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Prevention of Pain on Propofol Injection: A Comparison of Lignocaine with a Combination of Metoclopramide and Lignocaine.

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ABSTRACT

Background: The major disadvantage of propofol as an induction agent is the pain during injection. Lignocaine pretreatment is the most popular method for reducing this pain but this drug alone cannot eliminate the problem. The aim of this study was to examine the analgesic effect of lignocaine/metoclopramide combination, compared with lignocaine alone, during propofol injection in an adult Nigerian population at the Lagos University Teaching Hospital (LUTH). **Methods:** Seventy (70) American Society of Anesthesiologists (ASA) physical status class I and II adult patients; who came in for various elective surgical procedures under intravenous general anesthesia were randomly assigned to two different groups, A or B. Group A (n=35) received a combination of Inj. Lignocaine (20 mg IV) with Inj. Metoclopramide (10mg IV)mixed with Inj. Propofol (2.0mg/kg IV) and Group B (n=35)received Inj. Lignocaine (20mg IV) alone mixed with Inj. Propofol (2.0 mg/kg IV) into a dorsal hand vein. During a ten-second pause after the first 25% of the calculated propofol dose (mixed with study drugs) was given, the patients were asked standard questions regarding pain on injection before induction of anaesthesia. Thereafter, the induction of anesthesia was continued and completed with the remainder of the calculated propofol dose and endotracheal intubation facilitated with Inj. Pancuronium (0.1mg/kg IV) in the two groups. **Results:** With regard to (occurrence) incidence of pain on injection, the difference between the two groups was statistically significant ($P<0.05$) using the Chi-square test. There was no statistical difference in Verbal Pain Response (intensity) Scores ($P > 0.05$) using the Chi-square test, between the groups. After completion of the study, side effects (such as arrhythmias, injection site reactions, extra pyramidal reactions) were not observed following the use of the study drugs. **Conclusion:** A lignocaine/metoclopramide combination is more effective than lignocaine alone for reducing pain on injection of propofol in a dorsal hand vein.

***Key Words*:**Lignocaine, Metoclopramide, Propofol

INTRODUCTION

Propofol is a commonly used intravenous anesthetic in the world today especially in daycare settings, partly because of its rapid recovery profile.[1-4] A major disadvantage of propofol as an induction agent is pain on injection, which has been reported in 28-90% of patients.[5,6]

Propofol-induced painranked seventh among the thirty three low morbidity clinical outcomesby expert anesthesiologists when both clinical importance andfrequency were considered.[5]The mechanism of painful injection of propofol could be because of the generation of bradykinin on the vascular endothelium. Bradykinin is produced by contact between the lipid solvent for propofol and the plasma kallikrein-kinin system, and results in modification of the injected vein, such that the propofol molecules in the aqueous phase have easy access to the free nerve endings of the vessel, causing aggravation of the pain. Drugs like lignocaine and nafamostatmesilate (a kallikrein inhibitor) are considered to decrease the pain by reducing the plasma bradykinin concentration.[7,8]

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Other than this, many pharmacological[9-18] and non-pharmacological[19,20] strategies were demonstrated to decrease the pain during propofol injection.

Pretreatment with lignocaine has become a standard practice and is the most popular strategy to reduce the pain on injection of propofol.[2,8,21] However, Lignocaine(a local anaesthetic and class IB-antiarrhythmic drug) alone cannot entirely control propofol–induced pain with a failure rate of 32-48%.[6]

Metoclopramide(2-methoxy-5-chloroprocainamide) primarily antiemetic and a pro-kinetic drug shares similar, structural and physicochemical properties with lignocaine, procaine and procainamide and is a weak local anaesthetic in its own right.[22-25] Although metoclopramide like morphine may alter the movement of calcium ions across the membrane to produce a generalized analgesic effect, the exact mechanism whereby it prevents local injection pain is unknown.[26] Mokand colleagues[15] suggested a direct local anesthetic effect on peripheral nerves. In addition to this pharmacological property, metoclopramide has a weak general analgesic effect.[23,26,27]

The purpose of this study, therefore is to investigate the analgesic effect of lignocaine/metoclopramide combination, compared with lignocaine alone, during propofol injection in a population of Nigerian patients, and to confirm or refute other studies which demonstrated significant

reduction in propofol injection pain with lignocaine/metoclopramide combination, by evaluating pain scores.

