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A Comparative Double-Blind Randomized Clinical Trial Study on Effect of Various Analgesic Intravenous Injections on Propofol Post-injection Pain in Patients Undergoing Elective Surgery

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Study Area: Bandar Abbas, Iran

Coordinates: 27°11'N; 56°16'E,

Key words: Paracetamol, Dexamethasone, Pethidine,
Lidocaine, Ketamine

The study protocol was approved by the Ethics Committee of
Hormozgan University of Medical Sciences (Ethical code:
HUMS.REC.1395.037).

Abstract

Propofol is an intravenous anesthetic widely used in outpatient and short-duration surgeries for rapid recovery. Pain during injection may cause discomfort in some patients. Several medications have been suggested that reduce the severity of pain during propofol injection. The present study aimed to compare the effect of intravenous injection of paracetamol, dexamethasone, pethidine, lidocaine, and ketamine on propofol post-injection pain in patients undergoing elective surgery, following a double-blind randomized clinical trial on 306 patients aged from 18 to 65 who were candidates for elective surgery. Patients were divided into six groups each group consisted of 51 individuals. Mean age of participants in this study was 31.9 ± 9.5 out of which 209 (68.3%) were males and 97 (31.7%) were females. Lidocaine and paracetamol revealed the highest pain-free parameters among other groups. Pain severity was also less in lidocaine and dexamethasone groups than other groups. Finally, lidocaine was seen to be the most efficacious analgesic in reducing pain from propofol injection and could be safely advised for propofol-induced pain relieve.

Introduction:

For rapid recovery, Propofol is an intravenous anesthetic widely used in outpatient and short-duration surgeries due (Miller *et al.*, 2014). However, pain on injection was seen to cause discomfort in 45-75% of patients and several medications have been suggested that reduce the incidence and severity of pain during propofol injection. Various doses of lidocaine, ondansetron, metoclopramide, opiate, paracetamol, dexamethasone, pethidine, and ketamine reduce propofol-induced pain. Lidocaine is the most commonly used medication for pain relief after propofol injection. Bolus dose of lidocaine + propofol mixture is used to relieve pain (Dubey & Prasad, 2003). The Lidocaine is a local anesthetic that reduces pain through peripheral nerve blocks (PNBs) by stimulating peripheral nerve membranes and incidence of pain was reported as 32-48% on patients who were injected with lidocaine (Mohammadzadeh *et al.*, 2011). Paracetamol (acetaminophen, n-acetyl-p-amino-phenol) is a non-opioid antipyretic safe and effective analgesic reported fewer side effects than other medications (Amrimalah *et al.*, 2013). Acetaminophen has analgesic and antipyretic

effects similar to aspirin but the action site and analgesic mechanism are not very much clear yet (Shoeibi *et al.*, 2005). Dexamethasone is a corticosteroid used in several clinical trials to increase the duration of analgesia (Kakodkar, 2013). Pethidine is one of the most effective treatments for post-anesthetic pain and shivering (Wolfers, 1953). Ketamine is an anesthetic and noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, low-dose ketamine can reduce pain (Kurdi *et al.*, 2014; Alizadeh *et al.*, 2015). Given the significant incidence of pain among patients, it is essential to reduce pain in the operating room and prepare the patients for surgery by reducing their mental stress. Many methods have been proposed to reduce propofol-induced pain. However, including advantages, each medication has some disadvantages. Thus, it felt a priority to identify a safe and usable method for analgesia induction in the operating room. The present study aimed to compare the effect of intravenous injection of paracetamol, dexamethasone, pethidine, lidocaine and ketamine on propofol post-injection pain in patients undergoing elective surgery in Bandar Abbas.

