0.99	<.001§
Median(25th-75th percentile)	1(0-1)	2(2-3)	1(1-2)	
Range	0-2	1-3	0-3	

§ Mann Whitney test, * Fisher's exact test

Proportion of patients with verbal rating score of no pain and mild pain was significantly higher in group A as compared to group B and a verbal rating score of moderate pain & severe pain was significantly higher in group B as compared to group A (p value <0.0001). It is shown in table 2, figure 2.

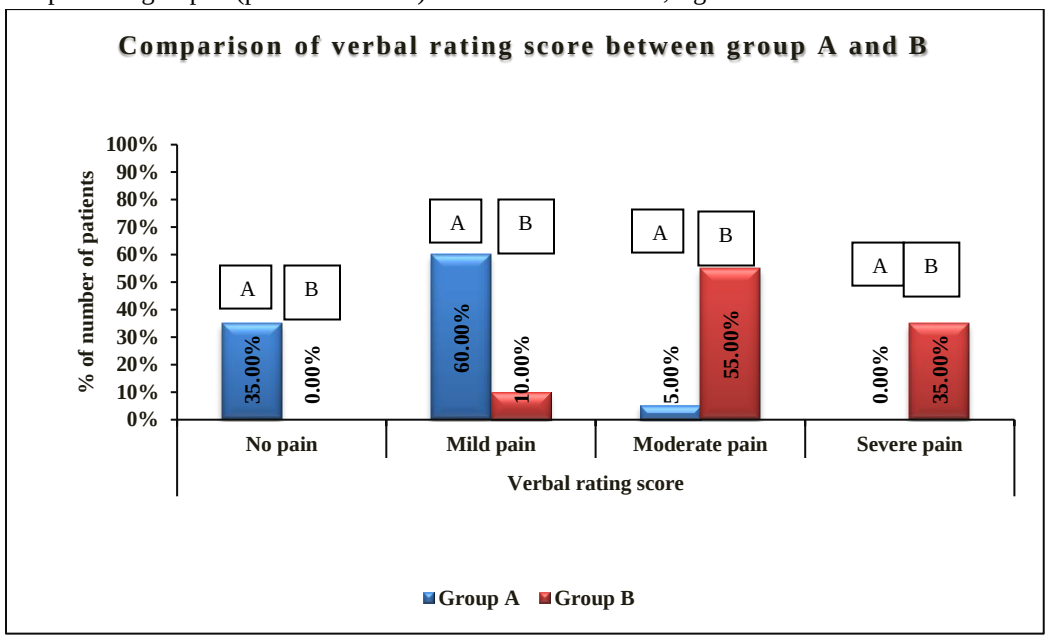

Figure 2: -Comparison of verbal rating score between group A and B.

Table 3- Comparison of heart rate between Group A and Group B

Heart rate (per minute)	Group A(n=20)	Group B(n=20)	Total	P value
Before intubation	87 ± 10.29	93.25 ± 11.04	90.12 ± 11	0.072‡
Immediately after intubation	85.5 ± 9.67	104.75 ± 10.62	95.12 ± 13.98	<.0001‡
5 minutes after intubation	84.4 ± 10.49	99.3 ± 8.92	91.85 ± 12.22	<.0001‡
10 minutes after intubation	83.6 ± 11.68	97.15 ± 9.19	90.38 ± 12.44	0.0002‡
15 minutes after intubation	81.95 ± 12.09	94.3 ± 9.54	88.12 ± 12.44	0.0009‡
20 minutes after intubation	81.55 ± 12.45	93.1 ± 9.4	87.32 ± 12.36	0.002‡

‡ **Independent t test**

Significant difference was seen in heart rate (per minute) immediately after intubation, 5 minutes, 10 minutes, 15 minutes, 20 minutes after intubation between group A and B. (p value <.05) It is shown in table 3, figure 3

