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Comparison of efficacy of three different venous occlusion duration on pre-treatment with injection ketamine to prevent propofol injection pain in patients undergoing surgery under general anaesthesia

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Abstract---Propofol is rapidly acting intravenous agent used for induction in general anaesthesia. It causes pain while administering, being uncomfortable to patients. So an observational study was done to compare the effects of different time duration of venous occlusion on pretreatment with injection Ketamine for prevention of pain at injection site. After approval of ethical committee and written informed consent, ASA grade I and II, 60 patients of either gender, aged between 18-60 years were assigned to three groups of 20 each under GA and divided as GROUP K20, K40, and K60 according to venous occlusion duration of 20,40,and 60 seconds respectively on administration of ketamine(0.2mg/kg)as pretreatment for propofol injection pain. Following injection of ketamine, 25% dose of propofol

was given and patient was asked for any sensation of pain at the site of injection and graded accordingly. Haemodynamics were compared in all the three groups. All 60 patients were reviewed for propofol pain and haemodynamics were recorded before pretreatment with ketamine and after pretreatment for 5 minutes and results evaluated through chi square test. P value was significant for 20 seconds (p value <0.001) but not for 40 and 60 seconds (p value 0.201) resulting in no difference in pain score between the two groups as compared to K20 group. Haemodynamics were comparable in all the three groups (p value >0.05). We concluded that venous occlusion of 40 seconds and 60 seconds on pretreatment with ketamine are equally effective to reduce propofol injection pain as compared to 20 seconds, hence 40 seconds venous occlusion can be done instead of 60 seconds providing comfort against tourniquet pain.

Keywords---propofol pain, venous occlusion, ketamine.

Introduction

The purpose of general anaesthesia is to make surgical patients insensitive to pain by providing unconsciousness and inducing sleep. The reflex activity towards surgical stimuli is prevented by muscle relaxants. Modern anaesthesia technique is known as balanced anaesthesia which comprises of hypnosis, analgesia and muscle relaxation.¹ The most popular drug used now a days for induction of anaesthesia is propofol. Propofol is γ -Aminobutyric acid agonist, a substituted isopropylphenol having analgesic, antiemetic and anaesthetic properties. It has rapid onset and short duration of action. It is thus the most preferred choice for induction and maintenance of anaesthesia, day care surgeries, surgeries and procedures requiring sedation for short interval and in ICUs.⁷ As propofol has its pros of rapid induction and short duration so does has its cons and one of most common of them is pain at injection site, its incidence varying between 20%-85% which is much higher considering other intravenous (IV) induction agents.⁸ The pain is influenced by injection site⁹, vein size, speed of introduction of drug¹⁰, formulation of drug.⁷

Pain can be immediate or delayed. The pain felt immediately is mainly due to irritation of endothelium of the vein and the pain which is felt after an interval of 10-20 seconds may be due to release of mediators like kininogen from kinin cascade.¹¹ Other hypothesis is the pain on propofol administration may have a direct or indirect interaction with sensory nerve fibres in venous adventitia. The mediators involved in releasing of neuropeptides, mainly TRPA1 and TRPV1 causes pain due to neurogenic inflammation.¹¹ Many methods are being applied over decades to reduce the injection site pain after propofol administration and can be divided into three types: non drug category, drug category, and combination of two.¹²

In drug category many drugs such as local anaesthetic (lignocaine) separately or as admixture¹³, benzodiazepines (midazolam), antiemetics (metoclopramide), barbiturates or NMDA receptor antagonist (ketamine), NSAIDs, and opioids are

used to reduce the pain. In non-drug category various techniques such as venous occlusion¹⁷, rapid injection of drug¹⁰, large bore cannulation¹⁸, large vein⁹, site of cannulation⁹, low temperature¹⁹ (decreasing neurogenic inflammation), changing Ph and bacteriostatic in formulation.¹³ Both these methods result in partial alleviation of propofol induced pain at injection site so a combined technique is used for developing a most effective method for prevention of pain. The most commonly researched method is use of venous occlusion combined with drugs such as lignocaine, ketamine or other NSAIDS or opioids.⁸

