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The Role of Hydrocortisone and Lignocaine in Attenuating Pain on Propofol Injection with Different Times

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Original Article

Summary

***Background**: Even with popularity of propofol in GA, pain on injection continues to be a distressing problem. Till now no any intervention had led to the complete reliefe of propofol injection pain. The pain is related to inflammatory response induced by propofol injection. Different methods and medication used to attenuate this pain.*

***Objective**: To compare the effect of HC and LG in attenuation of pain following I.V. injection of propofol at two time intervals.*

***Patient and method**: A prospective, randomized, controlled, study was conducted on 100 adult patients belonging to ASA physical status I or II, scheduled to undergo elective surgery. They were randomly allocated to four equally groups of 25 each. Group LG20, group LG40, group HC20 and group HC40. These groups received 2ml 2% LG 20 sec, 2ml 2% LG 40 sec, 20 mg HC 20 sec. and 20mg HC 40 sec, prior to propofol injection, respectively. Propofol was injected at two time intervals (at 20sec & 40sec) later according to the corresponding group. Patients pain level was assessed using a four-point VRS.*

***Result**: There was no significant difference of hemodynamics changes during propofol induction between all groups. There was statistically significant difference in pain incidence between group LG40 and HC40. There was statistically significant difference in pain incidence between patients' group LG20 and HC20 at 10 sec and 15 sec, but was not at 5 sec. There was no statistically significant difference in pain incidence between patients of the group HC20 & HC40, and between LG20 & LG40.*

***Conclusion**: LG, was superior to HC in attenuating propofol injection pain. Time had failed to have an influence on the effect of both study drugs.*

***Keywords:** Propofol, Lignocaine, Hydrocortisone, Injection Pain*

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1. INTRODUCTION

Propofol {2, 6-Di-isopropylphenol}, is a sterically hindered phenol i.v. anesthetic, first described in 1975, it is insoluble in water, and was first formulated in Cremophor EL in 1977(1,2), However, because of the high incidence of adverse allergic reactions, a new formulation was developed as a lipid emulsion in soybean oil and introduced into clinical trials in 1983(3), and became available commercially in 1986, it has achieved great popularity because of its favourable recovery features and its antiemetic effect (4). Propofol is suitable for the induction and maintenance of anesthesia, the induction dose is 1 to 2.5 mg/kg, and when used for induction of anesthesia in briefer procedures, results in a significantly earlier and quicker recovery and return of psychomotor function, the hypnotic action of propofol is mostly mediated by enhancing GABA- induced chloride current through its binding to the β-subunit of GABAa receptor(2).

The revised propofol preparation was an emulsion including 1% propofol, 10% soybean oil, and 1.2% purified egg phospholipid (emulsifier), with 2.25% of glycerol as a tonicity-adjusting agent, and sodium hydroxide to adjust the pH (1,3). This makes it appear as a highly opaque white fluid (1). Propofol has been referred to as milk of amnesia (a play on words of milk of magnesia), because of the milk-like appearance of its intravenous preparation (5). The emulsion is isotonic and of neutral pH, and initially did not include any preservative to prevent bacterial growth, as a consequence, several clusters of infections related to propofol misuse were reported leading to a preservative (EDTA, sodium metabisulfite, or benzyl alcohol) being added to the initial (6). Even with emulsions containing a preservative to limit bacterial growth, some precautions remain mandatory, once propofol is drawn up in a syringe from the ampoule or vial, it should be used without delay for a single patient and the remainder in the syringe discarded, propofol vial should never be used for several patients (1).

Despite the wide spread of propofol use in its current lipid formulations, some drawbacks remain and there is still room for improvement concerning emulsion stability, the need for antimicrobial drugs, hyperlipidemia, and the problem of pain on injection, since the lipid vector is not painful when given alone or when used to solubilize other drugs (7), this suggests that perhaps pain on propofol injection is due to propofol itself (8).

Pain on propofol injection has an incidence between 40-86% (9), and in some refrences

between 28-90% in adults during induction of anaesthesia and may be severe (10,11). Probably the most interesting formulation approved by the U.S. FDA is fospropofol (Aquavan), a phosphorylated prodrug of propofol which produces a unique and distinct pharmacokinetic and pharmacodynamic profile (2). A preparation of propofol in an emulsion of medium-chain triglyceride and soya (Propofol-LipuroR) has a lower incidence of pain and less severity(4).

