ORIGINAL RESEARCH

Effect of Nitroglycerine on Pain Caused by Intravenous Propofol Injection-Comparison with 0.9% Normal Saline

Rampal Singh[1], Gopal Krishan[2], Malti Agarwal[3], Lakhwinder Singh Kang[4], Vertika Singh[5], ABL Bhatnagar[5]

ABSTRACT

Introduction: Now a days propofol is being used very frequently for induction of general anaesthesia but often results in pain on injection, which is sometimes very painful which may cause discomfort to patient. This randomized clinical study was performed to evaluate the effects of intravenous nitroglycerine on pain severity in patients undergoing propofol injection.

Material and Methods: In this randomized control study, 100 patients with ASA class I or II, aged 18-50 years undergoing anaesthesia with propofol injection were selected for the study. Patients were randomly assigned to case (Group A) and control (Group B) groups and received either 20µg five mililitre (ml) of nitroglycerine or 0.9% (five ml) normal saline as placebo respectively. The severity of injection pain was assessed using a four-point scale.

Results: The pain severity in nitroglycerine group was significantly lower as compared with the placebo group (P<0.001). The homodynamic parameters showed no significant difference between two groups before and after the induction of anaesthesia.

Conclusion: Nitroglycerine when given intravenously before induction with propofol, causes significant pain reduction. It is safe and without side effects so it can be used for reduction of pain caused by propofol injection.

Keywords: Propofol; Nitroglycerine; Pain

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[1]Associate Professor, [2]Assistant Professor, [3]Professor and Head, [4]Professor, [5]Senior Resident, Department of Anaesthesia and Critical Care, Rohilkhand Medical College, Bareilly, uttar Pradesh, India.

Corresponding author: Dr Rampal Singh, Associate Professor, Department of Anesthesiology and Critical Care, Rohilkhand Medical College and Hospital, Pilibhit Bypass Road, Bareilly, uttar Pradesh, India

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INTRODUCTION

Since the introduction of propofol in 1977, it has been widely used as an intravenous anaesthetic agent but it causes severe pain on injection specially if given in a small vein.[1-4] Many pharmacological and non pharmacological methods have been used to prevent this pain.[5-14] The objective of this study was to evaluate the effect of nitroglycerine on pain severity in patients undergoing propofol induction.

MATERIAL AND METHOD

This randomized control study was conducted in department of anaesthesiology and critical care, Rohilkhand medical college and hospital. The sample size of 70 was calculated with the help of following formula:

$$\text{Sample Size} = \frac{Z^{2*}(p)^{*}(1\text{-}p)}{c^2}$$

Where Z = Z value (e.g., 1.96 for 95% confidence level), p=percentage picking a choice, expressed as decimal (0.5 used for sample size needed), c = confidence interval, expressed as decimal, (e.g., 0.04 = ± 4). To be more precise, the final sample size was decided to be 100 (50 in each group). A total 115 patients of American Society of Anaesthesiologist (ASA) class I and II, age between 18 to 50 years, were selected from surgery department posted for surgical procedures under general anaesthesia. 15 of these patients were excluded according to exclusion criteria and the remaining 100 patients were randomly selected. None of the participants had any history of receiving analgesia or sedation within last 24 hours. None of the selected patients had contraindications for nitroglycerine use. Informed written consent was obtained from all participants. Patients were randomly allocated to case (Group A) and control (Group B) groups using the computer generated random number table. Without any premedication after the applying of electrocardiogram, non-invasive blood pressure (systolic, diastolic and mean arterial pressure) and pulse oximetry for monitoring, two 20G cannulas were inserted into the dorsal vein of both hands. The right one was used for infusion of intravenous fluids and the left one was used for drug administration. Infusion of ringer lactate was started from right arm. Patients in the Group A received 20µg of nitroglycerine, diluted in five mL of 0.9% saline from the left arm in five seconds. We choose 20µg of nitroglycerine to achieve our goal, the local effects of nitroglycerine without any sever hemodynamic

