بسم الله الرحمن الرحيم

University of Khartoum
Faculty of Medicine
Postgraduate Medical Studies Board

Pretreatment with Labetalol Reduces Propofol Injection Pain

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A thesis submitted in partial fulfillment for the requirement of the Degree of Clinical MD in Anaesthesia
February, 2003

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Dedication

To my mother for her

love and support

Acknowledgement

I am most grateful after my God Almighty, to Dr. Ali Ahmed Salama for his valuable support and continuous advice.

I am gratefully indebted to Dr. Huda M. Ali for her advice and help in performing this study. I am also grateful to Mrs. Fathia Hassan for typing and preparation of this manuscript.

Abstract

A prospective randomized study was performed for 108 Sudanese patients in Khartoum Teaching Hospital (KTH) and Soba University Hospital (SUH) in the period from 1st of April to end of September 2002. All patients were selected according to the grading of the American Society of Anaesthesiologists (ASA) (grade I or II), their ages were between 18 – 60 years old.

The study aimed at reducing the incidence of Propofol injection pain by using Labetalol as a pre-treatment.

Data was collected using self-structured questionnaire. It was found that there was a significant reduction in Propofol injection pain by using Labetalol as pre-treatment in different doses (5mg-10mg). It was also found that the size of the cannula affects the incidence of pain i.e. the larger the size of the cannula the lower the incidence of pain.

It is concluded that the incidence of Propofol injection pain is reduced significantly by using Labetalol as a pre-treatment and cannula of large size.

ملخص الاطروحة

اجريت هذه الدراسة المستقبلية علي مائة وثمانية مريض (ومريضه) سوداني الجنسية بكل من مستشفي الخرطوم التعليمي ومستشفي سوبا الجامعي في الفترة من الاول من ابريل حتي نهاية شهر سبتمبر من العام 2002م .

اختيرت العينات عشوائيا وكان كل المرضي من الدرجة الاولي او الثانية (American Society of Anaesthiologists) لتصنيف جمعية اختصاصيي التخدير الامريكية للياقة الصحية وتراوحت اعمارهم من 18 سنة .– 60 سنة

الهدف من هذه الدراسة هو التقليل من حدوث الالم المصاحب لحقن عقار البروبوفول (Propofol) وذلك باستعمال عقار اللابتالول (Labetalol) قبل استعمال البروبوفول وقد تم جمع المعلومات عن طريق ملء الاستبيان .

لقد توصلت هذه الدراسة الي ان هنالك انخفاض ملموس احصائيا في حدوث الالم المصاحب لحقن عقار البروبوفول وذلك باستعمال اللابتالول في جرعات مختلفة كما وجد ان مقاس الكانيولا يؤثر علي نسبة حدوث هذا الالم . فنسبة حدوث هذا الالم اكبر مع استعمال الكانيولا ذات المقاس الاصغر . وقد خلصت هذه الدراسة الي انه يمكن تخفيض نسبة حدوث الالم المصاحب لحقن عقار البروبوفول باستعمال عقار اللابتالول واستعمال كانيولا ذات مقاس كبير .

LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologists
KTH	Khartoum Teaching Hospital
SUH	Soba University Hospital
ISA	Intrinsic Sympathomimetic Activity

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INTRODUCTION

It is well known that intravenous injection of propofol is associated with pain. The incidence ranges from 28% to 90% and may be recalled as an unpleasant experience by the patients. Many methods have been used to reduce the incidence and severity of this complication with varying success rates[1].

The incidence of pain relates to the size of the vein, the speed of injection and the temperature and concentration of propfol[2].

The incidence of pain is reduced if a large vein is used, if a small dose (10 mg) of lignocaine is injected shortly before propofol, or if lignocaine is mixed with propofol in the syringe (up to 1 ml of 0.5% or 1% lignocaine per 20 ml of propofol[3].

In this study labetalol which is alpha and beta blocker will be used for this purpose, as it may be a useful agent in reducing propofol injection pain through its blocking effect on alpha receptors located in the vein used for propofol injection, causing dilatation of that venous segment, increasing its blood flow.

