

The comparison of preemptive effects of propofol, remifentanyl and ketamine on post-operative pain scores and analgesic requirements in elective lower abdominal surgery under general anesthesia: A randomized, double-blinded study

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Background: In this randomized, double-blinded study, we investigated the preemptive effects of propofol, remifentanyl or ketamine on post-operative pain scores and analgesic requirements in elective lower abdominal surgeries under general anesthesia during the first 24 h of post-operative period. **Materials and Methods:** Seventy five patients, American Society of Anesthesiologists physical status I or II candidate for elective lower abdominal surgery under general anesthesia were randomized to three groups (25 each). According to their allocated group, patients received either propofol 0.25 mg/kg, remifentanyl 0.25 mic/kg or ketamine 0.3 mg/kg as preemptive analgesia immediately after the induction of general anesthesia. Post-operative pain scores with a numerical rating scale (visual analogue scale 0-10) were assessed and analgesic requirements and side-effects were compared through analysis using the SPSS version 18 in the post-operative period; post-anesthesia care unit 2, 6, 12 and 24 h. **Results:** Patients' demographics were similar in all groups. The pain scores were significantly lower in remifentanyl group immediately after recovery and also at 2 and 6 h post-operatively, but it reversed at 12 and 24 h after recovery comparing with propofol and ketamine. However, the mean of administered morphine in the first 24 h was significantly lower in propofol group (18.97 ± 6.6) comparing with remifentanyl group (21.96 ± 6.55) and ketamine group (24.26 ± 5.84) (P value, 0.01). **Conclusion:** Prophylactic preemptive single dose of intravenous (IV) 0.25 mg/kg propofol significantly decreased post-operative analgesia requirements comparing with IV 0.3 mg/kg ketamine or 0.25 μ g/kg remifentanyl.

Key words: Analgesic requirement, ketamine, post-operative pain score, preemptive analgesia, propofol, remifentanyl

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INTRODUCTION

Millions of people undergo a surgical operation every year and update data and modern surgical techniques are used for them. Effective pain control is essential during taking care of surgical patients. However, in spite of great improvements in pathophysiology and pharmacology of analgesics, many patients suffer from the debilitating post-operative pain. Obviously, the main goal of pain control is providing comfort to patients and decreasing the complications caused by inappropriate pain control.^[1]

According to the results obtained in different studies, it is believed that analgesic activities are more effective if they are carried out prior to injury, compared to being carried out after injury.^[2] Preemptive analgesia is an analgesic treatment preventing central sensitization and

the central pain process, called hyperalgesia and limits the patients' pain.^[3]

Administration of opioids prior to the first phase could prevent the development of the late phase. Hence, preventing the early nervous cascade could lead to the elimination of central sensitization.^[3]

Preemptive analgesia theoretically decreases post-operative pain and may prevent the development of chronic pain as well.^[4]

Though the basis for "preemptive analgesia" is widely known, different reports are available about its effectiveness.^[5] On the other hand, many different definitions have been proposed for preemptive analgesia. This has led to many ambiguities and controversies in this field. According to some studies, if active treatment

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is used, long and severe pain will develop and remain.^[4-10]

Furthermore, different and controversial results have been reported in the studies that have evaluated the effect of non-steroidal anti-inflammatory drugs, systematic opioids, ketamine, dextromethorphan, local anesthesia and epidural anesthesia agents on the body.^[10]

Ketamine anesthesia has been approved in post-operative pain control and it has been reported that low-dose ketamine significantly reduce the amount of morphine required and also nausea after abdominal surgery.^[11]

Propofol is a short-acting intravenous (IV) hypnotic agent used for induction and maintenance of general anesthesia and sedation for surgical operation and mechanical ventilation in adults.^[12] The mechanisms of action are as follows: Potentiation of gamma-aminobutyric acid type A (GABA-A) receptor activity by increasing channels block time and also playing the role as a sodium channel blocker.^[13-19]

Remifentanyl is a potent ultra-short-acting synthetic opioid analgesic drug, used during the surgical operation for pain relief and its anesthetic effects. Remifentanyl is used for sedation. It is also combined with other medications in general anesthesia.^[20]

We investigated the preemptive effects of propofol, remifentanyl or ketamine on post-operative pain scores and analgesic requirements in elective lower abdominal surgeries under general anesthesia during the first 24 h of post-operative period due to lack of any studies regarding the comparison.