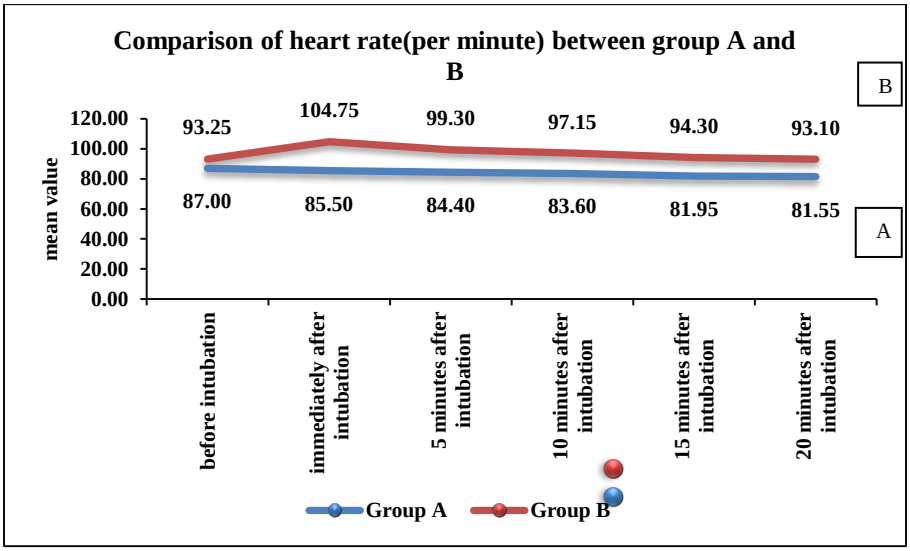

Figure 3: -Comparison of trend of heart rate(per minute) at different time intervals between group A and B.

Table 4:- Comparison of systolic blood pressure, diastolic blood pressure and mean arterial pressure (mm of hg) between Group A and Group B

	GROUP A			GROUP B			P value of MAP
	SBP	**DBP**	**MAP**	**SBP**	**DBP**	**MAP**	
BEFORE INTUBATION	119.1 ± 13.97	78.1±6.35	91.5±7.29	128.45±14.28	85.7±8.11	99.3±9.77	0.007‡
IMMEDIATELY AFTER INTUBATION	119.85 ± 16.06	77.15±7.56	91.15±8.22	136.45±9.8	92.6±6.52	107.4±7	<.0001‡
5 MINS AFTER INTUBATION	118.7±13.55	75.3±7.99	88.25±6.87	132.4±8.84	88.1±7.33	102.9±6.92	<.0001‡

10 MINS AFTER INTUBATION	116.95±12.04	74.45±7.94	89.2±7.35	128.7±11.89	82.5±7.56	97.7±7.95	0.001‡
15 MINS AFTER INTUBATION	113.85±11.08	76.1±6.37	88.5±5.88	125.9±11.08	82.1±6.82	96.7±6.99	0.0003‡
20 MINS AFTER INTUBATION	112±12.15	77±9.18	88.7±9.31	125±11.96	81.5±7.86	95.7±8.05	0.015‡

‡ **Independent t test**

Significant difference was seen in mean arterial pressure(mmHg) before intubation, immediately after intubation, 5 minutes, 10 minutes, 15 minutes, 20 minutes after intubation between group A and B. (p value <.05).

It is shown in table 4, figure 4.