LITERATURE REVIEW

Mechanisms of pain:

The mechanisms of pain when propofol is given intravenously have been postulated to be due to either a direct irritant effect giving rise to an immediate sensation of pain or an indirect effect via the release of mediators leading to a delayed onset. The latter theory involves the release of kininogens when propofol comes into contract with the vascular endothelium[1]. Furthermore, Klement and Arndt postulated that the afferent free nerve endings between the media and intima are the sensors for this pathway[4].

Propofol:

This phenol derivative was identified as a potentially useful intravenous anaesthetic agent in 1980, and became available commercially in 1986. It is more expensive than thiopentone or methohexitane, but has achieved great popularity because of its favorable recovery characteristics and its low emetic effect.

Physical properties and presentation:

Propofol is extremely lipid-soluble, but almost insoluble in water. The drug was formulated initially in Cremophor El. However, a number of other drugs formulated in this solubilizing agent were associated with release of histamine and an

unacceptably high incidence of anaphlactoid reactions, and similar reactions occurred with this formulation of propofol. Consequently, the drug was reformulated in a white, aqueous emulsion containing Soya bean oil and purified egg phosphatide.

- **Chemical structure:**

  2,6- Di-isopropylphenol.

- **Pharmacology:**

  Central nervous system:

  Anaesthesia is induced within 20-40s after iv administration. Transfer from blood to the sites of action in the brain is slower than with thiopentone, and there is a delay in disappearance of the eyelash reflex, normally used as a sign of unconsciousness after administration of barbiturate anaesthetic agents. Over dosage of propofol, with exaggerated side-effects, may result if this clinical sign is used, loss of verbal contact is a better end-point.

  Propofol reduces the duration of seizures induced by ECT in humans. However, there have been reports of convulsions following the use of propofol and it is recommended that caution should be exercised in administration of propofal to epileptic patients. Normally, cerebral metabolic rate, CBF and intracranial pressure are reduced.

Recovery of consciousness is rapid, and there is a minimal "hang over" effect even in the immediate postanaesthetic period.

Cardiovascular system:

Arterial pressure decreases to a greater degree after induction of anaesthesia with propofol than with thiopentone, the reduction results predominantly from vasodilation although there is a slight negative inotropic effect.

The pressor response to tracheal intubation is attenuated to a greater degree by propofol than thiopentone. Heart rate increases slightly after induction of anaesthesia with propofol.

Respiratory system:

After induction, apnoea occurs more commonly, and for a longer duration than after thiopentone. Tidal volume is lower and respiratory rate higher than in the conscious state. There is decreased ventilatory response to carbon dioxide.

Propofol has no effect on bronchial muscle tone and laryngospasm is particularly uncommon. The suppression of laryngeal reflexes results in a low incidence of cough or laryngospasm when a laryngeal mask airway (LMA) is introduced, and propofol is regarded by most anesthetists as the drug of choice when the LMA is to be used.

- **Skeletal muscle:**

  Tone is reduced, but movement may occur in response to surgical stimulation.

- **Gastrointestinal system:**

  Propofol has no effect on gastrointestinal motility in animals.

- **Uterus and placenta:**

  Little is known of the effects of propofol on uterine tone or of its placental transfer.

- **Hepatorenal:**

  There is a transient decrease in renal function, but the impairment is less than that associated with thiopentone. Hepatic blood flow is decreased by the reductions in arterial pressure and cardiac cut put.

- **Endocrine:**

  Plasm concentrations of cortisol are decreased after administration of propofol, but a normal response occurs to administration of synacthen.

- **Pharmacokinetics:**

  In common with other i.v. anaesthetic drugs, propofol is distributed rapidly, and blood concentrations decline exponentially.

Clearance of the drug from plasma is greater than would be expected if the drug was metabolized only in the liver, and it is believed that extrahepatic sites of metabolism exist. The kidneys excrete the metabolites of propofol (mainly glucuronides), only 0.3% of the administered dose of propofol is excreted unchanged. The elimination half-life of propofol is 3-4.8 hr., although it is effective half-life is much shorter 30-60 min.

Elimination of propofol remains relatively constant even after infusions lasting for several days.