In this study we used the combined non drug and drug category that is venous occlusion with pre-treatment of ketamine to alleviate injection site pain on propofol administration.¹² Ketamine is a phencyclidine derivative that is a non Y-Aminobutyric acid derivative producing dissociative anaesthesia due to its action of NMDA receptors causing dissociation between thalamocortical and limbic system, characterised by a cataleptic state resulting in eyes remaining open with slow nystagmus¹⁴. It causes intense analgesia and amnesia, even in sub-anaesthetic dose.¹⁵ Hence low doses of ketamine has peripheral local anaesthetic effects causing analgesia in part where venous occlusion is done.¹⁶ Various duration of venous occlusion was studied over time with most effective being the duration of 60 seconds which gives adequate time for drug to act locally. Since pressure from tourniquet application is itself a notorious thing for the patient and ketamine being a rapid acting drug, we try to justify the reduction in occlusion time from 60 sec without lowering the efficacy of ketamine for local site analgesia. Hence, we plan to do a comparative study of effects of different time duration for venous occlusion by tourniquet application for 20, 40, 60 seconds respectively on pre-treatment with Inj Ketamine for prevention of propofol pain at injection site in patients undergoing surgeries under GA.

Material and Methods

After taking approval form ethical committee and written informed consent signed from patients and their relatives, 60 patients (20 in each group) under ASA (American society of anaesthesiologist) grading I and II of either gender were selected and admitted in Dhiraj hospital S.B.K.S.M.I.R.C. Pipariya, Vadodara, Gujarat, scheduled for surgeries under general anaesthesia were subjected to this study. The whole procedure was explained to the patients and was done by consultant anaesthesiologist and observations were noted by me. The data were collected and analyzed statistically.

According to previous study in literature, the incidence of pain on intravenous injection of propofol was 80% and reduction of this pain to 50% was considered clinically significant. The minimum size for each group, assuming a value of 0.05 and a power value of 90% was thus calculated. It was twenty in each group. Patient willingly signing written informed consent, aged between 18 to 60 years and posted for elective surgeries under general anaesthesia were included in the study. Patients with poor respiratory or cardiovascular reserve, having ASA grading of III or more, with any previous history of allergy, known to be sensitive or having any other form of reaction to study drug, with anticipated difficult airway, prescribed sedatives or analgesics in the past 24 hours before surgery and having conditions in which tourniquet application is contraindicated, are

excluded from the study.

Patients fulfilling the above said inclusion exclusion criteria were subjected to this study. Detailed pre-anaesthetic check-up of all the patients posted for planned surgery were done a day prior to surgery and all the patients were kept nil by mouth for 6 hours preoperatively. A 20-gauge venous cannula was inserted, Inj. Ringer lactate was started and patient shifted to the operation theatre (OT). Multipara monitors were attached and baseline parameters were recorded. All patients were premedicated with Inj glycopyrrolate 0.004 mg/kg and inj ondansetron 0.08mg/kg intravenously (i.v.). Pre oxygenation with 100% oxygen was done. Venous occlusion was applied with sphygmomanometer cuff as a tourniquet at a pressure of about 70 mm of Hg and the allocated dose of ketamine i.e. 0.2 mg/kg (I.V.) was injected by the consultant anesthesiologist .Patients were divided into three groups as follows:-

- GROUP K 20 Patients given ketamine with 20 sec occlusion were grouped in K20
- GROUP K 40 Patients given ketamine with 40 sec occlusion were grouped in K40
- GROUP K 60 Patients given ketamine with 60 sec occlusion were grouped in K60

The tourniquet was released after 20 seconds in K20 group, after 40 seconds in the K40 group, and after 60 seconds in the K60 group. 25% of total calculated dose of Inj Propofol will be given over 10 seconds after which crystalloids were administered at maximal gravity flow. Before the administration of total calculated dose of injection propofol, each patient will be asked by an anesthesiologist to immediately rate any sensation of pain and graded as per verbal pain score as follows:

- 0 – No pain.
- 1 – Mild pain (discomfort in the hand or arm which is acceptable to the patient)
- 2 – Moderate pain (discomfort in hand or arm which is unacceptable)
- 3 – Severe pain (grimace or limb withdrawal).