MATERIALS AND METHODS

The approval of the Research and Ethics Committee of the Lagos University Teaching Hospital (LUTH), and informed consent of each patient were obtained. This interventional study was designed to examine the analgesic effect of lignocaine/metoclopramide combination and compare the effect with that of lignocaine alone, during propofol injection. The objectives are -

To investigate the incidence and intensity of pain following propofol injection after pretreatment with lignocaine/metoclopramide combination compared with lignocaine alone by VRS.

To determine the incidence of side effects of pretreatment drugs e.g. extrapyramidal effects, arrhythmias and injection site oedema / hyperemia.

Design: This was a comparative prospective randomized double blind control interventional study conducted over a period of six months among adult elective surgical patients at the Lagos University Teaching Hospital (LUTH).

Settings/participants: Seventy (70) American Society of Anesthesiology (ASA) physical class I or II adult elective surgical patients participated in the approved study. Excluded from the study were: patients < 18 and > 65 years, ASA class > II, patients having difficulty with communication or educationally challenged, those with a history of adverse response, allergy to any drug used in the study (propofol, lignocaine, or metoclopramide), and those who had received any analgesic drug within the 24hrs preceding surgery. Excluded also were emergency surgery and patients with full stomach, patients with compromised airway for whom intravenous induction will be a contraindication, anticipated difficult venous access, cardiac conduction defects and absence of informed written consent.

The sample size was determined by applying the formula for comparison of two proportions based on the work of Varkevisser CM, Pathmanathan I, and Brownlee A.[21]

$$n = \frac{(u+v)^2 \{p_1(100-p_1) + p_2(100-p_2)\}}{(p_1-p_2)^2}$$

Where n = the desired minimum sample size for each group.

u = One-sided percentage point of the normal distribution, corresponding to 1- the power.

v = Percentage point of the normal distribution, corresponding tothe (two-sided) significance level.

p = the estimated percentage of an attribute that is present in the population.[21]

At 95% confidence level, with 80% power, v = 1.96 and u = 0.84

p_1 = 40 and p_2 = 10 (Percentage reporting pain (prevalence) among patients in group B without metoclopramide and group A with metoclopramide respectively in previous study).[21]

$$n = \frac{(0.84 + 1.96)^2 \{40(100- 40) + 10(100-10)\}}{(40-10)^2}$$

$$n = \frac{7.84\ (3300)}{900}$$

n = 28.75

Therefore minimum sample size is 29 patients per group. In addition, a similar previous study was considered, where 30 patients per group were estimated to provide an 80% power to detect a difference using a two-sided test with significant finding.[21]In this study, however, 35 patients per group were recruited to make provision for possible dropouts.

All the patients were seen in the ward a day before surgery for pre-operative evaluation and results of routine investigations and their weights were documented in the case notes. Informed consent was obtained following detailed explanation of the study; including patients' familiarization with the pain assessment tool- Verbal Rating Scale (VRS), which was used for the study. All patients received oral diazepam 5 mg on the night before surgery for anxiolytics and no premedication was given in the morning of surgery.

On arrival in the operation theatre, vital signs monitoring was instituted using multi-parameter monitor (Cardiocarp /5). The values of baseline blood pressure (Diastolic, Systolic, and Mean Arterial Pressures), HR, ECG, ETC02, SPO_2- were recorded from five minutes pre-induction to the end of surgery. After baseline vital signs was obtained and recorded, an 18G cannula was inserted (without the use of topical anaesthesia) in the largest vein on the dorsum of the hand at least 10 minutes before induction of anaesthesia with the use of an infusion of 500mls normal saline(for hydration). The patient's experience of pain due to cannulation was distinguished from the pain resulting from injection of the study drugs, by observing pain free interval of at least 5 minutes after cannulation. No other drug (e.g. antibiotics and pre-medicant) was administered through the intravenous cannula before the study medications were injected.