Dosage and administration:

In healthy, unpremedicated adults, a dose of 1.5 -2.5 mg/kg is required to induce anaesthesia. The dose should be reduced in the elderly. In children, a dose of 3-3.5 mg/kg is usually required, the drug is not recommended for use in children less than 3 years of age.

Adverse effects:

1- Cardiovascular depression, unless the drug is given very slowly, cardiovascular depression following a bolus dose of propofol is greater than that associated with a bolus dose of a barbiturate, and is likely to cause profound hypotension in hypovolaemic or previously hypertensive patients and in those with cardiac disease.

2- Respiratory depression. Apnoea is more common and of longer duration than after barbiturate administration.

3- Excitatory phenomena. These are more frequent than with thiopentone, but less than with methohexitone.

4- Pain on injection. This occurs in up to 40% of patients. The incidence is reduced if a large vein is used, if a small dose (10 mg) of lignocaine is injected shortly before propofol, or if lignocaine is mixed with propofol in the syringe (up to 1 ml of 0.5% or 1% lignocaine per 20 ml of propofol).

5- Allergic reaction. Skin rashes occurs occasionally. Anaphylactic reactions have also been reported, but appear to be no more common than with thiopentone.

Indications:

1- Induction of anaesthesia. Propofol is indicated particularly when rapid early recovery of consciousness is required.

2- Sedation during surgery. Propofal has been used for sedation during regional analgesic techniques, and during endoscopy.

3- Total i.v. anaesthesia. Propofol is the most suitable of the agents currently available.

4- Sedation in intensive therapy unit.

Absolute contraindications:

Airway obstruction and known hypersensitivity to the drug are probably the only contraindications. Propofol appears to be safe in prophyric patients. At present, propofol should not be used for long-term sedation of children in ITU because of a number of reports of adverse outcome[3].

Labetalol:

Is a competitive α_1- β_1 and β_2 antagonist, which is a partial agonist at B2-receptors. It is four to seven times more potent at β - than at α -receptors and is useful for the prevention and treatment of perioperative hypertension, or to produce controlled hypotension. It is also available as an oral preparation for the treatment of chronic hypertension or the preoperative management of phaeochromocytoma. I.V. labetalol in small increments (5-10mg) produces a controlled decrease in arterial pressure over 5-10 min with no change in cardiac output or reflex tachycardia, suggesting that at this dose the vasodilating action predominates. At higher doses, the β effect becomes more prominent, with negative inotropic and chronotropic effects[3].

β-adrenoceptor antagonists:

In general, the β-adrenoreceptor antagonists (β-blockers) are structurally similar to the β-agonists, e.g. isoprenaline. However, alteration in molecular structure (primarily in the catechol ring) has produced compounds which do not activate adenylate cyclase and the second messenger system despite binding avidly to the β-adrenoceptor. These compounds possess high affinity for the receptor but little or no intrinsic activity and therefore, inhibit competitively the effects of the naturally occurring catecholamines.

Cardiovascular effects of β-blockers:

A- Antiarrhythmic activity:

Although the mechanism of antiarrhythmic action of β-blockers is unknown, it appears to be a property inherent in β-blockade itself, i.e. antagonism of catecholamine effects on the cardiac action potential and muscle contractility. The result is a slowing of rate of discharge from the sinus and any ectopic pace maker, and slowing of conduction and increased refractoriness of the atrioventricular node.

B- Negative inotropism:

The action of catecholamine agonists on the force of contraction of cardiac muscle is antagonized by β-blockade. The resulting negative inotropic effect is of little significance in normal hearts but may be disastrous if increased sympathetic tone is supporting the failing heart.

C- Antianginal activity:

Angina pectoris occurs when oxygen demand exceeds supply. The oxygen demand of the left ventricle depends on contractility, heart rate and the pressure within the ventricle during systole. The reduction in heart rate caused by β- blockade results in a decrease in cardiac work, which reduces oxygen demand. A slower heart rate also permits longer diastolic filling time and this allows greater coronary perfusion.