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Methodology:

This was a double-blind clinical trial. The statistical population consisted of all such patients who were referred for elective surgery under general anesthesia in Shahid Mohammadi Hospital in Bandar Abbas in 2015-2016. Inclusion criteria were no susceptibility to propofol, paracetamol, dexamethasone, pethidine, lidocaine and ketamine, cooperation and the ability to communicate with the research team, no underlying disease such as diabetes, hepatic disorders, cardiovascular disorders, no alcohol abuse, no opiate addiction, no chronic pain syndromes and thrombophlebitis, no intake of any analgesic and anesthetic. Patients above 65 years of age and unwillingness to participate were excluded from the study. Written consents were obtained from the patients. A convenient sampling method was used to select 306 patients aged between 18 to 65 with ASA I and II. The participants were selected using a random number table derived from Random Allocation Software and were randomly divided into six groups. Each group consisted of 51 patients. Information about the patients was recorded on a checklist including demographic variables (age, gender and BMI) ASA class and the main variable (pain severity).

After obtaining consent from the patients in a preoperative anesthetic visit, the project procedure and verbal scoring of response to pain severity were explained to the patients. Verbal descriptions of patients on pain severity were scored as follows. 0 = painless; 1 = mild pain, positive response but no facial expression of pain, 2 = moderate pain, positive response, behavioral symptoms of pain and a spontaneous pain report without asking; 3 = severe pain, a strong positive response, facial expression of pain and crying. The patients were divided into six groups; group A: 40 mg dose of 2% lidocaine diluted in normal saline, group B: 8 mg dose of dexamethasone diluted in normal saline, group C: 0.2 mg/kg (body-weight) ketamine diluted in normal saline, group D: 25 mg pethidine diluted in normal saline, group E: 100 mg paracetamol (manufactured in Iran) diluted in normal saline, group F: 5 ml of normal saline (placebo). The control group was also included in this study to compare pain severity in the five other groups in case of any problem in the administration of the medication and environmental conditions. Since no prodrug is currently used in many treatment centers prior to propofol injection, the inclusion of a control group in the study is justifiable for ethical issues. The study was double-blind since the patient delivered the card specific to this study to the nurse in the operating room. The nurses were also not aware of group classification. The nurse selected a card from the six cards based on the random number table derived from the Random Allocation Software and entered the card label in the patient record. 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 was measured and monitored in the operating room. 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, B, C, D, E or F based on the studied groups. The desired medication was injected into 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 1% propofol (30 mg) was injected into the vein 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). He 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 checklist. The pain severity was recorded in the checklist based on verbal descriptions. 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). The names and specifications of manufacturing companies are as follows: Dexamethasone by Drugpaksh Plant, Tehran, Iran; Apotel and pethidine by Exir Pharmaceutical Company, Boroujerd, Iran; lidocaine by Abourihan Pharmaceutical Company, Tehran, Iran; Ketamine by Allemagne Company, Germany; Propofol by B-Barun Metsungen AG. 34209 Melsungen, Germany.

The collected data were entered into SPSS v.18. The data were transformed as mean, standard deviation and percentage and was statistically analyzed using tests for equality of means, 't-test', 'chi-square', 'Mann-Whitney U test' and 'Fisher's exact test'.

Results:

In total, 306 patients, divided into six groups, 209 (68.3%) were males and 97 (31.7%) were females. Mean age of the patients was 31.9 ± 9.5 . The range of age groups was (18-65). There was no statistically significant difference in the distribution of gender and BMI between the groups. These frequencies are reported in Table-1.

Comparison towards the frequency of pain in a normal saline group with other test groups showed statistically significant differences. There were no statistically significant differences in a number of painless cases between paracetamol and dexamethasone groups, paracetamol and ketamine groups, paracetamol and pethidine groups and pethidine and ketamine groups. Detailed information is given in Table-2. The highest painless and mild pain cases were reported in lidocaine

treated group and the lowest painless and mild pain cases were reported in normal saline group. The details are reported in Table-3.