MATERIALS AND METHODS

This is a randomized double-blind clinical trial, approved by Research Committee of School of Medicine, Isfahan University of Medical Sciences in 2011.

Prior to study, all patients signed an informed written consent. The present clinical trial was carried out on 75 people, divided into three groups of 25 patients. The participants were in the age range of 18-65, with American Society of Anesthesiologists (ASA) physical status I-II (ASA I: Normal healthy patient, ASA II: Patient with mild systemic disease; no functional limitation) and were a candidate for lower abdomen elective surgery. All participants had normal values of blood urea nitrogen, Cr and liver function tests and were negative for history of psychological problems, convulsion or alcohol and opioid addiction. In addition, they had to be able to use verbal rating scale (VRS: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, 4 = extremely severe pain) or visual

analog scale (VAS: Patient explain the severity of his pain with numerical 0-10 scale). The participants were randomly divided into three groups using sealed envelopes with 25 patients in each group respectively.

(The sample size was estimated based on a power calculation, which showed that at least 25 patients per group were necessary to achieve 80% power to detect a 20% difference between the two groups in the VAS scoring with α equal to 0.05).

In each group, one drug was used as the preemptive analgesic. One group received remifentanyl (GSK Glaxosmith Kline Italy) (R) while the two other groups received propofol (Claris Lifescience Limited India) (P) and ketamine (Rotex Medica Germany) (K). Regarding the differences between colors and volumes of the drugs, the individual who injected the drugs was different from the one who evaluated and also all of our syringes were covered, to fulfill a double-blind study. The anesthesia method was the same in all three groups; thiopental 5 mg/kg, fentanyl 2 μ g/kg combined with atracurium 0.5 mg/kg, followed by morphine 0.2 mg/kg.

Maintenance of anesthesia was accomplished by 50% N₂O in O₂ through orotracheal tube in conjunction with propofol 100 μ g/kg/min IV infusions. In case of complicated operation or prolonged anesthesia (more than 3 h), the participant was excluded from the study. Immediately after induction of anesthesia, 0.3 mg/kg ketamine, 0.25 mg/kg propofol and 0.25 μ g/kg remifentanyl were administered in groups (K), (P) and (R) as preemptive anesthesia, respectively.

Systolic, diastolic and mean arterial blood pressure (BP), pulse and respiratory rate of patient with 15-min intervals were monitored and recorded during the operation. Furthermore, these variables were measured and recorded 2, 6, 12, 24 h post-operation. Post-recovery pain intensity of patients was measured and recorded in VAS and VRS tables in the recovery room immediately after the operation and also 2, 6, 12 and 24 h after the surgery. Furthermore, time interval between operation ending and first post-operative opioid dose received (pethidine 0.1 mg/kg or morphine 0.15 mg/kg, providing VAS reaches above 3) and recovery duration were recorded in three groups. The amount of opioid used was recorded in three groups in the first 24 h after the surgery. Sleep scores (according to the Ramsey Sedation Scale) were recorded in three groups 2, 6, 12 and 24 h after the operation as well. Meanwhile, complications which seemed to be caused by the drugs such as bradycardia (heart rate (HR) < 60), tachycardia (HR > 120), hypertension (BP \geq 140/90 mmHg), hypotension (BP \leq 90/60 mmHg) and hallucination were recorded. The data were analyzed by SPSS software version 20 and all dependent quantitative variables were

compared and analyzed in three groups. The variables include sleep score, respiratory rate, HR, arterial BP, VAS, VRS, amount of post-operative opioid used and time interval between end of the operation and the first post-operative opioid dose received.

RESULTS

According to the Chi-square test results, the three groups were not significantly different in gender ($P = 0.713$), job ($P = 0.419$), ASA ($P = 0.853$), type of surgical operation ($P = 0.126$) and post-operative analgesic method ($P = 0.284$). According to Fisher exact test, no statistical difference between 3 groups ($P = 0.99$).