D- Antihypertensive effect:

β- blockers are effective in controlling the arterial pressure of many hypertensive patients. The mechanism of action has not been elucidated fully but it is probable that some of the following are involved:

1- A direct effect on the cardiovascular system: This includes a reduction in cardiac output, which correlates

with a reduction in heart rate and some decrease in myocardial contractility.

2- A reduction in sympathetic activity: this may be mediated by an action of β-blockers in the hypothalmus, altering central control of sympathetic tone.

3- An effect on plasma renin concentrations: β-blockers have variable effects on resting and orthostatic release of renin. The non-selective drugs propranolol and timolol cause the greatest reduction, while drugs with ISA (oxprenolol, pindolol) or β_1-selectivity are less effective. In addition, no correlation has been found between renin-lowering effect and antihypertensive activity of these drugs or with dosage of β-blocker used.

4- An effect on peripheral resistance: β-blockade does not reduce peripheral resistance directly and may even cause an increase by allowing unopposed α-stimulation. As the vasodilating effect of catecholamines on skeletal muscle is β_2-mediated, unopposed α-stimulation would be expected to be less with cardioselective drugs or with those which possess ISA.

5- The membrane-stabilizing effect: This was considered of possible importance when early studied indicated that the antihypertensive effect of propanolol resembled that of quinidine. However, all β-blockers appear to reduce arterial pressure regardless of the presence of a membrane-stabilizing effect.

Adverse reactions to β-blockade:

1. Reactions resulting from β-blockade:

a- Induction of bronchospasm in patients who rely on sympathetically mediated bronchodilation (β_2) e.g. asthmatics, chronic bronchitis.

b- Precipitation of heart failure in patients with compromised cardiac function. Co-administration with other drugs affecting cardiac contractility (e.g. verapamil, quinidine) is potentially hazardous.

c- Production of cold extremities or worsening symptoms of Raynaud's phenomenon and peripheral vascular diseases.

d- Increased muscle fatigue, possibly resulting from blockade of B_2-mediated vasodilatation in muscles during exercise.

e- A withdrawal phenomenon may occur after abrupt cessation of long-term B-blocker antianginal therapy. This may

take the form of rebound tachycardia, worsening angina or precipitation of myocardial infarction.

2- Idiosyncratic reactions:

Central nervous system effects occur with some β-blockers, including nightmares, hallucinations, insomnia and depression[3].

Studies:-

In a study conducted by A. Khalid and M. Maroof (1996), the study was performed on three groups of patients, group A received 5mg Labetalol, B received 10mg Labetalol and group C, control group received 5ml normal saline as a pretreatment[5]. The venous drainage was occluded manually at mid forearm for one minute after pretreatment and after that Profofol was injected.

They found that Labetalol significantly reduced Propofol injectin pain ($P<0.05$). No significant change was found between groups A and B.

J. E. Fletcher, C.R. Seavell and D. J. Bowen (1994) studied the effect of pretreatment with Alfentanil in reducing Propofol injection pain[2].

Fourty-four patients were divided into two groups, group I received Alfentanil 1 mg (2ml) iv followed 15 s later by Propofol iv, whilst patients in group II received 2ml of normal saline.

Results of the study showed that those who received Alfentanil before injection of Propofol had less pain than those who received saline.

Michael H. Nathanson, Noor M. Gajraj and John A. Russell (1996) had a comparison study between Lidocaine and Alfentanil in prevention of Propofol injection pain[6].

Eighty-nine patients were divided into three groups, group L received Lidocaine 40mg added to 180mg Propofol, group A received Alfentanil 1mg 30 s prior to Propofol, group P, Placebo received normal saline.

The incidence of pain in the placebo group was (67%), and there was no significant different in the incidence of pain between the groups receiving Lidocaine or Alfentanil (13% and 24% respectively).

The use of Alfentanil is an acceptable alternative to Lidocaine when an opioid is to be administered as part of the anaesthetic technique.