effect such as sever tachycardia and hypotension. In many previous studies on nitroglycerine dosage, using 20µg of nitroglycerine intravenously did not cause any severe homodynamic effects. Patients in the control group received five mL of 0.9% saline from left arm in five seconds. Propofol bolus in dose of 1.5mg/kg was given after 20 seconds which was kept at room temperature which was administered over a period of five seconds. Any behavioural signs such as facial grimacing, arm withdrawal or tears were noted and recorded by the anaesthesiologist. Then pain on injection was assessed using a four-point scale as used by Pooya Derakhshan et al.: 'zero' for no pain, 'one' for mild pain (pain only in response to questioning and without any behavioural signs), 'two' for moderate pain (pain reported spontaneously without questioning), and 'three' for severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears).[15] For muscle relaxation, we used vecuronium bromide (0.12mg/kg). Systolic and diastolic blood pressures and heart rate were recorded 30seconds later. Oral intubation of the trachea was done three minutes after administration of vecuronium. Anaesthesia was continued with 30% oxygen, 70% nitrous oxide and 0.4% isoflurane. Within recovery period, the left hand was examined for pain, oedema, or other reactions by the anaesthesiologist. The age, sex, weight, homodynamic status (systolic and diastolic blood pressures and heart rate), drug adverse effects and pain severity were the study variables. Data was analyzed using SPSS 18.0 (SPSS Inc, Chicago, Illinois, United States). Differences were tested by independent-sample t test, Fisher exact test, and Chi square test and were considered statistically significant at *P*-value < 0.05.

RESULTS

Table one shows that two groups were comparable in the terms of Age, Gender, Weight and ASA Grade as shown in the above table and no statistically significant difference was found, *p*-value >0.05.

Para meters	Group A	Group B	*p*-value
Age (Years)	3 5.58±12.74	41.9±14.09	0.582
Weight (Kg)	56.1±8.85	56.7±9.10	0.750
Gender (M/F)	22/28	25/25	0.361
ASA (I/II)	36/14	39/11	0.320

Table-1: Demographic data

Table two and figure one shows no significant difference in blood pressure and pulse rate between two groups before and after induction. Table three and figure two shows that the pain severity in nitroglycerine group was significantly low in comparison with the control group (p<0.001).

DISCUSSION

The cause of the pain felt on intravenous injection of various drugs is not known. Klement and Arndt have suggested that it may be due to unphysiologic osmolality or pH of their formulation, but this should not apply to the commercially available solution of propofol which has near physiologic pH and osmolality.[16] Scott et al. have suggested that pain may be induced by a kinin cascade, although they base their theory not on any specific physiologic data but only on the observation that there can be a delayed onset to the pain.[17] Our data confirm the findings of others that the onset of pain may be either immediate or delayed. Like others, we also were able to demonstrate good correlation between pain felt at the time of injection and later recall. Hiroshi et al. have suggested that pain on propofol injection is due to presence of long and medium chain triglycerides.[18]

Our results show that pain on injection of propofol can be reduced by giving injection nitroglycerine 20µg, 20 seconds before injection of propofol. It was investigated in 100 patients of ASA classes I and II. The patients in group A developed less or no pain during the propofol injection which can be explained by the fact that released nitroglycerine (NO), activates soluble guanylyl cyclase and produces cyclic GMP from guanosine triphosphate in smooth muscle cells. Accumulation of cyclic GMP activates cyclic GMP-dependent protein kinase, which is involved in the opening of adenosine triphosphate (ATP)-sensitive K^+ channel, to produce spinal or peripheral antinociception and in Na^+/K^+-ATPase activation.[18] According to Mixcoatl-Zecuatl T et al. nitroglycerine also results in vasodilatation, decreased vascular resistance, lower blood pressure, inhibition of platelet aggregation and adhesion, inhibition of leukocyte adhesion and transmigration, and reduced vascular smooth muscle proliferation. Nitric oxide has an important role in afferent signalling of pain through the dorsal horn of the spinal cord and in autonomic control through nitrergic innervation. Release of NO from the peripheral endings of spinal afferents can stimulate many of their homeostatic actions. Moreover, NO generators have

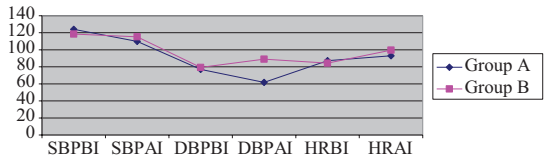
Homodynamic variabls	Group A	Group B	*P*-value
SBP[1] before induction mm Hg	124.06±13.08	118.42±6.88	0.707
SBP after induction mm Hg	109.82±15.43	115.24±14.81	0.123
DBP[2] before induction mm Hg	76.92±9.15	79.42±10.26	0.814
DBP after induction mm Hg	61.82±6.28	89.0±8.63	0.134
HR[3] (beats/minute) before induction	87.22±10.12	84.32±7.77	0.067
HR (beats/minute) after induction	93.06±10.12	99.62±8.57	0.758

