Ambient Science, 2018: Vol. 05(Sp1); 117-121
DOI:10.21276/ambi.2018.05.sp1.ra15

Published by: National Cave Research and Protection Organization, India

ambient SCIENCE
Vol. 05(Sp1):117-121
Year 2018

RESEARCH ARTICLE

Prophylactic Effect of Intravenous Administration of Sufentanil on Propofol Injection Pain

Hashem Jarineshin[1], Mehrdad Malekshoar[1], Majid Vatankhah[1]*, MaryamFarbodi[2]

[1]Department of Anesthesiology, Critical Care and Pain Management Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

[1]Critical Care and Pain Management Research Center Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

Study Area: Bandar Abbas, Iran
Coordinates: 27°11'N; 56°16'E

Key words: Systolic and diastolic blood pressures, Mean arterial pressure, heart beat

the ethics committee of Hormozgan University of Medical Sciences approved the project under the code HUMS.REC.1394.61.

Abstract

In most of the patients, propofol caused pain or discomfort during injection. Injection of various intravenous drugs prior to propofol is one of the methods for relieving propofol-induced pain. Different sources suggested unclear and confounding results on the effect of Sufentanil injection on the pain from propofol. Prophylactic effect of sufentanil on the severity of pain from propofol injection was investigated in this double-blind study in which 118 relevant patients have participated. The patients were randomly given 5 micrograms of Sufentanil to 59 patients and normal Saline to the remaining 59 ones. Pain severity, systolic and diastolic blood pressures, mean arterial pressure and heart beat rate were measured before and after propofol injection. The pain during injection was found to be significantly lower in the Sufentanil group. Sufentanil also reduced systolic and diastolic blood pressures, mean arterial pressure and heart rate.

Introduction:

Effective pain management is one of the important factors in preoperative and postoperative care. Despite many alterations and advancement in pain management issues, patients still suffer from moderate to severe inoperative and postoperative pain (Ellett, 2010). Propofol is an intravenous anesthetic drug widely used in outpatient and short-duration surgeries due to rapid recovery. However, pain due to the injection reported causing discomfort in 45-75% of patients. The pain from Propofol injection was ranked 7th in 33 common clinical anesthesia outcomes. The severity of this pain was reported to be 5.9 ± 3.2 in the Visual Analogue Scale (VAS; 0-10), which established an example of severe pain (Lindholm *et al.*, 2013). Till date several methods have been used to reduce pain during propofol injection including variations in injection speeds, fluid administration, dilution of the analgesic, cooling down and warming the medication, various formulation of the analgesic, cooling down the organs, administering local nitroglycerin at the injection site, injection of propofol in large veins and injection of various intravenous medications prior to propofol such as lidocaine, ondansetron, opiates, metoclopramide, and magnesium sulfate (Singh *et al.*, 2014; Ahmad *et al.*, 2013; Honarmand & Safavi, 2008). Administration of Opiates (alfentanil and fentanyl) was reported to be an effective pain management measure (Rahman *et al.*, 2007). Remifentanil is a new opiate with rapid action onset but lasting for short duration. Analgesic effect of this opioid in preventing propofol injection pain has been previously studied. Sufentanil is an opioid, which is more efficacious than Remifentanil and decreases blood pressure and heart rate less than Remifentanil (Honarmand & Safavi, 2008). On a review, Chung *et al.* (2011) reported that the effect of Sufentanil administration prior to propofol on injection pain was not known then. The pain during propofol injection is still a major clinical issue (Borazan et al., 2012). Considering the confounding outputs of the previous studies and estimating the greater efficacy of Sufentanil reveal less decrease in heart rate and blood pressure compared to other similar opioids, we aimed to design a randomized double-blind placebo-controlled trial to investigate prophylactic effect of Sufentanil on the incidence and severity of pain during propofol injection in comparison with normal saline.