Pain on injection relates to the fraction of propofol in the aqueous phase, representing that portion of drug not contained in the emulsion (12), which activate the nociceptors by the osmolality or ph of solution, amount of free agent in the aqueous phase of emulsion or activation by the release of endogenous mediators (13,14). Pain on injection of propofol can be immediate or delayed. Immediat pain probably result from a direct irritant effect, whereas delayed pain result from an indirect effect via the kinin cascade (15). delayed pain has latency of between 10-20 sec (16). Acute pain is often accompanied by inflammation, and certain inflammatory responses are exquisitely sensitive to LA via GPCRs. Studies on human polymorphonuclear leukocytes have helped to define the effects of LA on inflammation (17).

Several drugs and techniques have been used to attenuate this pain (18,19), with varying degree of success, prior injection of LG or less effectively by mixing LG with propofol prior to injection (2ml of 2% Lg in 18 ml propofol) (20), but it has failure rate between 13-32% (21,22), cooling (23,24), or warming (23), of the drug, diluting propofol solution(22) or use in large vein (4).

LG (25) is an amide LA agent introduced in 1947, it revolutionized regional anaesthesia because of its superior safety to previous agents (26). LG is still the current standard agent, which has been used safely and effectively for every type of LA procedure (4), it was the first amino amide–type LA and first synthesized under the name xylocaine by Swedish chemist Nils Löfgren in 1943(27). LG has pKa7.9 ,65% protein bound, 95% of an injected dose undergoes hepatic metabolism and is excreted renally. LG has a rapid onset of action by all routes (onset within 90 sec) and intermediate duration of action (effect last 20 min) (4).

Cortisol (Fig.1) (28), known more formally as HC, is a steroid hormone, more specifically a GCs, produced by zona fasciculata of the adrenal cortex (28,29), its released in response to stress and low level of blood GCs, and its primary functions are to increase blood sugar through gluconeogenesis, supress immune system, and aid in fat, protein and carbohydrate metabolism (28).

The release of cortisol is controlled by the hyothalamus, the secretion of CRH by the hypothalamus triggers cells in the neighboring anterior pituitary to secrete the ACTH, this pituitary hormone is the rate-limiting step in biosynthesis (28). GCs are used therapeutically in adrenal insuffiency, acute immunological reaction (anaphylaxis) and various conditions (4), and are important regulators of immune and inflammatory processe involved in host defense (28).

GCs affect homeostasis during stress in at least two ways (30,31). At lower physiologic concentrations they are "permissive" in that they potentiate the activities of other important metabolic regulators. In addition, they prepare the body for a response to altered homeostasis by upregulating the expression of receptors for inflammatory mediators, and act centrally to aid the processes underlying integration of sensory information as well as response selection. In addition, GCs may be "protective" this response occurs when GC activity is elevated (28). Included in these responses are the potent anti-inflammatory and immunosuppressive actions of GCs that may serve as a form of inhibitory feedback respons (31).

Exogenous GCs most often are given for their anti-inflammatory and immunosuppressive properties. GCs attenuate both the early and the late stages of inflammation. They suppress the initial vasodilation, infiltration of leukocyte, and pain, in addition GCs limit the proliferative events associated with wound healing and tissue repair. GCs also oppose inflammation-mediated changes in vascular permeability and thus reduce edema (28).

GCs are potent inhibitors of immune responses mediated by T cells and may also modulate B-cell-mediated humoral responses (32). These actions extend to the growth, differentiation, distribution, and function of monocytes, macrophages, and neutrophils (28). They inhibit and decrease the release of vasoactive and chemo-attractive factors, and inhibit different proinflammatory mediators (33,34), like prostaglandins and leukotrienes, cytokines, including interleukin, tumor necrosis and bradykinin (28). One of the proposed mechanisms for pain on propofol injection is mediated through the inflammatory pathway, by activation of the Kallikren-kinin system either by propofol or the lipid solvent (22).