Heart rate and blood pressure were noted before pre-treatment and after pre-treatment with ketamine and at 0, 1, 2 and 3 minutes after propofol bolus. Change in heart rate of +/- 20 beats and 20% rise or fall in blood pressure from the baseline were considered clinically significant in the study.

Results

Data were collected, tabulated. Numerical variables were presented as mean & standard deviation (SD) while categorical variables were presented as frequency and percentage. As regard numerical variables; unpaired student –t test were used whenever appropriate, for between-groups comparisons, while for categorical variables; chi-square test was used. A difference with significant level <0.05 will considered statistically significant. Results of comparison of the three groups using one way anova and posthoc tukey test with pain assessed using chi square

test. Spss 20.0 used. No significant changes in accordance with weight, age, gender and ASA grading in all the three groups indicating no influence of weight, age , gender and ASA grading on incidence of propofol pain.

Table 1
Comparison for age (yrs)

	Group K 20 (n=20)	Group K 40 (n=20)	Group K 60 (n=20)	ONE WAY ANOVA		POSTHOC TUKEY TEST		
				F value (*=welch test)	P VALUE	Group K 20 vs Group K 40 p value (difference)	Group K 20 vs Group K 60 p value (difference)	Group K 40 vs Group K 60 p value (difference)
AGE	29.25±11.63	32.3±10.75	36.85±13.18	2.067	0.136	0.698(- 3.05)	0.117(-7.6)	0.453(- 4.55)

Graph 1: Comparison of age (yrs) between three groups

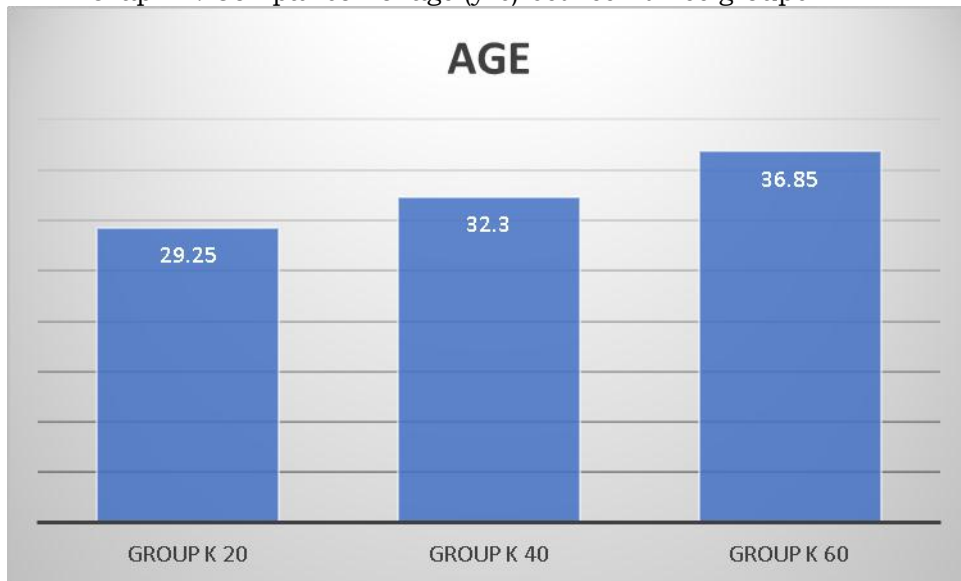
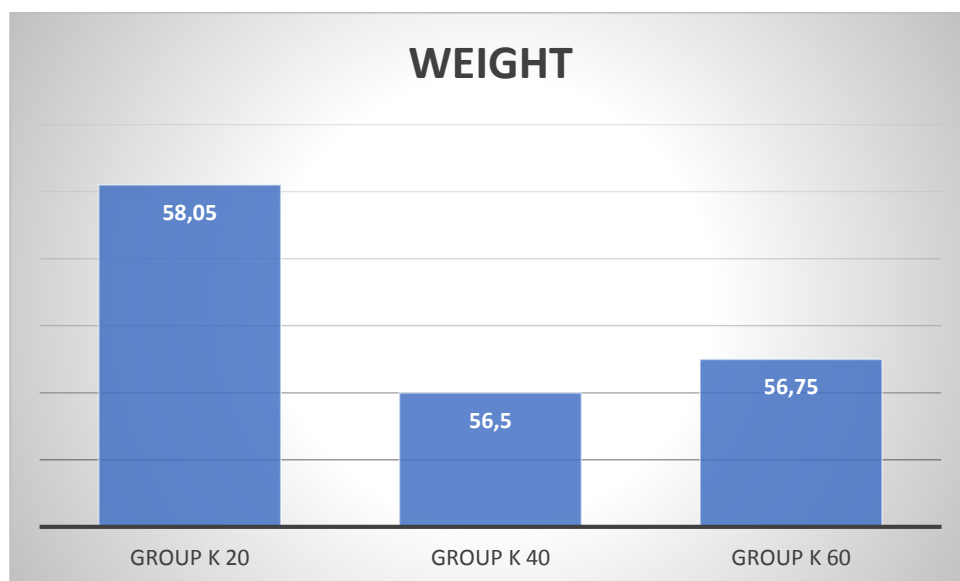