Douglas Wilkinson, Malcolm Anderson and Ian S. Gauntlett (1993) studied the effect of applying Nitroglycerine or Placebo ointment to the back of the hand before venipuncture and injection of Propofol[7]. An estimated 20 minutes before expected time of induction, a strip of ointment containing 5mg of Nitroglycerin

(active group n=28) or Placebo (Placebo group n=32) was widely applied over the back of one hand and covered by a bioocclusive dressing, when the patients arrived in the anaesthetic room, the ointment was removed and venipuncture performed using a 22-gauge cannula.

Eighteen patients (67%) pretreated with Nitroglycerin experienced no pain compared with ten patients (33%) in the Placebo group. Eleven in the Placebo group experienced moderate or severe pain compared with only one in the active group.

The results are likely due to a relative dilution of the drug, resulting from higher venous flow secondary to venodilatation.

S. Gupta, A. Ravalia and H. R. Jonnada have compared the new batch of Propofol marked by Abbott Laboratories, containing 10mg/ml Propofol as an active ingredient with soybean oil, purified egg phosphatide as egg lecithin, glycerol, sodium hydroxide and water for injection with Propofol marketed by Zeneca Limited, as Diprivan 1% containing 10mg/ml Propofol with glycerol, purified egg phosphatide, soybean oil, sodium hydroxide and water[8].

Both formulations were used, adding 1ml of 1% Lidocaine to 20ml and injected 2ml of the mixture into a vein on the dorsum of

hand by means of 20G intravenous cannula. They observed that the former formulation caused less pain on injeciton.

It is not clear as to why one formulation causes less pain. Klement and Arndt suggested that the pain is related to the concentration of Propofol in the aqueous phase and not due to the formulation, but the Propofol manufactured by Abbott has egg phosphatide as egg lacithin, which is not the case with Diprivan[9]. Whether egg lecithin reduces the incidence of pain is not known and needs further research.

W. H. Wong, K.F. Cheong, have evaluated the effect of Tramadol in reducing pain on Propofol injection[1].

The study involving 90 unpremedicated patients of ASA I, II, divided into three groups. Normal saline Placebo was given iv to patients in group I (n=30), Tramadol 50mg to group 2 (n=30) and Lignocaine 50mg to group 3 (n=30). Pain assessment was made immediately after Propofol injection. There was a significant reduction in the incidence of pain associated with Propofol administration in patients pretreatred with Lignocaine and Tramadol ($P<0.05$). Pretreatment with Tramadol was as effective as Lignocaine in reducing pain on Propofol injection.

Objectives

1. To compare the incidence of Propofol injection pain by using Labetalol as pre-treatment versus placebo.
2. To compare the incidence of Propofol injection pain with different doses of Labetalol.
3. To compare the effect of the size of the cannula on propofol injection pain.

METHODOLOGY

This study was performed in Soba University Hospital (SUH) and Khartoum Teaching Hospital (KTH) and has been done during the period from 1st of April to end of September, 2002.

The study has been approved by the Ethical Committee of the Faculty and patient verbal consent was obtained.

Inclusion Criteria:-

1. Patients of both sexes, ASA grade I or II scheduled for elective surgery.
2. Cooperative patients
3. Scheduled surgery

Exclusion Criteria:-

1. Any patient with contraindication to beta blockers.
2. Children.
3. Uncooperative patients e.g. mentally retarded, deaf.
4. ASA grade III and beyond
5. Emergency surgery

The study was conducted in a randomized, double-blind manner involving 108 Sudanese patients aged between 18-60 years old.

Patients were randomly divided into three equal groups (36 each). Group A received 5 mg labetalol, B received 10 mg labetalol, group C control group received 5 ml normal saline as placebo.

Prior to induction and upon arrival to the operating room, an iv line of different sizes ranging from 20-18 G cannula was placed in the dorsum of the hand (84% of the cases) or the lateral side of the hand (16% of the cases) of the same arm. All of them were given 1 mg atropine at induction. The patient's arm was elevated for 30 seconds before inflation of the cuff to 10 mmHg above baseline diastolic pressure. The study drug was injected and occlusion released one minute later. Propofol calculated at 2.5 mg/kg was then administered as a bolus dose and loss of verbal contact was used as a clinical sign of unconsciousness. All drugs were prepared and given by the same investigator who did not assess pain.

All patients were informed before, that propofol may cause pain on injection.