However, the groups were significantly different with regard to the complications (bradycardia, tachycardia, hypertension, hypotension and hallucination) of anesthetic drugs ($P = 0.026$). Ketamine caused more complications than the two other drugs (tachycardia, hypertension and hallucination) [Table 1]. According to Chi-square test, no statistical difference between 3 groups ($P = 0.52$).

The analysis of variance test (ANOVA) demonstrated that there was no significant difference in the mean

age ($P = 0.66$), mean weight ($P = 0.279$), time interval between the end of operation and the first opioid dose received ($P = 0.552$), duration of recovery ($P = 0.856$), duration of anesthesia ($P = 0.623$), duration of extubation ($P = 0.617$), mean dose of morphine during the operation ($P = 0.994$), mean VRS 24 h after recovery ($P_{24} = 0.453$), respiratory rate immediately after recovery ($P_0 = 0.793$) and 2 h after recovery ($P = 0.493$), HR in all times ($P_{15} = 0.417$), ($P_{30} = 0.382$), ($P_{45} = 0.275$), ($P_0 = 0.225$), ($P_2 = 0.249$), ($P_6 = 0.10$), ($P_{12} = 0.225$), ($P_{24} = 0.250$). Mean Arterial Pressure (MAP) at minutes 15, 30 and 45 during the operation ($P_{15} = 0.541$), ($P_{30} = 0.309$), ($P_{45} = 0.337$) and immediately after recovery ($P_0 = 0.621$) and 2, 6 and 24 h after recovery ($P_2 = 0.610$), ($P_6 = 0.322$), ($P_{24} = 0.323$) in the three groups were not also significantly different [Table 2]. The three groups were significantly different in the amount of post-operative morphine ($P = 0.01$); such that the lowest amount was used in the propofol group (18.97 ± 6.6), followed by the remifentanyl (21.96 ± 6.53); and the highest amount of morphine was administered in the ketamine group (24.6 ± 5.84) [Table 3].

The three groups were significantly different in mean VAS in all the times ($P_0 < 0.001$), ($P_2 < 0.001$), ($P_6 < 0.001$), ($P_{12} < 0.001$) and ($P_{24} = 0.009$). The lowest mean VAS immediately after recovery belonged to the remifentanyl group (4.78 ± 0.99), the propofol group (6.72 ± 1.25) and then the ketamine group (6.56 ± 1.37). The lowest mean VAS 2 h after recovery was related to the remifentanyl group (5 ± 1.21), followed by the propofol (5.93 ± 1.22) and then the ketamine groups (6.44 ± 1.1). However, the lowest mean VAS 6 h after recovery was related to the propofol group (4.41 ± 1.12) and then the remifentanyl (3.9 ± 1.38) and the ketamine groups (4.85 ± 1.29). The lowest mean VAS 24 h after recovery belonged to the propofol group (2.17 ± 1.04), then the ketamine group (2.78 ± 1.05) and the highest mean

Table 1: Frequency distribution of post-operative analgesic method and perioperative complications in the three groups

Group	Remifentanyl Case (%)	Propofol Case (%)	Ketamine Case (%)	P value
Analgesic method				
IM	2 (8)	2 (8)	1 (4)	0.99
IV	23 (92)	23 (92)	24 (96)	
Complications				
No	20 (80)	20 (80)	17 (68)	0.52
Yes	5 (20)	5 (20)	8 (32)	

IM=Intramuscular; IV=Intravenous

Table 2: Means MAP values in different times in the three groups

MAP	Remifentanyl mean±SD	Propofol mean±SD	Ketamine mean±SD	P value
15 min during the operation	10.16±0.74	9.95±0.71	10.14±0.79	0.541
30 min during the operation	10.12±0.74	9.79±0.85	9.99±0.68	0.309
45 min during the operation	9.75±0.53	9.56±0.76	9.81±0.65	0.337
Immediately after recovery	9.83±0.43	9.68±0.58	9.83±0.68	0.621
2 h after recovery	9.62±0.35	9.49±0.49	9.57±0.6	0.610
6 h after recovery	9.54±0.54	9.32±0.56	9.36±0.5	0.322
12 h after recovery	9.52±0.54	9.06±0.48	9.21±0.61	0.012
24 h after recovery	9.37±0.56	9.15±0.55	9.16±0.59	0.323
P		0.14		