Table 2
Comparison for gender

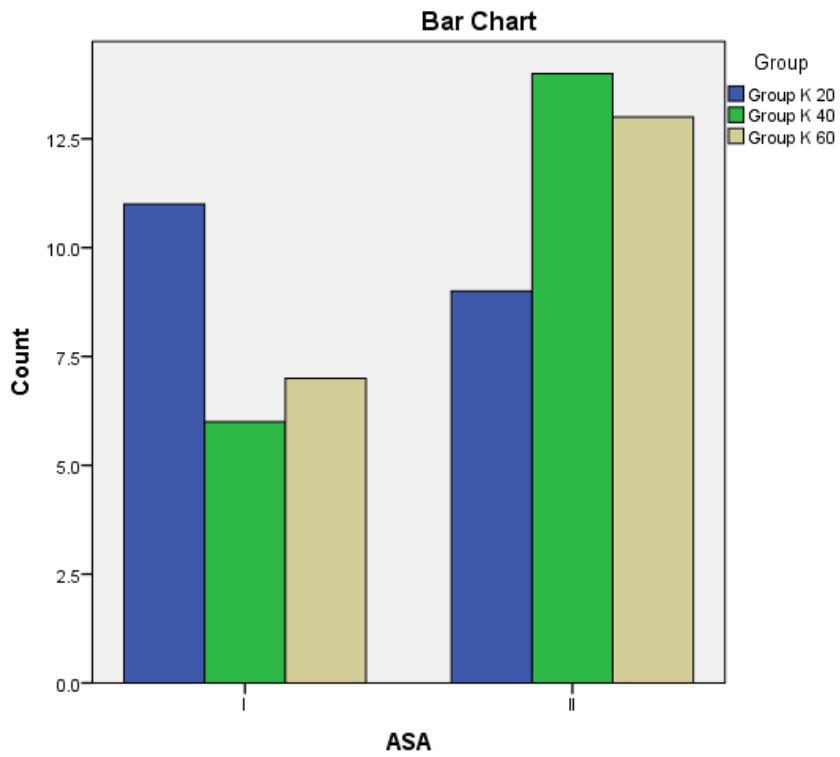
Crosstab			Group			Total
			Group K 20	Group K 40	Group K 60	
GENDER	FEMALE	Count	13 (65%)	11 (55%)	11 (55%)	35 (58.3%)
	MALE	Count	7 (35%)	9 (45%)	9 (45%)	25 (41.7%)