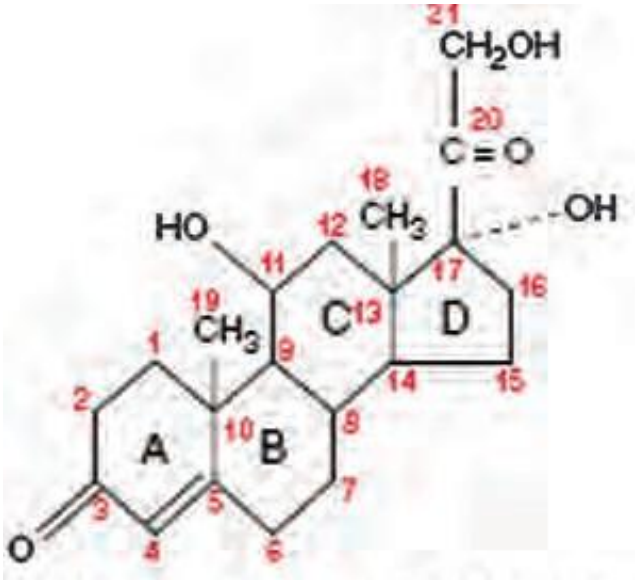

Fig.1 Cortisol structure (22)

2. PATIENTS and METHODS

A prospective, randomized, controlled, study was conducted at the Department of surgery, AL-Yarmook Teaching Hospital, Baghdad, between January and April 2014. This study was approved by the Arabic board of medical specialization (Arabic scientific committee of Anesthesiology and Intensive Care). Informed consent was taken from 100 patients of either gender, aged between 20 and 55 years and weighing between 50-100 kgs belonging to ASA grade I or II scheduled to undergo elective surgery and requiring GA demanding ETT with controlled ventilation.

Exclusion criteria include:

1. Patient refusal.
2. Patients with history of allergy to propofol and any medicine used in the study.
3. Patients with neurological or CVD disease.
4. Patients with obesity.
5. Patients with predicted airway difficulty.
6. Pregnant patients.
7. Patients on medication with pain modifying drugs.
8. Patient age above 55 or below 20 years.
9. Patient weight below 50 kgs.

Patients were assigned equally into four groups, 25 in each. Group LG20 received 2ml 2% LG 20 sec prior to propofol injection, LG40 receive 2ml 2% LG 40 sec prior to propofol

injection, HC20mg (100 mg vial diluted to 5 ml with N/S and 20 mg inected) 20sec prior to propofol injection and HC 20 mg (100mg vial diluted to 5 ml with N/S and 20 mg injected) m40 sec prior to propofol injection.

All patients were explained about the verbal rating scale for assessment of pain on propofol injection. On arrival in the operation theatre, an 18G i.v. cannula was placed without the use of LA infiltration in the largest vein on the dorsum of the hand and lactated Ringer's infusion was started. Venous occlusion was achieved by using venous tourniquet which pressure was high enough to prevent the free flow of Ringer's lactate. The study drug was then injected. 20 sec after the administration of study drug, occlusion was released for groups LG20 and HC20 and after 40 sec for groups LG40 and HC40, and then 5 ml of the calculated propofol dose was injected over 15 sec. After the injection, crystalloid i.v. fluid was administered at maximum gravity flow. Pain had been evaluated according to VRS every five seconds during injection of propofol. patien had been asked to grade any associated pain or discomfort using a four-point VRS. Pain was graded from 0 to 3 in accordance to scale advocated by McCrirrick and Hunter (23):

0 - no pain or no response to injection

1 - mild pain reported in response to questioning only without any behavioral signs.

2 - moderate 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.

The remainder of the calculated (2-2.5 mg/kg) propofol dose was then administered and ketamine (0.5 mg/kg) was given to all patients. Following loss of consciousness, pancuronium bromide (0.1 mg/kg body weight) was administered to facilitate endotracheal intubation. Anesthesia was maintained with halothane 1% with controlled ventilation using ETT (sizes7.0,7.5,8.0). Non-invasive blood pressure (systolic, diastolic and MAP) and heart rate were recorded. These parameters were recorded before induction of anesthesia and at 1 and 3 minutes after propofol injection, to verify any hemodynamic differences between each group.

Statistical Analysis

Analysis of data was carried out using the available statistical package of SPSS-22 (Statistical Packages for Social Sciences- version 22).

Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values).

The significance of difference of different percentages (qualitative data) were tested using chi-square test (□2-test) with application of Yate's correction or Fisher Exact test whenever applicable.The significance of difference of different means (quantitative data) were tested using analysis of variance test (ANOVA-test). Statistical significance was considered whenever the P value was equal or less than 0.05.