MAP=Mean arterial pressure

Table 3: Mean amount of post-operative morphine administered in the three groups

Group	Remifentanyl mean±SD	Propofol mean±SD	Ketamine mean±SD	P value
Amount of post-operative morphine administered	21.96±6.53	18.97±6.6	24.26±5.84	0.01

Table 4: Means VAS values in the three groups in different times after recovery

VAS	Remifentanyl mean±SD	Propofol mean±SD	Ketamine mean±SD	P value
Immediately after recovery	4.78±0.99	6.72±1.25	6.56±1.37	0.001<
2 h after recovery	5±1.21	5.93±1.22	6.44±1.1	0.001<
6 h after recovery	4.74±1.14	4.41±1.12	5.6±0.97	0.001<
12 h after recovery	3.9±1.38	3.3±1.36	4.85±1.29	0.001<
24 h after recovery	3.17±1.4	2.14±1.04	2.78±1.05	0.009
P value	>0.05	0=0.11	>0.05	

VRS=Verbal rating scale

value related to the remifentanyl group (3.17 ± 1.4) [Table 4]. According to repeated measures ANOVA, there was no statistically difference between 3 groups ($P = 0.11$).

By comparing the mean values of VAS in the three groups using analysis of variance, it is observed that the groups were significantly different in the mean VAS score immediately, 2, 6 and 12 h after recovery ($P_0 < 0.001$), ($P_2 < 0.001$), ($P_6 < 0.001$) and ($P_{12} < 0.034$). The lowest mean VAS immediately after recovery related to the remifentanyl group (1.57 ± 1.16) and there was no significant difference between the ketamine (3.30 ± 0.72) and propofol groups (3.31 ± 0.66). However, the lowest mean VRS 2 h after recovery related to the remifentanyl group (1.61 ± 0.99), followed by the propofol (2.76 ± 0.69) and ketamine groups (3.07 ± 0.67). The lowest mean VAS 6 h after recovery related to the remifentanyl group (1.65 ± 0.65) and then the propofol (2.03 ± 0.63) and ketamine groups (2.44 ± 0.58). The lowest mean VAS 12 h after recovery related to the remifentanyl group (1.57 ± 0.79), then the propofol group (1.62 ± 0.62) and the ketamine group (2.04 ± 0.71). With regard to the mean VAS 24 h after recovery, the lowest mean related to the propofol group (1 ± 0.66), after that the remifentanyl group (1.17 ± 1.03) and the highest mean related to the ketamine group (1.26 ± 0.66) [Table 5]. According to repeated measures ANOVA, there is a statistically difference between 3 groups ($P = 0.002$).

Analysis of variance showed statistically significant difference among the groups with regard to the respiratory rate during the operation with 15 min intervals and also 6, 12 and 24 h after the operation ($P_{15} = 0.001$), ($P_{30} = 0.002$), ($P_{45} < 0.001$), ($P_6 = 0.01$), ($P_{12} = 0.001$) and ($P_{24} < 0.001$). In most times, the ketamine group had the highest mean respiratory rate (RR15 = 14.22 ± 1.28), (RR30 = 14.26 ± 1.35), (RR45 = 14.37 ± 1.27), (RR6 = 15.33 ± 0.92), (RR12 = 14.89 ± 1.12), (RR24 = 15.07 ± 1.52) and there was no great different between the propofol group (12.97 ± 0.98), (13.03 ± 1.05), (13.3 ± 1.05), (14.76 ± 1.53), (13.69 ± 1.36), (12.45 ± 1.05) and the remifentanyl group (13.70 ± 1.26), (13.43 ± 1.31), (13.43 ± 1.31), (14.22 ± 1.20), (13.70 ± 1.33), (13.39 ± 1.53). Analysis of variance indicated that the mean MAP values of the three groups 12 h after recovery were

significantly different ($P = 0.012$). The mean value in the propofol group was the least (9.06 ± 0.48), followed by the remifentanyl group (9.52 ± 0.54) and then the ketamine group (9.21 ± 0.61) [Table 2]. According to repeated measures ANOVA, no statistically difference between 3 groups ($P = 0.14$).