Methodology:

We conducted a double-blind study on 118 patients with ASA I and II having age between 18 to 65 years old, visited Shahid Mohammadi Hospital, Bandar Abbas in 2015. All the participants were eligible for the study as per the inclusion criteria. Participants were randomly divided into test and control groups by the project executive without telling us. Exclusion criteria were sensitivity to

*Corresponding Author: hormozgan91@yahoo.com

ISSN- 2348 5191 (Print) & 2348 8980 (Electronic)

Ambient Science, 2018: Vol. 05(Sp1); 117-121
DOI:10.21276/ambi.2018.05.sp1.ra15

Propofol and Sufentanil, uncooperative patients and incapability to communicate with the research team, comorbidities such as diabetes, hepatic disorders, cardiovascular disorders, alcohol-related diseases, opiate addiction (oral and injection abuse), chronic pain syndromes and thrombophlebitis, intake of any analgesic and anesthetic, people over 65 years of age and unwillingness to participate in the study. The participants were selected using simple random sampling method and a random number table. The sample size was followed as per the previous studies (Honarmand & Safavi, 2009; Kazemnejad *et al*., 2008) and calculated using the prescribed formula used by Honarmand & Safavi, (2009). Accordingly, 59 people were included in each treatment group.

Data collection tool was a questionnaire consisting of particulars on demographic variables (age, gender, and weight), ASA class and pain severity (the main variable). Informed consent forms were obtained from the patients in the preoperative anesthetic visit. The project procedure and verbal rating of pain severity from Propofol injection were explained to the patients. Verbal description of the patients was scored based on the four-point scale of Ambesh *et al*. (1999) as follows: 0: No pain (negative response to the investigator); 1: Mild pain (reported pain in response to the investigator without behavioral symptoms); 2: Moderate pain (reported pain in response to the investigator with behavioral symptoms or a reported spontaneous pain with behavioral symptoms but reported without asking the patient); 3: Severe pain (reported pain in response to the investigator as a strong verbal response along with wincing, raising and moving the arm or teary eyes). The participants for the study were selected on the random number table using the Random Allocation Software from those patients candidates who went through surgery. They were divided into two groups (Group A: sufentanil, manufactured by the Rockettes Medica in Germany and Group B: physiologic normal saline manufactured by Samen Company in Mashhad). The patients were transferred to the operating room beds. The catheter was inserted into the peripheral vein in the back of the hand using the catheter no. 20 (preferably non-dominant hand). The serum containing Ringer's solutions (the amount of fluid prescribed for the patient) was given to the patients. Non-invasive blood pressure, electrocardiogram, arterial oxygen saturation were measured and monitored in the operating room. Baseline hemodynamic variables (systolic blood pressure, diastolic blood pressure, mean arterial pressure and heart rate) were measured and recorded. Studied medications were diluted using normal saline by the anesthetist at the room temperature at equal volumes (5 ml). The syringe was labeled as A or B based on the studied groups. The desired medication (Group A: 5µg sufentanil diluted with normal saline to 5 ml; Group B: 5 ml normal saline) was injected to the patient in 5 seconds by an investigator or the anesthetist who was aware of the type of medication (to treat the patient in case of any complication). After 30 seconds, 3 ml of propofol 1% (manufactured by Teda Company in India) was injected into the vein (equivalent to 30 mg) at a rate of 0.5 ml per second. The injection was carried out by an anesthetist other than the investigator (who was not informed of the type of medication). We explicitly asked the patient about his pain or discomfort at the injection site and specified the patient's response as yes or no in the questionnaire. The pain severity was recorded in the questionnaire based on verbal descriptions. Baseline hemodynamic variables (systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate) were also measured and recorded after the injection. The general anesthesia procedure was continued (induction with propofol at 2 mg/kg, mask ventilation of the lungs, administration of inhaled anesthetic or other opiates if necessary). Data were analyzed using SPSS v.18. Descriptive statistics were used to describe the collected data. Pearson correlation, chi-square, t-test and nonparametric tests (if necessary) were used for data analysis.