3. RESULTS

The four groups were comparable in respect to age (p-0.996) and weight (p-198) (Table 1).

There was no significant difference in the ASA classification of patients between all groups(p-261) (Table 2). There was no statistically significant difference in pain reduction at 5 sec in all groups (Table 3). There was no statistically significant differences in pain at 5 sec, 10 sec, and 15 sec between neither group HC20 and HC40 nor group LG20 and Lg40 (Table 4).

The greatest statistically significant difference in pain reduction was between group LG20 and group HC20 (P-0.001) (Figure 2). There was statistically significant difference in pain at 5 sec, 10 sec, 15 sec between groups HC40 and LG40 (Figure 3). Regarding groups HC20 and LG20, there was statistically significant difference in pain at 10 sec, 15 sec, but at 5 sec, There was no statistically significant difference in pain reduction. There was no significant difference in haemodynamic changes during propofol induction between groups (Table 5).

Table 1. Comparison of Demographic Data between the groups0.996

	Hydrocortisone 20		Hydrocortisone 40		Lignocaine 20		Lignocaine 40		P value
	No	%	No	%	No	%	No	%	
Age (year)									
20--24	4	16.0	4	16.0	6	24.0	5	20.0	
25--29	4	16.0	3	12.0	3	12.0	4	16.0	
30--34	5	20.0	5	20.0	3	12.0	3	12.0	
35--39	2	8.0	3	12.0	3	12.0	5	20.0	
40--44	4	16.0	3	12.0	4	16.0	4	16.0	
≥ 45	6	24.0	7	28.0	6	24.0	4	16.0	
Mean ± SD (Range)	36.1±11.2 (21-54)		37.4±10.8 (20-55)		35.4±11.0 (20-54)		34.9±10.2 (20-56)		0.855
Weight (Kg) Mean± SD (Range)	76.4±10.4 (57-93)		71.0±9.7 (55-96)		73.3±8.6 (55-92)		74.1±6.7 (62-93)		0.198

*Significant difference among proportions using Pearson Chi-square test at 0.05 level
#Significant difference among means using ANOVA test at 0.05 level

Table 2. Comparison of ASA classification data between the groups

ASA	Hydrocortisone 20		Hydrocortisone 40		Lignocaine 20		Lignocaine 40		P value
	No	%	No	%	No	%	No	%	
I	12	48.0	12	48.0	13	52.0	18	72.0	0.261
II	13	52.0	13	52.0	12	48.0	7	28.0	

*Significant difference among proportions using Pearson Chi-square test at 0.05 level

Table 3. Comparison of pain scores between all groups

		Hydrocortisone 20		Hydrocortisone 40		Lignocaine 20		Lignocaine 40		P value
		No	%	No	%	No	%	No	%	
Pain score 5 Sec	0	19	76.0	19	76.0	24	96.0	24	96.0	0.155
	1	4	16.0	6	24.0	1	4.0	1	4.0	
	2	1	4.0	-	-	-	-	-	-	
	3	1	4.0	-	-	-	-	-	-	
Pain score 10 Sec	0	11	44.0	11	44.0	21	84.0	19	76.0	0.015*
	1	8	32.0	9	36.0	4	16.0	6	24.0	
	2	5	20.0	5	20.0	-	-	-	-	
	3	1	4.0	-	-	-	-	-	-	
Pain score 15 Sec	0	4	16.0	3	12.0	16	64.0	13	52.0	0.001*
	1	8	32.0	10	40.0	7	28.0	7	28.0	
	2	9	36.0	8	32.0	2	8.0	5	20.0	
	3	4	16.0	4	16.0	-	-	-	-	
*Significant difference among proportions using Pearson Chi-square test at 0.05 level										

Table 4. Comparison of pain scores (p value) between different groups

	H20 x H40	L20 x L40	H20 x L20	H40 x L40
Pain score 5 Sec	0.494	-	0.223	0.042*
Pain score 10 Sec	0.787	0.480	0.015*	0.021*
Pain score 15 Sec	0.935	0.450	0.001*	0.009*
*Significant using Pearson Chi-square test at 0.05 level				