Table-1: Drug groups distribution among Gender and BMI

Parace- tamol	Dexame- thasone	Lido- caine	Keta- mine	Pethi- dine	Normal saline	p value
Gender: Male						
33	36	35	39	34	32	
64.7%	70.6%	68.6%	76.5%	66.7%	62.7%	
Gender: Female						
18	15	16	12	17	19	
35.3%	29.4%	31.4%	23.5%	33.3%	37.3%	≥0.732
Total						
51	51	51	51	51	51	
16.66%	16.66%	16.66%	16.66%	16.66%	16.66%	
BMI (mean ± SD)						
21.3±3.4	25.2±2.6	28.1±3.1	25.7±3.1	26.3±3.2	24.2±4.1	≥0.274

Table-2: Comparative analysis on frequency of pain in various drug groups

Group	Pain		p value
	Yes	No	
Normal saline	51 (100%)	0 (0%)	<0.001
Paracetamol	36 (70.6%)	15 (29.4%)	
Normal saline	51 (100%)	0 (0%)	<0.001
Dexamethasone	21 (41.2%)	30 (58.8%)	
Normal saline	51 (100%)	0 (0%)	<0.001
Lidocaine	3 (5.9%)	48 (94.1%)	
Normal saline	51 (100%)	0 (0%)	<0.001
Ketamine	40 (78.4%)	11 (21.65%)	
Normal saline	51 (100%)	0 (0%)	<0.001
Pethidine	41 (80.4%)	10 (19.6%)	
Paracetamol	36 (70.6%)	15 (29.4%)	≤0.03
Dexamethasone	21 (41.2%)	30 (58.8%)	
Paracetamol	36 (70.6%)	15 (29.4%)	<0.001
Lidocaine	3 (5.9%)	48 (94.1%)	
Paracetamol	36 (70.6%)	15 (29.4%)	≥0.363
Ketamine	40 (78.4%)	11 (21.65%)	
Paracetamol	36 (70.6%)	15 (29.4%)	≥0.250
Pethidine	41 (80.4%)	10 (19.6%)	
Dexamethasone	21 (41.2%)	30 (58.8%)	<0.001
Lidocaine	3 (5.9%)	48 (94.1%)	
Dexamethasone	21 (41.2%)	30 (58.8%)	<0.001
Ketamine	40 (78.4%)	11 (21.65%)	
Dexamethasone	21 (41.2%)	30 (58.8%)	<0.001
Pethidine	41 (80.4%)	10 (19.6%)	
Lidocaine	3 (5.9%)	48 (94.1%)	<0.001
Ketamine	40 (78.4%)	11 (21.65%)	
Lidocaine	3 (5.9%)	48 (94.1%)	<0.001
Pethidine	41 (80.4%)	10 (19.6%)	
Ketamine	40 (78.4%)	11 (21.65%)	≥0.807
Pethidine	41 (80.4%)	10 (19.6%)	

There was a statistically significant relationship between gender and pain in the lidocaine group ($p < 0.008$). However, this relationship was not statistically differ in other groups Table-4.

Table-3: Comparative chart showing pain severity in different drug groups (p value <0.001)

Group	Pain severity			
	Painless	Mild	Moderate	Severe
Paracetamol	15 (29.4%)	31 (60.8%)	5 (9.8%)	0 (0%)
Dexamethasone	30 (58.8%)	15 (29.4%)	6 (11.8%)	0 (0%)
Ketamine	11 (21.6%)	14 (27.5%)	21 (41.2%)	5 (9.8%)
Pethidine	10 (19.6%)	33 (64.7%)	8 (15.7%)	0 (0%)
Normal saline	0 (0%)	1 (2%)	20 (39.2%)	30 (58.8%)

Table-4: Relationship between gender and pain

Group	Gender	Pain		p value
		Yes	No	
Paracetamol	Male	24 (72.7%)	9 (27.3%)	≥0.560
	Female	12 (66.7%)	6 (33.3%)	
Dexamethasone	Male	16 (44.4%)	20 (55.6%)	≥0.463
	Female	5 (33.3%)	10 (66.7%)	
Lidocaine	Male	0 (0%)	35 (100%)	≤0.008
	Female	3 (18.8%)	13 (81.3%)	
Ketamine	Male	33 (84.6%)	6 (15.4%)	≤0.053
	Female	7 (58.3%)	5 (41.7%)	
Pethidine	Male	28 (82.4%)	6 (17.6%)	≥0.618
	Female	13 (76.6%)	4 (23.5%)	
Normal saline	Male	32 (100%)	0 (0%)	---
	Female	19 (100%)	0 (0%)	