Results:

Comparative demographic parameters of the patients from both the group are presented in Table-1 which revealed no statistically significant difference.

Table-1: Demographic characteristics of patients

Variable	Group		p-value
	Test (Sufentanil)	Control (N. Saline)	
Age	32.59±11.90	34.27±9.09	≥0.096*
Male	61% (n = 36)	61% (n = 36)	..
Female	39% (n = 23)	39% (n = 23)	≥1.000*
Weight (kg)	59.46±15.73	63.64±11.09	≥0.064*
ASA-I	79.7% (n = 47)	91.5% (n = 54)	..
ASA-II	20.3% (n= 12)	8.5% (n = 5)	≥0.066*

*Statistically not significant

One patient (1.7%) in the Sufentanil group and three patients (5.1%) in the normal saline group suffered from pain before the injection. Fisher's exact test results showed no statistically significant difference in pain variable before injection between the two groups.

Table-2: Investigation and comparison of pre-injection pain in two groups (Fisher's exact test, p value ≥0.619)

Parameter			Pre-injection pain		Total
			Yes	No	
Group:	Sufentanil	N	1	58	59
		%	1.7	98.3	100
	Normal saline	N	3	56	59
		%	5.1	94.9	100
Total		N	114	118	
		%	3.4	96.6	100

Ambient Science, 2018: Vol. 05(Sp1); 117-121
DOI:10.21276/ambi.2018.05.sp1.ra15

In our study, the post-injection pain between the two groups revealed a significant difference ($p < 0.001$). All the patients felt pain in the normal saline group but only 64.4% of the patients felt pain belonging to the sufentanil group.

Table-3: Investigation and comparison of post-injection pain in two groups. (X2 test- 25.546; p value- >0.001)

Parameter			Pre-injection pain		Total
			Yes	No	
Group:	Sufentanil	N	38	21	59
		%	64.4	35.6	100
	Normal saline	N	59	0	59
		%	100	0	100
Total		N	97	21	118
		%	82.2	17.8	100

Chi-square test results showed a statistically significant difference in post-injection pain severity between the two groups ($p < 0.001$). Accordingly, 1.7% felt mild pain, 35.6% felt moderate pain and 62.7% felt severe pain in the normal saline group. However, 71.1% felt mild pain, 28.9% felt moderate pain and none of the patients experienced severe pain in the Sufentanil group.

Table-4: Investigation and comparison of post-injection pain in two groups. (X2 test- 62.658; p value- >0.001)

Parameter			Pain Severity			Total
			Mild	Moderate	Severe	
Group:	Sufentanil	N	27	11	0	38
		%	71.1	28.9	0	100
	Normal saline	N	1	21	37	59
		%	1.7	35.6	62.7	100
Total		N	28	32	37	97
		%	28.9	33	38.1	100

There was no significant difference in systolic blood pressure before the injection between the two groups ($p \geq 0.15$), a significant difference in systolic blood pressure after the injection between the two groups ($p < 0.009$) was seen. The Wilcoxon signed-rank test results showed a significant difference in mean systolic blood pressure before and after the injection in the Sufentanil group ($p < 0.001$). There was no significant difference in mean systolic blood pressure before and after the injection in the normal saline group ($p \geq 0.186$). There was no significant difference in diastolic blood pressure before the injection between the two groups ($p \geq 0.618$) but, it differed between the two groups significantly after the injection ($p < 0.001$). The Wilcoxon signed-rank test results showed a significant difference in mean diastolic blood pressure before and after the injection in the sufentanil group ($p < 0.001$). There was also seen a significant difference in mean diastolic blood pressure before and after the injection in the normal saline group ($p < 0.001$). Injection of Propofol significantly decreased diastolic blood pressure in both the groups but a greater decrease in diastolic blood pressure was reported in the Sufentanil group than in the normal saline group. There was no significant difference in mean arterial pressure before the injection between the two groups ($p \geq 0.305$). However, there was a significant difference between the two groups in terms of mean arterial pressure after the injection ($p < 0.001$). The Wilcoxon signed-rank test results showed a significant difference in mean blood pressure before and after the injection in the Sufentanil group ($p < 0.001$). There was also a significant difference in mean blood pressure before and after the injection in the normal saline group ($p < 0.032$). Sufentanil significantly reduced mean arterial pressure after propofol injection. There was no significant difference in heart rate before the injection between the two groups ($p \geq 0.717$) but, there was a significant difference in heart rate after the injection between the two groups ($p < 0.001$). The Wilcoxon signed-rank test results showed no significant difference in mean heart rate before and after the injection in the sufentanil group ($p > 0.116$). There was a significant difference in mean heart rate before and after the injection in the normal saline group ($p < 0.001$). Less increase in heart rate was reported in the Sufentanil group than in the normal saline group after Propofol injection.