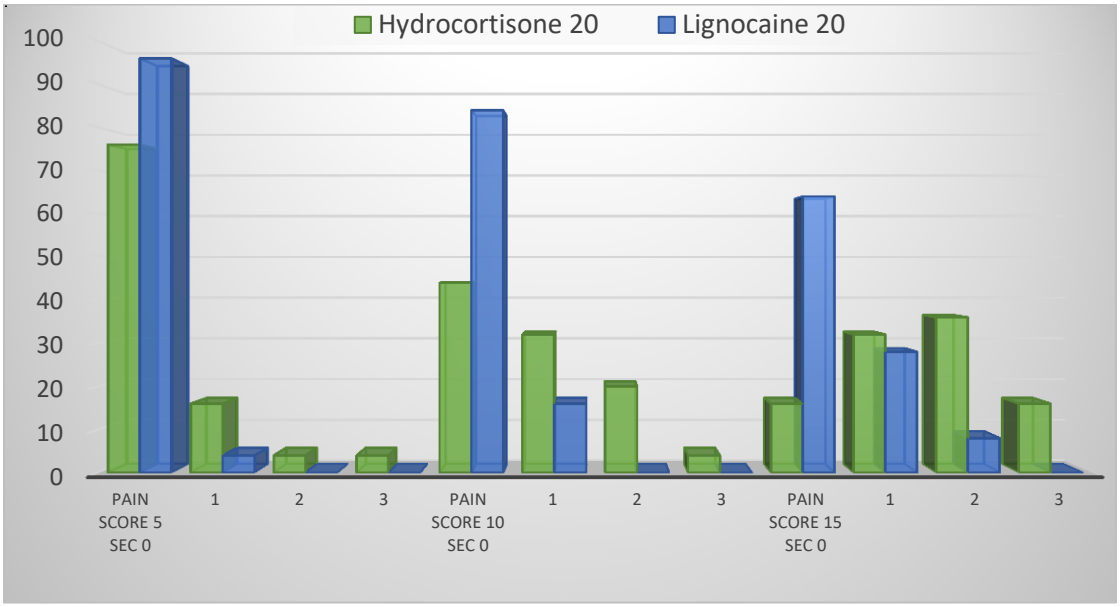

Figure 2. comparison of pain scores between group HC20 & LG20

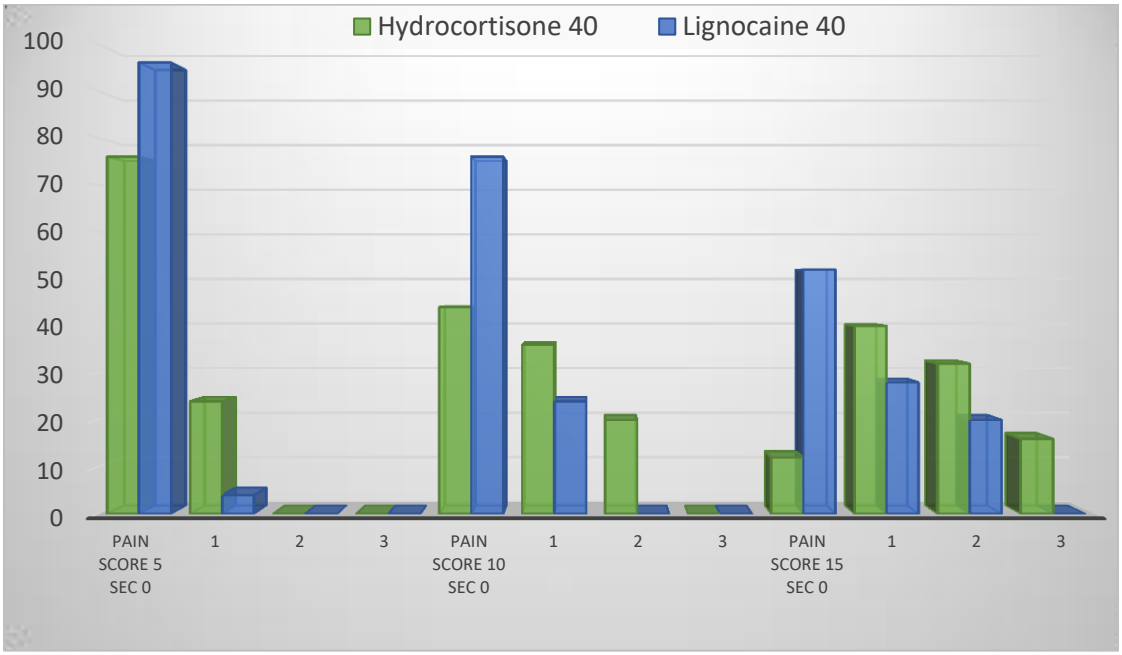

Figure 3. comparison of pain scores between group HC40 & LG40

Table 5. comparison of haemodynamic parameters between different study groups

	Hydrocortisone 20	Hydrocortisone 40	Lignocaine 20	Lignocaine 40	P value
SBP Pre-Op (mmHg)	116.8±7.5 (100-130)	113.6±7.0 (100-130)	114.7±7.9 (100-130)	112.4±7.1 (100-130)	0.189
Mint 1	121.2±8.1 (100-135)	115.6±7.1 (100-130)	116.8±7.5 (100-130)	113.6±7.0 (100-130)	0.081
Mint 3	118.4±7.8 (100-130)	117.5±7.4 (100-130)	116.8±7.5 (100-130)	113.6±7.0 (100-130)	0.053
DBP Pre-Op (mmHg)	72.8±7.4 (60-80)	70.4±7.3 (60-80)	73.9±7.1 (60-80)	72.6±6.9 (60-80)	0.451
Mint 1	78.4±7.9 (60-95)	70.4±7.3 (60-80)	72.8±7.4 (60-80)	75.5±8.2 (60-80)	0.092
Mint 3	72.6±7.7 (60-80)	70.4±7.3 (60-80)	72.8±7.4 (60-80)	73.3±8.0 (60-80)	0.451
HR Pre-Op (beat/min)	91.0±13.5 (68-117)	89.0±12.4 (68-117)	90.4±13.1 (68-117)	86.1±12.1 (68-117)	0.537
Mint 1	98.0±15.9 (81-135)	97.1±14.8 (81-135)	99.2±13.9 (81-135)	97.5±16.0 (81-135)	0.811
Mint 3	90.4±14.6 (72-121)	89.4±15.5 (72-121)	88.8±14.9 (72-121)	89.8±15.1 (72-121)	0.902
MAP Pre-Op (mmHg)	87.5±6.8 (73-97)	84.8±6.7 (73-97)	88.1±6.0 (73-97)	85.9±7.7 (73-97)	0.279
Mint 1	91.4±10.3 (79-115)	88.8±10.7 (77-117)	89.6±10.4 (79-113)	87.3±9.97 (77-117)	0.783
Mint 3	83.9±10.2 (71-107)	83.1±10.2 (71-104)	84.1±11.0 (71-107)	83.6±9.8 (71-104)	0.985

Data were presented as Mean ± SD (Range)
#Significant difference among means using ANOVA test at 0.05 level

4. DISCUSSION