1. SBP=systolic blood pressure, 2. DBP=diastolic blood pressure, 3. HR=heart rate

Table-2: Hemodynamic status

Pain severity	Group A	Group B	*P*-value
None	49	1	<0.001
Mild	1	3	-
Moderate	0	3	-
Severe	0	43	-

Table-3: Pain severity



SBPBI=sytolic blood pressure before induction, SBPAI= sytolic blood pressure after induction, DBPBI= diastolic blood pressure before induction, DBPAI= diastolic blood pressure after induction, HRBI=heart rate before induction, HRAI=heart rate after induction

Figure-1: Line Diagram Showing Comparision Of Hemodynamic Changes Between Group A and Group B

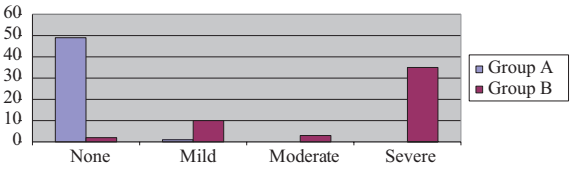


Figure-2: Bar Diagram showing comparision of pain severity between group A and group B

anti-inflammatory effects by blocking the neurogenic component of inflammatory oedema when used topically.[19] We believe that our results were likely due to a relative dilution of the drug, resulting in a higher venous flow secondary to vasodilatation.

Wilkinson D et al. described that pain of propofol injection can be reduced by application of nitroglycerine ointment on dorsum of hand.[20-21]

Moreover nitroglycerine has analgesic property itself. Sen S et al., Higa M et al., Lauretti et al., Berrazueta JR et al., Siamdoust SAR et al. also described the analgesic property of nitroglycerine.[22-27]

Likewise, Turan et al. suggested the application of transdermal nitroglycerine for reduction of pain severity of propofol injection.[28] However, O'hara et al. demonstrated that in comparison to nitroglycerine ointment to the back of the hand overlying the site of drug injection, lidocaine is associated with a decreased incidence of propofol induced pain.[29]

In our study instead of using topical nitroglycerine, we used intravenous nitroglycerine and found a significant pain reduction after propofol injection which may be due to its direct vasodilatation effect on intravenous administration. We therefore postulated that vein size, vasospasm, and perhaps blood flow might be important in determining painful injections. We believe that our results are likely due to a relative dilution of the drug, resulting from higher venous flow secondary to vasodilatation. This is consistent with the observation that diluting propofol reduces pain and supports the suggestion that reducing drug contact with the vessel wall makes pain less likely.

Singh DK et al. demonstrated vasodilating properties of nitroglycerine and advocated its use to facilitate venipuncture and postulated that nitroglycerine reduces pain on injection by vasodilatation leading to a relative dilution of the drug. He also concluded that granisetron, nitroglycerine, and magnesium sulphate were consecutively the most effective drugs in attenuating pain of intravenously injected propofol.[30]

Lohmann et al. demonstrated dilation of the vein by more than 50% in over half the subjects treated with nitroglycerine ointment within 15 min of application.[31]

Pooya et al. also concluded that nitroglycerine may be a safe and effective adjuvant for pain reduction in patients under propofol injection.[32]

Although premedication has not been shown to reduce the incidence of painful injection with propofol, it can reduce its severity. In our practice we have observed that patients who are anxious and have cold venoconstricted hands appear more likely to complain of painful injection. It is this group of anxious, unpremedicate patients who are most likely to receive propofol, which is widely used in ambulatory surgery. To assess the effectiveness of nitroglycerine in reducing propofol injection pain relative to other techniques, we compared our results with previous studies. The results of these studies are not directly comparable because, for example, there are differences in the percentage of placebo patients feeling no pain in the different studies. The patient populations are likely to be different, and some studies include premedication whereas others do not. However, our results indicate that a comparably high percentage of treated patients do not feel pain on injection with propofol. Further studies are required to directly compare the efficacy of nitroglycerine with that of lidocaine.

CONCLUSION

The use of intravenous nitroglycerine injection may improve analgesic effects without any sever hemodynamic consequences and additional adverse effects. Hence, its use to reduce the propofol injection-induced pain can be recommended.

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