Interventions: The patients were randomly assigned by balloting to one of two groups.Group A- patients received lignocaine 20mg (1ml of 2%) / metoclopramide 10mg (2mls) in combination with 2 mg/kg propofol. Group B– patients received 20mg (1ml of 2%) lignocaine mixed with 2 mg/kg propofol, injected into a dorsal hand vein. All the studied drugs were injected on the dorsum of the hand (at room temperature) through the injection port proximal to the intravenous cannula at a rate of 0.5ml/s. During a ten-second pause after the first 25% of the calculated propofol dose was given, the

patients were asked standard questions regarding injection pain (distinct from the pain of cannulation). The investigator recorded the patient's response, and both the investigator and the patient were blinded to the study drugs (by ensuring third party anesthetist preparation of similar 20mls syringes (depending on the random group assignment after balloting). The incidence (the number of patients with pain) and intensity (the degree or severity of pain) were assessed using a four point Verbal Rating Scale 0 to 3, as follows: 0-None (no pain to questioning), 1-Mild pain (pain reported only in response to questioning without any behavioral signs e.g. arm withdrawal), 2-Moderate pain (pain reported in response to questioning and accompanied by a behavioral sign of arm withdrawal, facial grimace or pain reported spontaneously without questioning), 3-Severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).

Thereafter, induction of anesthesia was continued and completed with the remainder of the calculated propofol dose (2 mg/kg) and endotracheal intubation was performed three minutes after the administration of pancuronium 0.1mg/kg intravenously (for muscle relaxation), during which anesthesia was maintained using intermittent positive pressure ventilation (IPPV) via the anesthetic machine to deliver isoflurane 1-2% in 100% (oxygen). Fentanyl 1-2 mcg/kg intravenous was given for intra operative analgesia as appropriate. Residual muscle paralysis was reversed with neostigmine 2.5mg mixed with atropine 1.2mg. At the end of surgery and following extubation, the patients were transferred to the recovery room with the monitor in situ and oxygen was administered by facemask. The recovery room nurses and the investigator were unaware of the treatment group.

Safety and tolerability were evaluated based on observation of adverse effects such as arrhythmias, injection site reactions (oedema/hyperemia), extra pyramidal reactions, immediately after induction and 2hrs post-recovery. Adverse effects was documented, as 0= none or 1= presence of adverse effect. The injection site reaction was assessed for evidence of local reactivity such as signs of inflammation along the veins (including hyperemia and any swelling at the injection site), immediately after induction and at 2hours following anesthesia.

Data entry and analysis were done with the computer analytical package; SPSS 14 .0 Inc. Chicago, Illinois.

Categorical variables: Pain intensity, Pain Recall and the Gender were measured and recorded.

Continuous variables: Demographic and clinical Data were measured and recorded- Age, Weight, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Heart Rate (HR) and Hemoglobin Oxygen Saturation (SPO_2).

RESULTS

Seventy patients were randomly included in this study divided into two groups A or B; one patient was dropped from the study in each group due to painful cannulation and for lack of further co-operation to continue with the study. The demographic data was compared between the two groups, as shown in Table 1. Using the students T-test for paired data, there was no significant differences between the groups with respect to age, gender, weight, and ASA Classification. There was no significant differences (P>0.05) in age (P=0.33), sex (P=0.25), weight (P=0.19) and ASA Classification (P=0.42), between the two groups.

The mean age was 39.09± 12.11 years using the students T-test for paired data in group A and 36.14 ± 12.97years in group B (P=0.33, P>0.05) .

The mean weight was 68.49 ± 10.61 kg in group A and 65.16 ± 10.60kg in group B (P=0.19, P>0.05).