There are very few studies on use of HC as pretreatment for decreasing pain associated with propofol injection. This study was conducted to compare the effect of LG and HC in attenuating pain of propofol, and to rule out if time of pretreatment study drug injection has an effect on propfol pain.

A previous study on role of HC in attenuating pain on propofol injection in comparison with

LG (35), was carried out by Monu yadav. He conducted a prospective randomized double-blind, placebo-controlled study on 72 adult patients belonging to ASA physical status I or II, he used two different doses of HC (10 mg & 25 mg) in comparison to 2ml 2% LG, all injected 30 sec prior to propfol, while in our study the study drugs were injected at two different pretreatment times (20 sec & 40 sec). He found that the incidence of pain was significantly less in group LG than other groups, which is similar to our study, as there was significant difference between groups LG 20 & HC20, and LG40 & HC40.

Another randomized, placebo-controlled, double-blind study was carried out by Nathanson MH, Gajraj NM, Russell JA, to compare the use of alfentanil 1 mg and lidocaine 40 mg for the reduction of pain during injection of propofol (36). They found that both treatment groups had a significantly lower incidence of pain than the placebo group ($P < 0.002$), and There was no significant difference in the incidence of pain between the groups receiving LG or alfentanil (13% and 24%, respectively). Regarding the result about the effect of LG in this study, it support the results of our study.