Total	Count	20 (100%)	20 (100%)	20 (100%)	60 (100%)
Chi-Square Tests					
	Value	df	P value (<0.05 is significant)		
Pearson Chi-Square	.549	2	0.760		

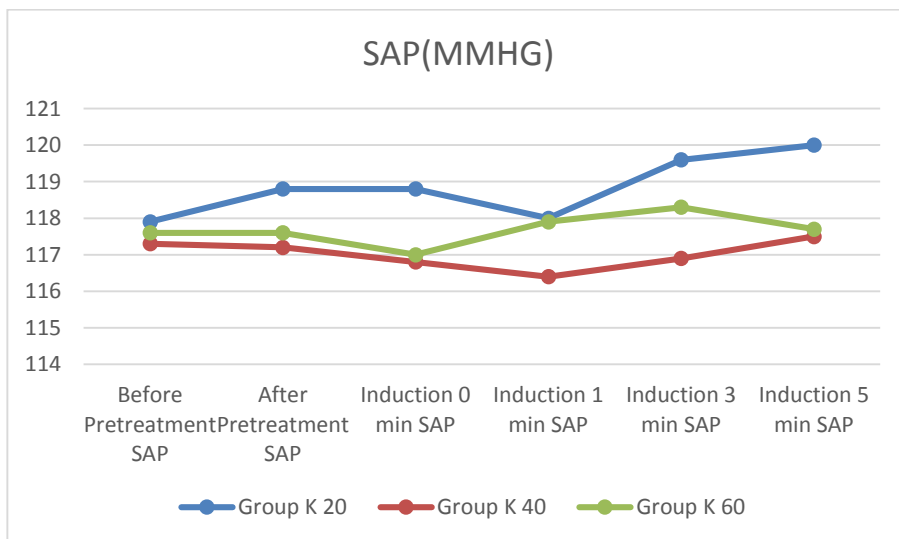
	Group K 20 (n=20)	Group K 40 (n=20)	Group K 60 (n=20)	ONE WAY ANOVA		POSTHOC TUKEY TEST		
				F value (*=welch test)	P VALUE	Group K 20 vs Group K 40 p value (difference)	Group K 20 vs Group K 60 p value (difference)	Group K 40 vs Group K 60 p value (difference)
WEIGHT	58.05±9.91	56.5±8.9	56.75±8.63	0.165	0.848	1.55 (0.854)	1.3 (0.895)	-0.25 (0.996)