Discussion:

Propofol is a popular intravenous anesthetic, a fast and reliable for inducing anesthesia and recovery rapidly. Unfortunately, Propofol injection even causes pain and discomfort in patients (Tekye *et al.*, 2006). Sufentanil is an opioid analgesic the effect of which in preventing pain during Propofol injection has not been well understood. Prevention of pain during Propofol injection has been investigated in this study by applying Sufentanil and normal saline. No significant difference between the two groups in terms of demographic variables. The patients were matched in terms of ASA I and II to prevent; (i) the possible clinical impact of a complicated systemic disorder on pain assessment; (ii) the potential adverse effects of Propofol injection on patients with higher ASA class; (iii) observance of ethical issues during the project. Patients with ASA I and II were also selected in similar studies (Honarmand & Safavi, 2008; Tekye *et al.*, 2006; Sadri *et al.*, 2003). The same age group was also selected to avoid bias in data analysis. The same number of men and women was also selected in both groups in this study. This issue was somehow considered in previous studies. Propofol is formulated with long-chain triglycerides in most cases. Several mechanisms have been proposed for the initiation of pain during Propofol injection but some studies have shown that Propofol free concentrations in the aqueous phase may be the most crucial factor for causing pain. Medium chain triglycerides (MCT) and high chain triglyceride (LCT) emulsions have pharmacologically less Propofol free concentrations in the aqueous phase

Ambient Science, 2018: Vol. 05(Sp1); 117-121
DOI:10.21276/ambi.2018.05.sp1.ra15

compared to standard propofol. Various studies reported a high incidence of pain in case of MCT and LCT formulation of Propofol (28% -37%) (Skla, 1997). Rau *et al.* (2001) acknowledged the same. Total 37.8% of the patients were painless and no patient experienced severe pain. Pain during injection was not a serious complication during anesthesia induction but it causes discomfort during anesthesia (Redhead *et al.*, 2005). Different studies have suggested preventing pain during Propofol injection. However, it is difficult to discuss and compare pain severity due to the involvement of various other factors which were usually overlooked. The highest prevalence of pain during propofol injection was 100% in the control group and 64.4% in the Sufentanil group. This was somehow similar to the experience of pain with the administration of 40 mg Lidocaine before Propofol injection in other studies (76.7%) (Honarmand & Safavi, 2008). Song *et al*. (2004) administered 0.1µg/kg Sufentanil prior to Diprivan injection (standard propofol) and Ampofol (a lower-lipid propofol emulsion) and reported the prevalence of pain as 6% and 26% for such two propofol respectively. However, our study differs in several ways from the other studies.