Parmar AK , Koay CK had carried out a prospective, randomised, double-blind trial to assess the effectiveness of cold propofol compared to propofol premixed with LG in minimising pain on injection. They used propofol + LG 0.1 mg/kg, propofol + LG 0.2 m/kg, cold propofol and a control group consisting of propofol premixed with N/S maintained at room temperature. They found that cold propofol is associated with a very high incidence of injection pain, while LG pretreatment had less incidence of pain which is the case in our study.

Another single-blind, randomised, controlled study carried out by Barker P, Langton JA, Murphy P, Rowbotham DJ. to compare between the effect of administration of cold saline, cold propofol and propofol with LG (38) on attenuation of pain on propofol injection, he used 0.05% LG, propofol at 4 degrees C and unmodified propofol preceded by 10 ml of N/S at 4 degrees C.

They found that Prior injection of cold saline reduced the incidence of pain and discomfort significantly (22%) compared with unmodified propofol (75%; p less than 0.005) and was similar to that after cold propofol (33%) and propofol with LG (44%). There was no significant difference between the treatment groups

5. CONCLUSIONS

LG, as a sole pretreatment agent, was superior to HC in attenuating propofol injection pain. Time had failed to have an influence on the effect of both study drugs.We recommended to use LG for prevention of propofol injection pain.

Ethical Clearance : Ethical clearance and approval of the study are ascertained by the authors. All ethical issues and data collection were in accordance with the World Medical Association Declaration of Helsinki 2013 of ethical principles for medical research involving human subjects. Data and privacy of patients were kept confidentially.

Conflict of interest: Authors declared none

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6. REFERENCES

1. *Alex E, Mervyn M,Evan K. Pharmacokinetics of intravenous Anesthetics. Anaesthetic Pharmacology basic principles & clinical Practice, 2nd.Unites state, Cambridge, 2011; 443-9.*
2. *Lars E, Lee F, Jeanine W, William Y. Anaesthetic pharmacology. Ronald M. Miller's Anaesthesia,7th. Churchill Livingstone Elsevier, 2010; 720-1.*
3. *Lonnqvist PA, MacKenzie J, Soni AK,Conacher ID. Paravertebral blockade. Failure rate and complications. Anaesthesia 1995; 50: 8135.*
4. *A. Aitkenhead, G. Smith, D. Rowbotham. Intravenous anaesthetic agents. Text book of anaesthesia,5th. Netherland, Churchill Livingstone Elsevier, 2007; 42.*
5. *Euliano TY, Gravenstein JS (2004). "A brief pharmacology related to anesthesia". Essential anesthesia: from science to practice. Cambridge, UK: Cambridge University Press. p. 173. ISBN 0-521-53600-6. Retrieved 2009-06-02.*
6. *Gajraj NM, Nathanson MH. Preventing pain during injection of propofol: the optimal dose of lidocaine. J Clin Anesth1996; 8: 575-7.*
7. *Doenicke AW, Roizen MF, Hoernecke R, Lorenz W, Ostwald P. Solvent for etomidate may cause pain and adverse effects. Br J Anaesth 1999; 83: 464–6.*
8. *Doenicke AW, Roizen MF, Rau J, Kellermann W, Babl J. Reducing pain during propofol injection: the role of the solvent. Anesth Analg 1996; 82: 472–4.*
9. *Angst MS, Mackey SC, Zupfer GH, Tataru CD, Brock-Utne JG. Reduction of propofol injection pain with a double lumen i.v. set.J Clin Aneasth.1997,9:462-6.*
10. *Stark RD, Binks SM, Dutka VN,O Conner KM, Arnstein MJA, Glen JB. A review of the safety and tolerance of propofol (Diprivan). Postgraduate Medical Journal 1985,61(Suppl.3):152-6.*
11. *Mangar D, Holak EJ. Tourniquet at 50 mmhg followed by intravenous lidocaine diminishes hand pain associated with propofol injection. Anaesthesia and analgesia 1992,74:250-2.*
12. *Baker MT, Naguib M. Propofol:the challenge of formulation.anaesthesiology.2005 oct,103(4):860-76.*
13. *Klement W, Arndt JO. Pain on injection of propofol: effects of concentration and diluents. Br J Anaesth. 1991,67:281- 4*
14. *nathanson MH, Gajraj NM, Russell JA. Prevention of pain on injection of propofol: A comparison of lidocaine with alfentanyl.Anaesth Analg.1996,82:469-71*