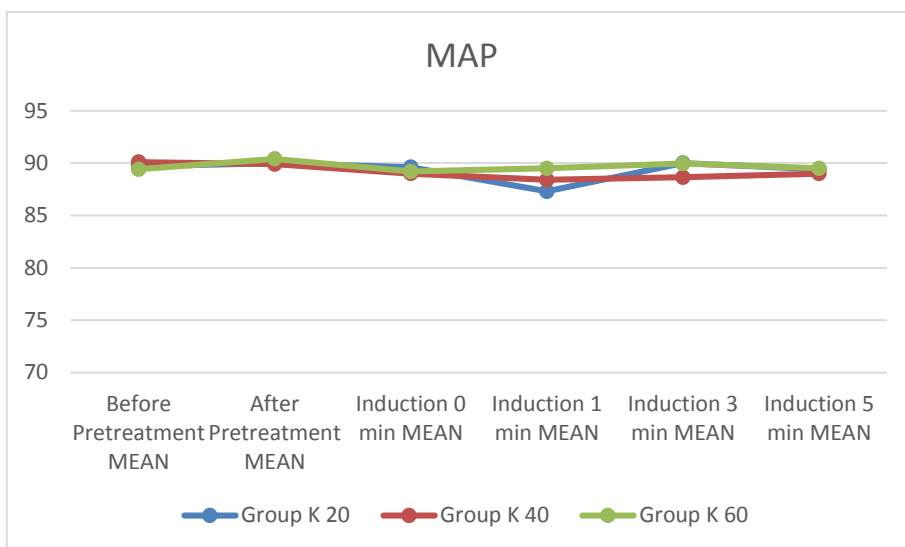
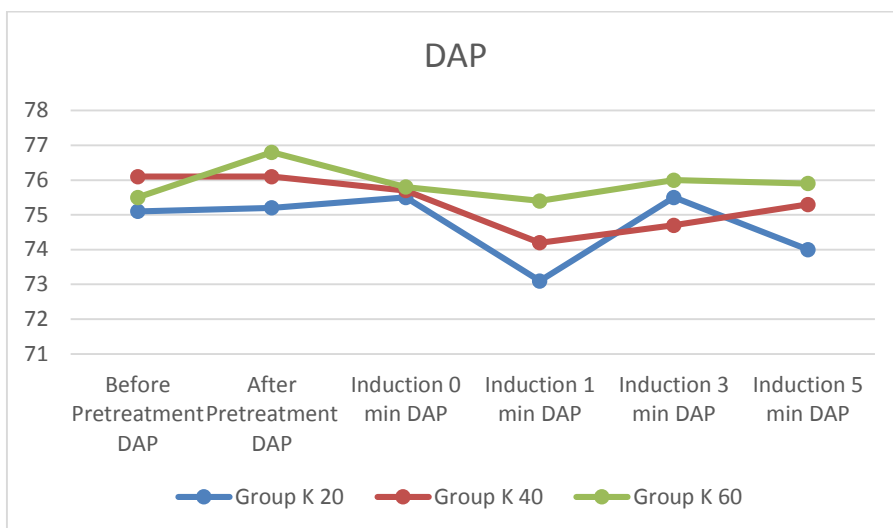


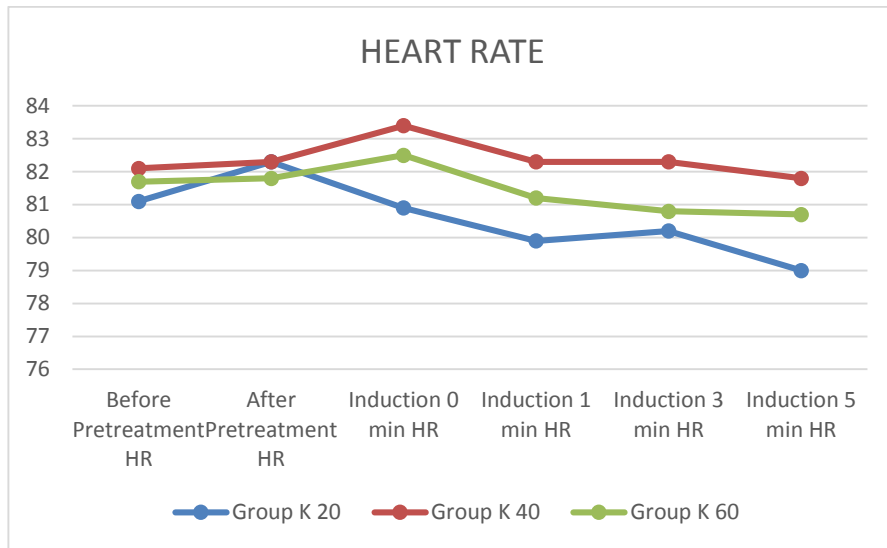
Crosstab						
			Group			Total
			Group K 20	Group K 40	Group K 60	
ASA	I	Count and %	11 (55%)	6 (30%)	7 (35%)	24 (40%)
	II	Count and %	9 (45%)	14 (70%)	13 (65%)	36 (60%)
Total		Count and %	20 (100%)	20 (100%)	20 (100%)	60(100%)
Chi-Square Tests						
			Value	df	P value (<0.05 is significant)	
Pearson Chi-Square			2.917	2	0.233	