Song *et al*. (2004) induced anesthesia using 0.1 mg/kg sufentanil and/or 1µg / kg intravenous Fentanyl while injecting 2 mg/kg intravenous propofol. They measured the pain severity during propofol injection by using a 4-point pain scale (0 = painless, 1 = mild, 2 = moderate, 3 = severe) at every 5-10 seconds until complete anesthesia induction. However, the pain severity was measured using the four-point scale in the present study was based on behavioral responses to pain (Ambesh *et al.*, 1999). This differences in the protocol didn't justify to compare our results with them. In our study, the feeling of pain from propofol injection was significantly lower in the Sufentanil group as compared to the control group. This result has strengthened the results of Zhang *et al.* (2014), Chung *et al*. (2011) and Sadri *et al.* (2003). The prevalence of pain st6udied by Zhang *et al*. (2014) in the Sufentanil group was 34.5% and by Chung *et al*. (2011) was 22.2%, which were both significantly lower than their respective control groups. This finding contradicts the findings of Safavi et al. (Honarmand & Safavi, 2008) who believed that Sufentanil was inefficacious in relieving pain.

Although 5µg dose of Sufentanil was administered in this study, 10µg Sufentanil was administered in the study by Honarmand & Safavi (2008). Zhang *et al.* (2014) administered 0.2µg/kg dose of Sufentanil. High doses of Sufentanil produce some side effects which includes drowsiness, relief, decreased consciousness, postoperative nausea, vomiting, and constipation. The prevalence of respiratory depression (the most severe side effect due to high-dose Sufentanil) was 0.1-1% and no complication was reported in the patients (Honarmand & Safavi, 2008). Propofol was injected 30 seconds after administration of Sufentanil in the study. However, propofol was injected 60 seconds after the administration of Sufentanil in the study by Honarmand & Safavi, (2008) and the onset of analgesic action of Sufentanil was 60 seconds after intravenous injection and peaks after 5-7 minutes. The half-life of sufentanil was 2.1 minutes. It binds to plasma protein by 92.5%, which is greater than fentanyl (44%). There was no significant difference in heart rate, systolic and diastolic blood pressures and mean arterial pressure between Sufentanil and control group in the study by Honarmand & Safavi, (2008). Hypotension was reported in 20% of the patients in the Sufentanil and Remifentanil groups and 5% of the patients in the control group but the difference was not statistically significant. Heart rate < 50 bits per minute was reported in none of the patients. More or less same finding was reported by Sadri *et al.* (2003). However, Zhang *et al.* (2014) and Chung *et al.* (2011) reported that Sufentanil reduced systolic and diastolic blood pressures and heart rate. Our results strengthened the same. Despite many advantages, propofol can cause hypotension due to a reduction in stressed volume attributable to reduced venous and arterial resistance with no change in cardiac output. propofol-induced systematic hypotension results from vasodilatation and weakened myocardium. propofol is suitable for induction and maintenance of anesthesia. It is also an approved analgesic for induction of anesthesia in neurosurgery and cardiac surgery. The most important side effect of anesthesia induction is the reduction in arterial pressure. Low-dose and slow administration of the analgesic in patients who have already received enough fluid may regulate lower arterial pressure (Honarmand & Safavi, (2008). Similar studies reported confounding results on the effects of Sufentanil on hemodynamic changes.

Conclusively, though the limitations of this study was small statistical data and the short duration of the study and the hypotension and bradycardia were also not assessed in the two groups, than also the results of this study advocate that Sufentanil significantly reduces pain and discomfort during propofol injection and prevents an increase in blood pressure and heart rate caused by pain.

Acknowledgment:

We are grateful to all those peoplewho helped us in this project, especially the respected professors, and staff of the Anesthesiology Department of Shahid Mohammadi Hospital, BandarAbbas, Iran.

References:

Ahmad, S., De Oliveira, G.S., Fitzgerald, P.C. & McCarthy, R.J. (2013): The Effect of Intravenous Dexamethasone and Lidocaine on propofol-Induced Vascular Pain: A Randomized Double-Blinded Placebo-Controlled Trial. *Pain Res Treat.*, 2013:734531.

Ambesh, S.P., Dubey, P.K. & Sinha, P.K. (1999): Ondansetron

Ambient Science, 2018: Vol. 05(Sp1); 117-121
DOI:10.21276/ambi.2018.05.sp1.ra15

Pretreatment to Alleviate Pain on propofol Injection: A Randomized, Controlled, Double-Blinded Study. *Anesth. Analg.*, 89:197–199.