Every 10s during injection of propofol, the patients were asked by a blind second investigator if they had any discomfort in their arm. If they answered ‘yes’ they were asked if it was ‘mild’ or ‘severe’. Patients were questioned until they fell asleep.

Mild pain was defined as discomfort in the arm or hand, but which was not a cause of any distress, severe pain was based both on the patients’ comments and the presence of features such as grimacing or limb withdrawal.

Statistical analysis was performed by computer using the Statistical Package for Social Science (SPSS/PC).

Chi-square test was used for comparison of the study groups, where the variable is considered significant when the P value is less than 0.05.

RESULTS

- This study has been conducted for one hundred and eight Sudanese patients of ASA grade I and II in Khartoum Teaching Hospital (KTH) and Soba University Hospital (SUH) during the period from 1st of April to the end of September, 2002.
- The majority (34%) were of the age group from 21-30 years old (Fig.1).
- Females were (84%), (16%) were males (Fig. 2).
- Most of the operations (68%) were major operations, while the rest (32%) were minor operations (Fig. 3).
- Different sizes of cannulae have been used, (49%) were of size 20 G, (51%) were of size 18 G, others sizes were not used (Fig. 4).
- Different sites of cannulae were used, the majority (84 %) were at the dorsum of the hand, while (16%) were at the lateral side of the hand, other sites were not used (Fig. 5).
- Patients were randomly divided into three equal groups (36 each). Group A received 5 mg Labetalol, group B received 10 mg Labetalol, group C control group received 5 ml normal saline as placebo.

- The incidence and grade of pain on Propofol injection (verbal and behaviour) was found to be the same.
- In group A (n=36), (75%) did not experience any pain, (25%) have mild pain and no one has severe pain (Fig. 6, Table I).
- In group B (n=36), (86%) did not experience any pain, (14%) have mild pain and no one has severe pain (Fig.6, Table I).
- In the control group (n=36), (61%) have no pain, (22%) have mild pain and (17%) have severe pain, so Labetalol has been found to reduce post Propofol injection pain significantly ($P<0.01$) (Fig. 6, Table I).
- The incidence of Propofol injection pain was studied in relation to the size of the cannula in each group.
- In group A (n=36), the highest incidence of pain (mild pain) was found with the 20 G cannula (31%), compared with (22%) with 18 G, those who have no pain with size 18 G were more than those with size 20 G cannula (78%) and (69%) respectively (Fig. 7, Table II).
- With both sizes of cannulae no severe pain was experienced (Fig.7, Table II).

- This results was found to be insignificant (p>0.1) (Table II).
- In group B (n=36), the highest incidence of pain (mild pain) was found with the 20G cannula (24%), compared with (0%) with 18G cannula, those who have no pain with size 18G were (100%), and those with size 20G were (76%), in both sizes no severe pain was experienced (Fig. 8, Table III).
- This result was found to be significant (P<0.05) (Table III).
- In group C (n=36), the highest incidence of pain (mild pain) was found with the 20G cannula (26%), compared with (12%) with size 18G cannula (Fig. 9, Table IV).
- The incidence of severe pain with size 18 G cannula was found to be slightly higher (23%) than with the 20 G cannula (21%) (Fig. 9, Table IV).
- Those who have no pain with size 18G were more (65%) than those with size 20G cannula (53%) (Fig. 9, Table IV).
- This result was found to be insignificant (P>0.1) (Table IV).

- The incidence of propofol injection pain (both mild and severe) was studied in relation to the size of the cannula for the whole patients (all groups) in the study (Table V).
- The incidence of pain when using cannula size 20 G was found to be (34%), while it was reduced to (20%) when using a large size of cannula 18 G (Fig. 10, Table V).
- When using cannula size 20 G (66%) of the patients experienced no pain, while this percentage was raised to (80%) when using a large size of cannula 18 G (Fig. 10, Table V).
- The size of the cannula affects the incidence of post propofol injection pain, and this pain will significantly be reduced if a large size cannula has been used ($P<0.005$) (Table V).