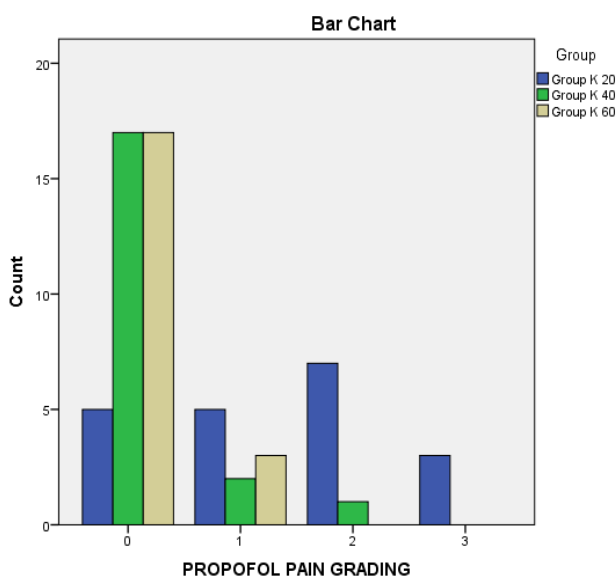
No significant change in hemodynamics in the three groups indicating all three are equally performing (p value > 0.05)







Comparison of these three groups showed that patients in group K20 with ketamine pre-treatment in conjunction with venous occlusion for 20 seconds showed total 75% of patients complaining of pain out of which 25 % patients had mild, 35 % patients had moderate and 15 % patients had severe pain. It was also observed that patients in group K40 with ketamine pre-treatment in conjunction with venous occlusion for 40 seconds showed total 15% of patients complaining of pain out of which 10 % patients had mild, 5 % patients had moderate and no patients had severe pain. It was also observed that patients in group K60 with ketamine pre-treatment in conjunction with venous occlusion for 60 seconds showed total 15% of patients complaining of pain out of which 15 % patients had mild, no patients had moderate and severe pain. The P value was significant for K20 group (P value <0.001) but not significant for K40 and K60 group (p value 0.201). hence it was interpreted that group K40 and group K60 were equal performing in relation with propofol pain at injection site.



Crosstab					
PROPOFOL PAIN GRADING	NUMBER OF PATIENTS	Group			Total
		Group K 20	Group K 40	Group K 60	
0	Count	5 (25.0%)	17 (85.0%)	17 (85.0%)	46 (76.7%)
1	Count	5 (25%)	2 (10%)	3 (15%)	8 (13.3%)
2	Count	7 (35%)	1 (5%)	0 (0%)	5 (8.3%)
3	Count	3 (15%)	0 (0%)	0 (0%)	1 (1.7%)
Total	Count	20 (100%)	20 (100%)	20 (100%)	60 (100%)
Chi-Square Tests					
	Value	Df	P value (<0.05 is significant)		
Pearson Chi-Square K20 VS K40 and K20 VS K60	25.535	6	(S) <0.001		
	Value	Df	P value (<0.05 is significant)		
Pearson Chi-Square K40 VS K60	8.537	6	0.201		

Discussion

Propofol known as the milk of anaesthesia is a rapidly acting intravenous induction agent used for induction in general anaesthesia, as a sedative in short procedures, in ICU for sedation and as an antipruritic, antiemetic and anticonvulsant. Being chemically a phenol, propofol depicts the property of being irritant when coming in contact with mucous membrane and skin, causing pain while administering intravenously, which ranges from mild to excruciating pain, being uncomfortable and inconvenient for the patients.

Patients who undergo general anaesthesia or any other procedure requiring sedation for decreasing their pain perioperatively, paradoxically remembers as the pain caused by propofol as the most painful part of the perioperative period. ¹

The cause of this pain on propofol injection is not clear, although there are various proposed mechanisms for the same that is stimulation of nociceptors, at free nerve endings between intima and venous wall, triggered kinin cascade, effect on pH. Hence to ease this part of unpleasant experience many methods, like drugs, no drug or combination of both were used to alleviate local site injection pain caused due to propofol administration. Various previous researches showed different methods used for alleviating propofol pain. The most commonly used drugs among them being lignocaine and ketamine with or without venous occlusion due to their locally acting analgesic properties.