Borazan, H., Sahin, O., Kececioglu, A., Uluer, M.S., Et, T. & Otelcioglu, S. (2012): Prevention of propofol injection pain in children: a comparison of pretreatment with tramadol and propofol-lidocaine mixture. *Int J Med Sci.*, 9(6):492-497.

Chung, D.H., Kim, N.S., Lee, M.K., Jo, H.K. (2011): The effect and optimal dose of sufentanil in reducing injection pain of microemulsion propofol. *Korean J Anesthesiol.*, 60(2):83-89.

Ellett, M.L. (2010): A literature review of the safety and efficacy of using propofol for sedation in endoscopy. *Gastroenterol Nurs.*, 33(2):111-117.

Honarmand, A. & Safavi, M. (2008): Prevention of propofol-Induced Injection Pain by Sufentanil. *Clin. Drug Investig.*, 28(1):27–35.

Kazemnejad, K., Rajaii, S., Ghorchaii, A. & Taziki, M. The effect of lidocaine in reducing pain following propofol injection (Lipuro%1). *J. Gorgan Univ. Med. Sci.*, 9(4):31-35.

Lindholm, E.E., Aune, E., Norén, C.B., Seljeflot, I., Hayes, T., Otterstad, J.E. & Kirkeboen, K.A. (2013): The anesthesia in abdominal aortic surgery (ABSENT) study: a prospective, randomized, controlled trial comparing troponin T release with fentanyl-sevoflurane and propofol-remifentanil anesthesia in major vascular surgery. *Anesthesiology.* 119(4):802-812.

Rau, J., Roizen, M.F., Doenicke, A.W., O'Connor, M.F. & Strohschneider, U. (2001): propofol in an emulsion of long- and medium-chain triglycerides: the effect on pain. *Anesth Analg.*, 93(2):382-384.

Rahman, A-R.A., Al-Mujadi, H., Petrova, I.M., Marzouk, H., Batra, Y. & Al-Qattan, A. (2007): Prevention of pain on injection of propofol: a comparison of remifentanil with alfentanil in children. *Minerva Anestesiol.*, 73(4):219-223.

Redhead, H.M., Jones, C.B. & Bobey, D.G. (2000): Pharmaceutical and antimicrobial differences between propofol products. *Am. J. Health Syst. Pharm.*, 57:1174–1176.

Sadri, B., Nejad S.H.N., Entezari, S.R. & Yazdi, R.S (2003): The effect of intravenous Sufentanil in enhancement of analgesia level of intrathecal Bupivacaine. *Razi J. Med. Sci.*, 10(36):561-565.

Singh D, Jagannath S, Priye S. Prevention of propofol injection pain: Comparison between lidocaine and ramosetron. *J. Anaesthesiol. Clin. Pharmacol.*, 30(2):213-216.

Sklar, G.E. (1997): propofol and postoperative infections. *Ann. Pharmacother.*, 31(12):1521-1523.

Song, D., Hamza, M., White, P.F., Klein, K., Recart, A. & Khodaparast, O. (2004): The pharmacodynamic effects of a lower lipid emulsion of propofol: a comparison with the standard propofol emulsion. *Anesth. Analg.*, 98(3):687-691.

Tekye, M.S.M. Reza, S.A.A. & Aghaee, R. (2006): Comparison of analgesic effects of intravenous Sufentanil and Sufentanil Plus Methylpredinisolone after arthroscopic knee surgery. *J. Iran. Soc. Anaesthol. Intensive Care*, 28(53):23-30.

Zhang, L., Bao, Y. & ShiI, D. (2014): Comparing the pain of propofol via different combinations of fentanyl, sufentanil or remifentanil in gastrointestinal endoscopy. *Acta Cir. Bras.*, 29(10):675-680.