ASA Classification I/II, in group A= 24/11 and in group B =27/8(P=0.42).

Male / Female ratio, in-group A =13/22 and in-group B= 14/21 (P=0.25).

The incidence of pain on intravenous injection of propofol was 11.77% in-group A whiles the incidence in-group B was 32.35%, as shown in Table 2.

Group A showed a statistically significant less incidence of pain than group B, (P= 0.041, P< 0.05) using the Chi-square test and Fishers exact test (0.038) for categorical data.

Group A had one patient with severe pain (pain intensity scores 2 or 3) compared with Group B (with 7 patients), though there was no statistical intergroup differences in pain intensity scores (P= 0.118, P > 0.05) using the Chi-square test for categorical data; as shown in table 2 and figure 2.

Thirty patients in-group A and twenty-three in-group B gave a median pain score (VRS) of 0. There was no statistical difference in verbal pain (intensity) response scores (VRS) between both groups (P= 0.118, P > 0.05) using the Chi-square test, as shown in Table 2.

The Odds Ratio (OR) Odds A/B = 3.552, is statistically significant at 95% CI Level (1.005-12.552), the intervention (treatment) is of relative benefit over control.

Noneof the 34 patients in either group had any side effects such as arrhythmias, injection site reactions (oedema / hyperemia), extra pyramidal reactions and complications attributable to the use of any of the study drugs.

Table 1: Demographic data and Clinical characteristics.

Variables	Group A (Intervention) n = 35	Group B (Control) n=35	p value: Level of Significance
Age/yearsMean ± SD	39.09 ± 12.11	36.14 ± 12.97	0.33 (N.S)
Weight (kg)Mean ± SD	68.49 ± 10.61	65.16 ± 10.60	0.19 (N.S)
Gender Ratio(M:F)	13:22	14:21	0.25 (N.S)
ASA Classification Ratio of (I:II)	24:11	27:8	0.42 (N.S)

Values are mean ± SD or ratio; M = Male; F = Female
Group A= Intervention =Metoclorpramide + Lignocaine
Group B = Control = Lignocaine only.
N.S = not significant

Table 2: Comparison of pain scores (VRS-4) in the two groups.

Group (n)	Score 0	Score I	Score II	Score III	Presence of pain (%)
A(34)	30(88.23%)	3(8.82%)	1(2.94%)	0	4 (11.77%)
A(34)	23(67.64%)	4(11.76%)	4(11.76%)	3(8.82%)	11(32.35%)

Pearson chi-square for pain incidence is 0.041 ($p< 0.05$); Pearson chi-square for pain intensity score is 0.118($p >0.05$).

DISCUSSION

There is paucity of literature on this subject in the West African sub region involving the use of metoclopramide/lignocaine combination for prevention of propofol injection pain. Different scores of pain measurement (mostly VAS or VRS) were used in the systematic review, on propofol injection pain by Picard and Tramer.[28]

Previously, a simplified scoring system of mild, moderate, severe was adopted for postoperative pain assessment in preference to the VAS by Famewo[29].owing to the low level of literacy of Nigerian patients. The Visual Analogue and Verbal rating Scales have been validated in Nigerian patients by Soyannwo and colleagues.[30] to include the impact of psychosocial and cultural factors on pain perception and also demonstrated that Nigerians are able to use the more complicated tools. The study concluded that both VAS and VRS constitute useful tools for pain assessment in Nigerian patients.

In our study, the incidence of pain on injection of propofol was 11.8% with the use of lignocaine/metoclopramide combination, compared with 32% using lignocaine alone; this finding demonstrate that a lignocaine/metoclopramide combination was more effective than lignocaine alone, in reducing the incidence of pain on injection of propofol. Picard and Tramer[28] showed that 70% of the patients reported pain on injection of propofol without any intervention. Many different factors have been associated with propofol injection pain, including the temperature of the solution, size of the vein and speed of injection.[2,19,20] However in our study, these factors were controlled between the groups by using veins of similar size on the hand, 0.5ml/s injection rate and propofol at room temperature.