It has been proposed that while lignocaine is not much effective without venous occlusion as it provides enough time to the drug to block delta fibres as these are responsible for transmission of pain in the endothelial layer of vessels. Ketamine causes intense analgesia and amnesia, even in sub anaesthetic dose, due to non requirement of lipid emulsion vehicle. Hence low doses of ketamine has peripheral local anaesthetic effects causing analgesia in part where venous occlusion is done.³⁰.

- Neha mehra et al, in 2017 also used the same dose of ketamine 0.2mg/kg but without venous occlusion and showed 83.1 % patients having no pain after ketamine pretreatment.⁴⁹It was very similar to our study as we too used ketamine 0.2mg/kg and 85% patients showed no signs of pain (grade zero) on propofol injection site.
- Naglaa mohammad et al, in 2018 did a randomised trial comparing ketamine 0.2mg/kg with saline and concluded 55% reduction of pain at local site of injection compared to saline group 93% in ketamine group with no adverse effects.⁴⁸Similarly we used ketamine 0.2mg/kg as pre-treatment dose and observed reduction at local site injection pain in 25% of patients in group k20 and 85% in group k40 and in group k60 with no adverse reactions in all the three groups.
- Mohamad ommid et al, in 2019 compared low dose ketamine 0.15kg/kg with fentanyl 1.5mcg/kg with venous occlusion for 60 seconds and compared results of both categories. It was comparable with our study as we also used ketamine with venous occlusion as pre-treatment but with the dose of 0.2 mg/kg.⁴⁵
- Madhu KP et al, in 2019 compared low dose ketamine 0.1mg/kg with 0.2 mg/kg as pre-treatment for propofol injection site pain without venous occlusion and concluded that ketamine 0.2mg/kg was most effective.⁴⁴ It was similar to our study as we too used ketamine 0.2 mg/kg as pre-treatment but with venous occlusion.
- Bikash khadka et al, in 2021 compared ketamine 0.2mg/kg and lignocaine 0.5mg/kg as pre-treatment for propofol local site injection pain reduction with venous occlusion for 60 seconds in all patients and concluded that ketamine to be more effective than lignocaine.⁴⁶It was similar to our study as we also used ketamine with venous occlusion as pre-treatment for propofol local site injection pain alleviation. but unlike their study, in our

study we compared the different time interval of venous occlusion (20,40,60 seconds).

After reviewing all these studies, we formulated our study combining fixed dose of injection ketamine 0.2mg/kg to evaluate efficacy of different time duration of venous occlusion (20, 40, 60, seconds) as pre-treatment for reduction of pain at the local site with injection propofol. In our study it was observed that patients in group K20 with ketamine pre-treatment in conjugation with venous occlusion for 20 seconds showed total 75% of patients complaining of pain out of which 25 % patients had mild, 35 % patient's had moderate and 15 % patients had severe pain. It was also observed that patients in group K40 with ketamine pre-treatment in conjugation with venous occlusion for 40 seconds showed total 15% of patients complaining of pain out of which 10 % patients had mild, 5 % patients had moderate and no patients had severe pain.

It was also observed that patients in group K60 with ketamine pre-treatment in conjugation with venous occlusion for 60 seconds showed total 15% of patients complaining of pain out of which 15 % patients had mild, no patients had moderate and severe pain. The P value was significant for K20 group (P value < 0.001) but not significant for K40 and K60 group (p value 0.201). Hence it was observed that venous occlusion with 40 seconds was as effective as 60 seconds but 20 seconds venous occlusion is not that effective in alleviating incidence of propofol pain on injection site locally. In our study it was observed there is no statistical difference in weight, age, gender, ASA grading, systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and SpO₂ readings in all the three groups.

Conclusion

The study concluded that venous occlusion of 40 seconds and 60 seconds after pre-treatment with ketamine 0.2mg/kg is equally effective in alleviating pain at local site of propofol injection compared to 20 seconds. Hence reduction in venous occlusion time from 60 seconds to 40 seconds is as effective as 60 seconds and also provides comfort to the patient from tourniquet pain.

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