15.Cheong MA, Kim KS, Choi WJ: Ephedrine reduces the pain from Propofol injection. Anesth Analg; 2002, 95(5):129396-.
16.Briggs LP, Clarcke RSJ, Dunde JW,moore J, Bahar M,Wright PJ,Use of di-isoporpyl phenol as main agent for short procedures, British Journal of Anesthesia 1981,53:1197-20.
17.Alex E, Mervyn M, Evan K. Essential drugs in anesthetic,Practice. Anaesthetic Pharmacology basic principles and clinical Practice, 2nd edition. Unites state, Cambridge, 2011; 593.
18.Picard P, Tramer MR. Prevention of pain on injection with propofol: A quantitaive systematic review. Anaesth Analg, 2000,90:963-9.
19.Pang WW , Mok MS, Huang S, Hwang MH. The analgesic effect of,fentanyl, morphine, meperidine, and lidocaine in the peripheral veins: A comparative study.Anaesth Analg. 1998,86:382-6.
20.J. Butterworth, D. Mackey, J. Wasnick, Intravenous Anaesthetics. Morgan M. Clinical Anaesthesiology, 5th. Mc Graw Hill, 2013;200.
21.King SY, Davis FM, wells JE, Murchison DJ, Pryor PJ.Lidocaine for the prevention of pain due to injection of propofol.Anaesth Analg.1992,74:246-9.
22.Scott RP, Saunders DA, Norman J. Propofol: Clinical strategies for preventing the pain of injection. Anaesthesia. 1988;43:492–4.
23.McCrirric A, hunter S. Pain on injection of propofol: the effect of injectate temperature. Anaesth.1990, 45:443-4.
24. Barker P, Langton JA, Murphy P, Rowbotham DJ. Effect of prior administration of cold saline on pain during propofol injection: A comparison with cold propofol and propofol with lignocaine.Anaesthesia. 1991;46:1069–70.
25.J. Butterworth, D. Mackey, J. Wasnick, Intravenous Anaesthetics, Clinical AnaesthesiologyMorgan m.5th edition. Mc Graw Hill, 2013;267.
26.S. Yentis, N. Hirsch, G. Smith, propofol, anaesthesia and intensive care A-Z An Encyclopaedia of principles and practice, 5th edition.Churchill Livingstone Elsevier, 2013;447.
27. Wildsmith JAW. "Lidocaine: A more complex story than'simple' chemistry suggests". The Proceedings of the History of Anaesthesia Society, 2011; 43: 9–16.
28.Alex E, Mervyn M, Evan K, Essential drugs in anesthetic practice,Anaesthetic Pharmacology basic principles and clinical Practice, 2nd edition. Unites state, Cambridge, 2011;815.
29.Scott E (2011-9-22) cortisol and stress:how to stayhealthy,about.com.retrieved 2011-11-29.
30. Buckingham JC, Fink G. Glucocorticoids, role in stress. Stress Science: Neuroendocrinology. Academic Press, San Diego, CA, USA. 2010 Apr 6:381-8.
31.Munck A, Naraj-Fejes-Toth A. The upsand downs of glucocorticoid physiology: permissive and suppressiveeffects revisited. Mol Cell Endocrinol1992; 90: C1–4.
32.Rook G. Glucocorticoids and immune function. Balliere's Clinical Endocrinol 1999; 13: 567–81.
33. Sanderson JT. The steroid hormone biosynthesis pathway as a target for endocrine-disrupting chemicals. Toxicological sciences. 2006 Nov 1;94(1):3-21.
34.Klement W, Arndt JO. Pain on i.v. injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. Br J Anaesth. 1991;66:189–95.
35.M. Yadav, P. Durga, R. Gopinath. Role of Steroids in Prevention of Pain on Propofol Injection. Journal of Anesthesia & Clinical Research 2011;27: 470-4.
36.N. MH1, G. NM, R. JA. Prevention of pain on injection of propofol: a comparison of lidocaine with alfentanil. Anesth Analg1996;82:469-71.
37.P. AK, K. CK. Pain on injection of propofol. A comparison of cold propofol with propofol premixed with lignocaine. Anaesthesia 1998;53:79-83.
38.Barker P, Langton JA, Murphy P, Rowbotham DJ. Effect of prior administration of cold saline on pain during propofol injection. A comparison with cold propofol and propofol with lignocaine. Anaesthesia 1991;46:1069-70.