TABLE I:

Incidence and grade of pain on Propofol injection

(verbal and behaviour)

Group	No	Pain (No & %)		
		None	**Mild**	**Severe**
A Labetalol 5mg	36	27 (75%)	9 (25%)	0 (0%)
B Labetalol 10mg	36	31 (86%)	5 (14%)	0 (0%)
C Placebo (NS)	36	22 (61%)	8 (22%)	6 (17%)

P < 0.01 (Significant)

TABLE II:

Percentage of incidence of Propofol injection pain in Relation to the sizes of cannulae using Labetalol (5mg) as a pretreatment

Group A

Size of cannula	Pain (No & %)		
	None	**Mild**	**Severe**
20G (n=13)	9 (69%)	4 (31%)	0 (0%)
18G (n=23)	18 (78 %)	5 (22%)	0 (0%)

P > 0.1 (not significant)

TABLE III:

Percentage of incidence of Propofol injection pain in relation To the sizes of cannulae using Labetalol (10 mg) as a pretreatment

Group B

Size of cannula	Pain (No & %)		
	None	**Mild**	**Severe**
20G (n=21)	16 (76%)	5 (24%)	0(0%)
18G (n=15)	15 (100%)	0(0%)	0(0%)

P < 0.05 (significant)

TABLE IV:

Percentage of incidence of Propofol injection pain in relation to the sizes of cannulae using normal saline as a placebo Group C

Size of cannula	Pain (No & %)		
	None	**Mild**	**Severe**
20G (n=19)	10 (53%)	5 (26%)	4 (21%)
18G (n=15)	11 (65%)	2 (12%)	4 (23%)

P > 0.1 (not significant)

TABLE V:

Percentage of incidence of Propofol injection pain (mild + severe) in relation to the sizes of cannulae (All groups)

Size of cannula	Pain	Group A	Group B	Group C	**Total No**	%
20 G	No Yes	9 4	16 5	10 9	35 18	66% 34%

18 G	No Yes	18 5	15 0	11 6	44 11	80% 20%

P < 0.005 (Significant)

nn

pp

bb

SS

tt

DISCUSSION

This study evaluated the effect of Labetalol in a randomized double-blind way on post-Propofol injection pain. Labetalol 5 mg was given intravenously to patients in group A (n=36), 10 mg of Labetalol was given to patients in group B (n=36), and normal saline 5 ml was given to patients in group C (n=36).

In this study it was found that Labetalol provided pain free Propofol injection in about (75% - 86%) of patients pre-treated with it in groups A and B respectively, and it was a significant result ($P<0.01$) (Fig. 6, Table I).

Many methods have been used to reduce the incidence and severity of post-Propofol injection pain.

Results obtained from a study conducted by A. Khalid and M. Maroof (1996) were almost similar to these results[5]. They performed the study on three groups of patients, group A received 5mg Labetalol, B received 10 mg Labetalol and group C received 5 ml normal saline as pre-treatment. They found that Labetalol significantly reduced Propofol injection pain ($P<0.05$), and the incidence of free pain was about (80-83%) of patients pre-treated with it.

In our study in both groups A and B there was no severe pain experienced by any patient, which is the same result obtained by the previous study. In our study the incidence of severe pain in group C (control group) was (17%), in the previous study it was higher (27%) (Fig. 6, Table I).

In both studies the same drug (Labetalol) was used as pre-treatment, while the differences between them that we used two different sizes of cannula (20 G – 18 G) and two different sites of injection were used, the dorsum of the hand and the lateral side of the hand, and for occlusion of the venous drainage sphygmomanometer cuff was used and inflated to 10 mmHg above baseline diastolic pressure, while in Khalid and Maroof

study only size 20 G cannula was used on the dorsum of the hand while venous drainage was occluded manually at mid forearm.

In our study the size of the cannula was found to be affecting the incidence of Propofol injection pain, and this incidence was reduced from (34%) when using cannula size 20 G to (20%) when using cannula size 18 G, so using a large size cannula is reducing the incidence of Propofol injection pain significantly ($P < 0.005$) (Fig. 10, Table V).