Lignocaine and Metoclopramide are two drugs commonly used in anaesthetic practice, in various clinical situation.[26,32] Whereas intravenous lignocaine is the commonest analgesic adjunct used by anaesthetists to prevent propofol injection pain, the analgesic effect of metoclopramide has been reported by research findings.[26-28] The use of metoclopramide for ameliorating pain of propofol injection is well documented in literature.[26,27] The local anaesthetic effect of metoclopramide was demonstrated clinically by the works of Ates and colleagues,[22] Intravenous metoclopramide for the reduction of propofol injection pain at the induction of anaesthesia was demonstrated by Liaw and colleagues.[33] Iwama et al.[8,34] postulated a possible mechanism whereby propofol induces pain on injection, might be due to the lipid solvent which activates the plasma kallikrein-kinin system and generate bradykinin that causes hyperpermeability of the vessel and thus dilates the injected local vein. Picard and Tramer[28] in a systematic literature review involving 6,264 patients of 56 reports on the prevention of propofol (2mg/kg) injection pain, showed that three different techniques/methods of pain alleviation were used in the various studies, including lignocaine administered i.v before injection of propofol, after mixing with propofol, and lignocaine given with a tourniquet (intravenous retention for 1-2 minutes before injection of propofol). Consequently, intravenous retention of lignocaine with tourniquet was found to be the most useful model for investigating the peripheral actions of a study drug in the absence of a central effect.[21] The strategy most commonly used clinically, involves the mixing of lignocaine with propofol, which was adopted in our study for simplicity.[20,28,34,35]

The failure rate of lignocaine for prevention of propofol injection pain is between 32% and 48%[6]. Mecklem[36] compared the

metoclopramide/propofol mixture with a lignocaine/propofol combination and observed that the incidence of injection pain was similar in both groups.

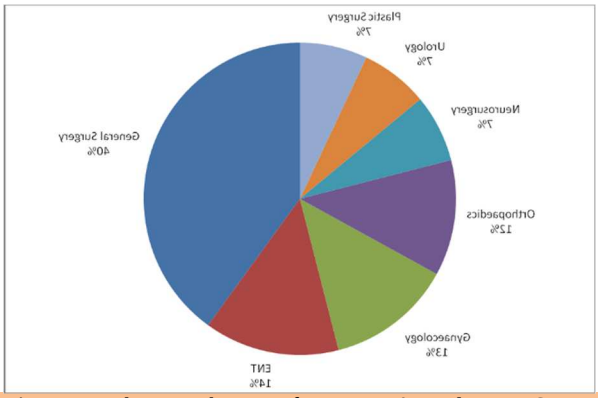

Figure 1: The Distribution of Patients According to Surgical Specialty.