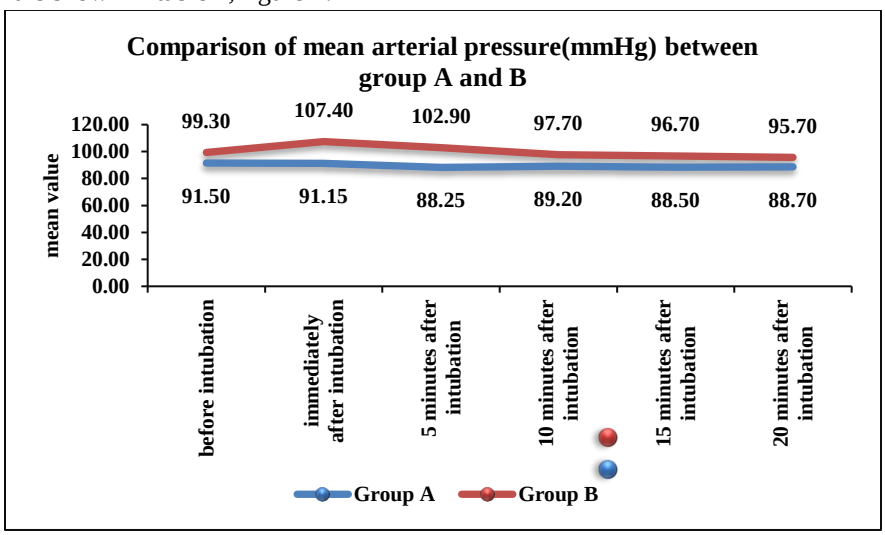

Figure 4:-Comparison of trend of mean arterial pressure(mmHg) at different time intervals between group A and B.

DISCUSSION

The pain perceived due to propofol is associated with dissociation of propofol across the blood vessels and activating the plasma kallikrein-kinin system that releases bradykinin. Although lignocaine is a local anaesthetic, it has been postulated that low dose systemic lignocaine, includes action on C- afferent neuronal activity, actions in spinal dorsal horn, reductions of the post synaptic depolarization mediated by N-methyl-D-aspartate receptors, and blocking peripheral and central voltage gated sodium channels in the dorsal root ganglion[14].

Regardless of having studies which have shown reduction of pain in propofol injection by intravenous lignocaine, there are still patients who do suffer from mild to moderate pain while injection, causing anxiety and poor induction experience. Hence, this study was done to study different techniques of injecting lignocaine to evaluate if there could be a way to alleviate this experience.

In this study, efficacy of injecting lignocaine by two different methods were studied, Group A (n= 20) were given 60 mg diluted IV 2% lignocaine (preservative free- 60 mg in 4 cc) by intermittent venous occlusion (occlusion time 15 seconds/cc; 5 seconds gap; 4 occlusions) and group B (n=20) were given 60 mg diluted IV 2% lignocaine (preservative free- 60 mg in 4cc) without venous occlusion slowly over 30 seconds. 4-point verbal rating score was used to assess the pain in both groups. Pain was significantly lower in Group A (with intermittent venous occlusion) with a p value <0.001.

Sedat et al. did a study on 100 women which were divided into 5 groups and compared effectiveness of various venous occlusion times with lignocaine analgesia to prevent pain of propofol injection[13]. They concluded that in Group 2,3 and 4, in which venous occlusion was applied, 30%, 35% and 10% of patients respectively reported pain.

Kim et al. did a study on 68 patients with different doses of lignocaine (40mg, 60 mg and 80mg) and gave IV propofol after 1 minute of venous occlusion and found 60 mg to be the most effective minimum dose of lignocaine for pre-treatment before injecting propofol. Only 8.7% of patients had moderate to severe pain in Group L60 (where 60mg of IV lignocaine was used), compared to 63.6% and 21.7% in Group L40 and Group L80 respectively[15].

Islam M massad et al. conducted a study to compare different duration of venous occlusion to reduce pain of propofol injection on 150 patients, while they concluded that venous occlusion is an effective method, they found no significant difference between duration of occlusion at 15, 30 or 60 seconds[16]. In their study, 14 patients (28%) had pain in Group I (15 seconds), 16 patients (32%) had pain in Group II (30 seconds) and 9 patients (18%) had pain in Group III (60 seconds).

While comparing our study, better results were seen, i.e., in Group A (with intermittent venous occlusion) 95% patients (35%- no pain and 60%- mild pain) didn't have any pain whereas Group B (without venous occlusion) 52.5% patients (17.5% with no pain and 35% with mild pain) didn't have any pain.

Although difference was seen statistically significant in pressor response (HR and MAP) in group A and Group B, such a small variation is not clinically significant. The small difference which occurred could be due to adequate time which was given to lignocaine to act in Group A.

CONCLUSION

Reduction of pain due to propofol injection with our method of intermittent venous occlusion i.e. occlusion time 15 seconds/cc; 5 seconds gap; 4 occlusions, shows better results.

LIMITATIONS

1. To avoid confounding effect of fentanyl, more research is required without the use of fentanyl.
2. Different dilutions of lignocaine can be studied to find out exact effective dilution.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil

Conflicts of interest

The authors have no conflicts of interest regarding this investigation**.**

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