In another study conducted by JE Fletcher, CR Seavell and DJ Bowen (1994), they studied the effect of pre-treatment of Alfentanil in reducing Propofol injection pain[(2)]. Fourty four patients were divided into 2 groups, group1 received Alfentanil 1 mg (2ml) iv followed 15 s later by Propofol iv, patients in group 2 received 2 ml of normal saline as a polacebo. All drugs were administered through 22 G cannula on the dorsum of the hand. In this study conducted by JE Fletcher the incidence of Propofol injection pain (mild and severe) was (84%) when no Alfentanil was given, and this declined to (36%) when Alfentanil preceded Propofol, so it was found that Alfentanil pre-treatment reduced pin on injection of Propofol significantly ($P=0.001$). In Fletcher's study the incidence of severe pain in the group of patients pre-treated with Alfentanil was (4%) compared to (41%) with the group

received normal saline. The differences between Fletcher's study and ours lie in the study drug (Alfentanil vs Labetalol) and the time of tourniquet applied (one minute), in Fletcher's study tourniquet was not used and the interval between the administration of Alfentanil and Propofol was only 15 s, and small size cannula 22 G was used.

In a study conducted by Douglas Wilkinson, Malcolm Anderson and Ian S Gauntlett (1993), they studied the effect of applying nitroglycerine or placebo ointment to the back of the hand before venipuncture and injection of Propofol, cannula size 22 G was used[7]. Significantly more patients (67%) in the nitroglycerine group were free of pain on injection compared with the placebo group (33%) ($P<0.05$). The incidence of moderate or severe pain in the active group was (4%), whereas (37%) of the patients in the placebo group had moderate or severe pain ($P<0.05$). Application of nitroglycerine ointment over the venipuncture site may also facilitate venipuncture[10,11]. This result is close to our result, when using small size cannula 20 G (66%) of patients were free of Profofol injection pain, while when using a large size cannula 18 G (80%) of the patients experienced no pain on injection of Propofol ($P <0.005$) (Fig. 10, Table V).

WH Wong, KF Cheong have evaluated the effect of Tramadol in reducing Propofol injection pain[1]. The patients were divided into 3 groups, in group 1 normal saline was given as placebo, Tramadol 50 mg was given to group 2, and Lignocaine 50 mg to group 3. Tourniquet was applied at the forearm for 1 minute. In the group of patients pre-treated with Tramadol (70%) of them experienced no Propofol injection pain, while in the Lignocaine group (73%) of the patients experienced no pain and this incidence was only (17%) in the placebo group.

Severe pain occurred in (43%) in the placebo group as compared to (3%) in the Tramadol group and nil in the Lignocaine group. There was a significant reduction in the incidence of pain associated with Propofol administration in patients pre-treated with Tramadol and Lignocaine ($P<0.05$). There is no significant difference in the incidence of pain between the Tramadol and Lignocaine groups, in addition to the possibility of Tramadol providing good analgesia for mild to moderate peri-operative pain[12,13].

In our study there were no clinically important problems attributable to Labetalol observed, as occluding venous drainage before Labetalol injection allows it to act locally while systemic effect is avoided. Labetalol may be a useful agent in addition to other drugs used to reduce Propofol injection pain, especially when its use will be continued as for hypotensive anaesthesia.

CONCLUSION

From this study it is concluded that:-

1. The use of Labetalol as a pretreatment to Propofol injection reduces the pain experienced by most patients.
2. Using high dose (10 mg) of Labetalol significantly reduces this type of pain compared with small dose (5 mg).
3. Using large size of cannula with Labetalol (10 mg) will reduce that pain significantly.
4. The pain experienced by the patients when using Labetalol 5 mg or 10 mg was mild pain, there was no severe pain experience.
5. With normal saline as a placebo the incidence of severe pain is high.

6. The size of the cannula affects the incidence of propofol injection pain, and this pain will significantly be reduced if a large size cannula is used.

RECOMMENDATIONS

1. It is recommended to use Labetalol intravenously as a pretreatment to intravenous Propofol.
2. Labetalol 10mg is better than 5mg in reducing Propofol injection pain and is recommended.
3. A large size cannula is recommended (18 G or more) as it reduces the Propofol injection pain significantly.

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