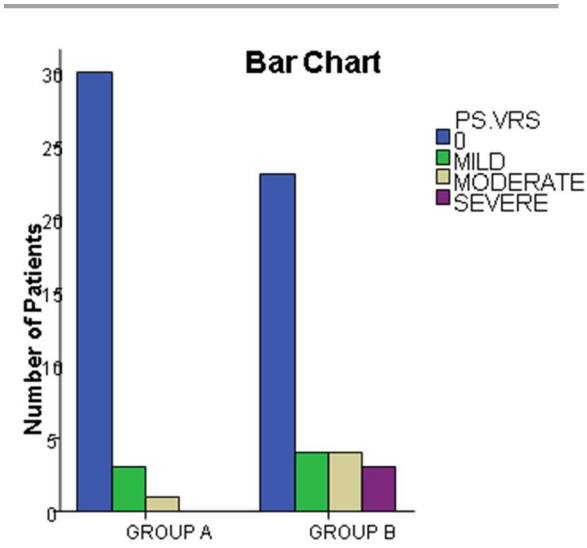

Figure 2: Intergroup Pain Score Comparison

In our study, the pain incidence (11.8%) in group A was less than in group B (32.4%) due to the combination of 20mg lignocaine with 10mg metoclopramide, compared with 32.4% of patients in group B with addition of 20mg lignocaine only. This agrees with the findings of Fujii and colleagues[27] who reported 10% in the combination group (20mg lignocaine / 10mg metoclopramide) and 28% in the lignocaine only group, using venous retention by tourniquet (of adjuvant drugs) for 1 minute followed by i.v 2 mg/kg propofol. Edomwonyi and colleagues[37] reported a 25% pain incidence with the addition of 10mg lignocaine to 2.5mg/kg propofol after intramuscular 30mg pentazocine was used as a premedicant in Nigerian patients. The lower pain incidence can be explained by the pentazocine premedication. Edomwonyi[38] also, in an earlier study on Co-induction of anaesthesia reported 13.3% incidence of pain on injection of propofol in Nigerian patients (after prior administration of i.m 30mg pentazocine, intravenous 20mg lignocaine followed by intravenous 2 mg/kg propofol). The above findings implied that combination of drugs are more effective than single agent (e.g. lignocaine) alone.

The dose of lignocaine used in our study was based upon previous studies investigating the minimum effective dose of lignocaine to prevent injection pain due to propofol.[39] The dose of metoclopramide administered was 10mg, higher doses more than 20mg occasionally causes extrapyramidal reactions.[15,33,36[In related studies on injection pain, Fuji[40] showed that lignocaine/metoclopramide 40mg/5mg or 40mg/10mg was associated with lower pain incidence, but not lower pain intensity scores, on injection of 2mg/kg propofol than lignocaine/metoclopramide 40mg/2.5mg or lignocaine 40mg/saline (with venous occlusion), before induction of anaesthesia; similarly our study fail to demonstrate significant difference in pain severity/intensity scores.

Edomwonyi[37] compared the side effects of propofol and midazolam with respect to pain on injection, local venous reaction (signs of inflammation along the veins) was observed in 20% of patients in the propofol group; our study did not detect any local intolerance or complications attributable to any of the study drugs, except for pain on injection. The apparent absence of local reactions in our study may be due to the fact that observation for side effects was not carried out beyond 2hours of recovery from anaesthesia. Doses of metoclopramide greater than 20mg (as a single dose) occasionally cause dystonic and extrapyramidal reactions.[27,40]

CONCLUSION

The administration of lignocaine / metoclopramide combination was associated with a significant reduction in the incidence of pain compared with lignocaine alone for the prevention of pain on injection of propofol without significant differences in mean pain intensity scores. A lignocaine/metoclopramide combination is more effective than lignocaine alone for reducing pain on injection of propofol.

RECOMMENDATIONS

Based on the findings in our study, it is recommended that: Metoclopramide is a useful analgesic adjunct for routine administration along with lignocaine to prevent propofol injection pain.A dose of 10mg Metoclopramide is optimal

when added in combination with 20mg lignocaine to prevent propofol injection pain.

LIMITATIONS

This study had the following limitations:
All the patients received the same dose of oral diazepam for anxiolysis, irrespective of weight due to the available formulation of diazepam tablets. The active intermediate metabolite (nor diazepam) may modify the observed pain threshold/recall, and pressor response as benzodiazepines are known to have a moderating effect on intraoperative cardiovascular responses.
Small veins on the dorsum of the hand may be difficult to cannulate and repeated attempts may be painful thus influencing pain threshold and pain reporting; and were avoided as much as possible.
Pain of cannulation may be confused with pain of propofol injection; therefore cannulation was concluded at least 5 minutes before induction and distinction between the two were made during VRS assessment.
Disparity in volumes and the dilution effect in both groups when compared will influence the outcome of the study.
A placebo control group is required to calculate the risk difference and the NNT for lignocaine, in other to compare the absolute treatment efficacy between metoclopramide lignocaine / combination and the use of lignocaine alone for the prevention of propofol injection pain.

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