Table-5: Comparison among mean age groups and report of pain in different drug groups

Group	Having pain	Without pain	Total	p value
	# M±SD	# M±SD	# M±SD	
Paracetm.	36 29.86±8.16	15 27.40±6.03	51 29.13±7.62	≥0.869
Dexame.	21 32.47±15.71	30 29.80±6.90	51 30.90±11.33	≥0.737
Lidocaine	3 32.00±11.53	48 35.89±13.43	51 35.66±13.26	≥0.663
Ketamine	40 30.27±7.24	11 30.18±13.54	51 30.25±8.80	≥0.809
Pethidine	41 30.51±6.39	10 31.40±6.51	51 30.68±6.36	≥0.432
Nor. Sal.	51 35.00±9.76	0 ---	51 35.00±9.76	---

Table-6: BMI and pain record in different drug groups

Group	BMI	Pain		p value
	Group	Yes	No	
Paracetamol	19-25	34 (69.4%)	15 (30.6%)	
	25-30	2 (100%)	0 (0%)	
	>30	0 (0%)	0 (0%)	≥0.352
Dexamethasone	19-25	21 (42%)	29 (58%)	
	25-30	0 (0%)	1 (100%)	
	>30	0 (0%)	1 (100%)	≥0.398
Lidocaine	19-25	3 (6.7%)	42 (93.3%)	
	25-30	0 (0%)	5 (100%)	
	>30	0 (0%)	1 (100%)	≥0.809
Ketamine	19-25	37 (77.1%)	11 (22.9%)	
	25-30	3 (100%)	0 (0%)	
	>30	0 (0%)	0 (0%)	≥0.349
Pethidine	19-25	38 (79.2%)	10 (20.8%)	
	25-30	2 (100%)	0 (0%)	
	>30	1 (100%)	0 (0%)	≥0.678
Normal saline	19-25	50 (100%)	0 (0%)	
	25-30	1 (100%)	0 (0%)	
	>30	0 (0%)	0 (0%)	

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To evaluate the effect of age on a report of pain in each age group, mean age was compared in the groups with and without a report of pain. However, there was no statistically significant difference between age and report of pain in the groups (Table-5).

To determine the relationship between BMI and report of pain, the patients were divided into three groups of 19-25, 25-30 and above 30. However, no significant statistical relationship was found between these two factors (Table 6).

Discussion:

Pain on propofol injection can be a stressful experience for the patient. The chances of pain on propofol injection vary between 28% and 90% during anesthesia induction and it can also be severe. The chances of pain on propofol injection vary from 28% to 85% in children. The pain is more prevalent in younger children probably due to small vessels. There is no difference between the two genders in terms of incidence of pain. The pain from propofol injection is higher than other anesthetics. The incidences of pain during thiopental and methohexitone injection were reported as 7% and 12-64% respectively. The incidences of pain during midazolam and etomidate injection were respectively 1% and 24-48% (Mangar & Holak, 1992; Valtonen *et al.*, 1988; 1989; Cameron *et al.*, 1992). Propofol is a phenol compound not similar to other anesthetics. It weighs as 1278 Daltons, a colorless and liquify at room temperature (Lee, 2010). Propofol was initially formulated as a mixture of 2% propofol + polyethylene castor oil + 8% ethanol. Later, it was formulated as 1% propofol + 16% chromophore. It was later reformulated as propofol + soybean oil to relieve pain from injection. Currently, propofol is available as 1% propofol + 10% soybean oil (Clarke *et al.*, 1975). In the present study the effect of intravenous injection of paracetamol, dexamethasone, pethidine, lidocaine and ketamine was studied on pain from propofol injection. The highest painless and mild pain cases were reported in the lidocaine group (94.1%) and the least cases were reported in normal saline (0%) and pethidine (19.6%) groups. The pain severity was less than other groups in the lidocaine group. However, pain severity was greater in normal saline and pethidine groups. In our study, the results showed that age, gender and BMI do not interfere with report of pain from propofol injection. The results of this study also showed a statistically significant difference in pain relief between normal saline and all test groups (dexamethasone, paracetamol, pethidine, lidocaine, and ketamine). This result was consistent with the results of the studies by Ahmad *et al.* (2013), Canbay *et al.* (2008), El-Radaideh, (2007), Euasobhon *et al.* (2016), Shoeibi *et al.* (2005) and Yadav *et al.* (2011). Lidocaine was more efficacious in relieving pain from propofol injection compared to other medications in this study. The difference between the

lidocaine group and the other groups was statistically significant. This result was also strengthened the earlier results of Yadav *et al.* (2011), Ahmad *et al.* (2013), Canbay *et al.* (2008), Euasobhon *et al.* (2016), El-Radaideh, (2007), Vahid Alizadeh *et al.* (2016) and Jalota *et al.* (2011).

Dexamethasone was the second most efficacious medication for reducing pain from propofol injection in this study. In our study, three cases reported pain in the lidocaine group while 21 cases reported pain in the dexamethasone group. The difference between the two groups was statistically significant. The difference between dexamethasone and normal saline (all cases reported pain) was also statistically significant. Shoeibi *et al.* (2005) reported that dexamethasone was more efficacious in reducing pain than normal saline. On the other hand, Ahmad *et al.* (2013) showed no significant difference in pain relief between lidocaine and dexamethasone groups. However, they found a significant difference between dexamethasone and normal saline. Yadav *et al.* (2011) also administered hydrocortisone to relieve pain but found no significant difference in pain relief. Their finding was not consistent with our present results. In the present study, 41 cases reported pain in the pethidine group and a statistically significant difference was found between pethidine and lidocaine in relieving pain. There was also a significant difference between lidocaine and normal saline groups in relieving pain. This difference was not statistically significant in comparison of pethidine with paracetamol and ketamine in relieving pain. Canbay *et al.* (2008) also showed that acetaminophen was significantly less efficacious than lidocaine but more efficacious than normal saline in relieving pain. El-Radaideh, (2007) also found that acetaminophen was less efficacious than lidocaine and fentanyl but more efficacious than normal saline in reducing pain. Ketamine and pethidine were also investigated in our study. These medications were less efficacious in reducing pain severity than other groups but more efficacious than normal saline in reducing pain. Euasobhon *et al.* (2016) showed that although ketamine and pethidine did not noticeably reduce pain severity they were significantly more efficacious than normal saline in reducing pain in a meta-analysis. Their results strengthen our results of the present study. The findings of this study showed no significant relationship between the occurrence of pain and gender except for the lidocaine group. The relationship between the occurrence of pain and gender was only significant in the lidocaine group. The relationship between the incidence of pain and age was not significant in any group in our study it support the study of Shoeibi *et al.* (2005). In the present study, we found no significant relationship between BMI and the incidence of pain in any group which resembles the findings of Canbay *et al.* (2008).

Conclusion:

Lidocaine, dexamethasone, and paracetamol were more efficacious than other studied medications for pain relief in our study. Lidocaine also had the highest number of painless cases. Since propofol is used to induce anesthesia in a wide range of surgeries, it is suggested to administer lidocaine as a suitable anesthetic to reduce pain from propofol injection. However, it is recommended to conduct more studies with a larger sample size to examine the effects of other medications on the pain caused by propofol injection. According to the findings of our study and some of the earlier referred studies, it is recommended to administer lidocaine as an efficacious anesthetic to reduce the pain caused by propofol injection.

Acknowledgment:

We are grateful to all those people who helped us in this project, especially the respected professors, and staff of the Anesthesiology Department of Shahid Mohammadi Hospital in Bandar Abbas..

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