The results obtained from the Kruskal-Wallis test indicated that the groups were not significantly different with regard to the education level ($P = 0.67$), median sleep score immediately after recovery ($P = 0.485$), 12 h after recovery ($P = 0.142$) and 24 h after recovery ($P = 1$). However, the test showed that there is a significant difference among the median sleep scores 2 and 6 h after recovery in the three groups. In the ketamine group, 2 h after recovery, none of the patients were restless, anxious and agitated; 17 patients (68%) were cooperative and oriented; 3 people (12%) just obeyed the orders; and 5 patients (20%) just responded to glabella tap or loud auditory stimulus. In the propofol group, 25 patients (100%) were cooperative and oriented. In the remifentanyl group, none were restless, anxious or agitated; 23 patients (92%) were cooperative and oriented; none of them obeyed the orders; and 2 people (8%) just responded to glabella tap and/or loud auditory stimulus. In the ketamine group, 6 h after recovery ($P = 0.009$), 20 patients (80%) were cooperative and oriented; 3 people (12%) obeyed the orders; and 2 patients (8%) just responded to glabella tap and/or loud auditory stimulus. In the propofol group, all patients (100%) were cooperative and oriented. In the remifentanyl group, 23 patients (92%) were cooperative and oriented; 2 people (8%) just obeyed the orders; and none responded only to glabella tap and/or loud auditory stimulus.

DISCUSSION

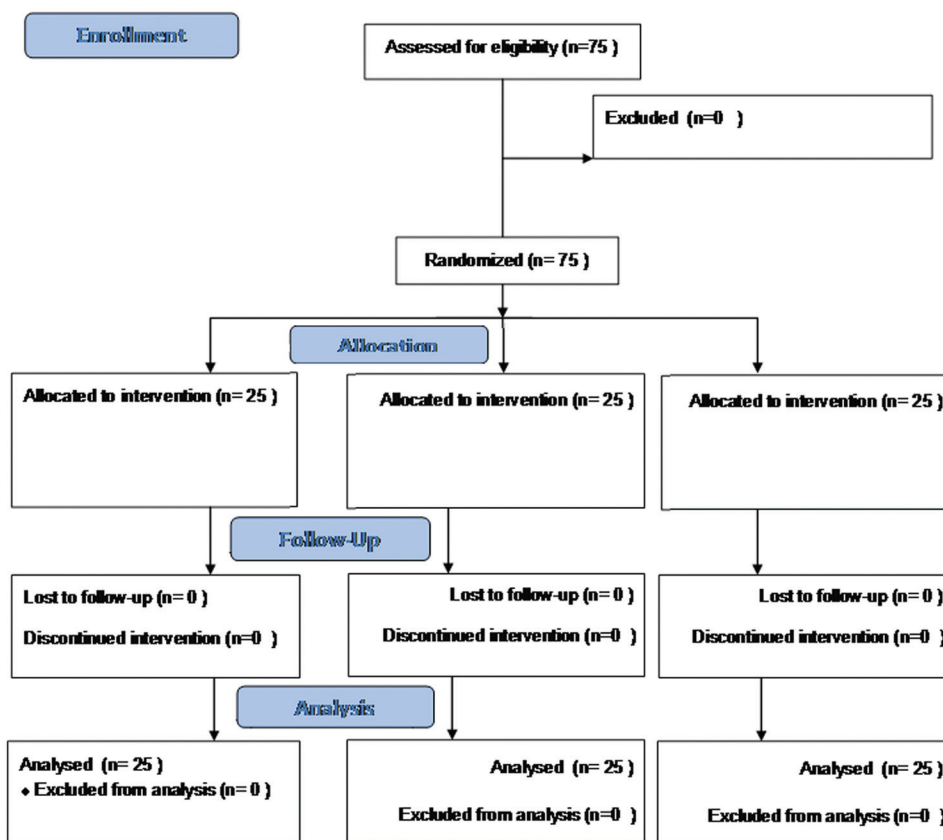
No study has been carried out so far to compare ketamine, propofol and remifentanyl. This is the first time to compare these drugs. Based on the results of a clinical trial carried out in 2006, single-dose ketamine (0/4 mg/kg) does not perform as preemptive analgesia in patients underwent hysterectomy.^[21] Consistently, ketamine had the least effect in the present study.

In a trial carried out on mice in 1994, it was supposed that sedative agents such as IV administration of pentobarbitone and propofol may regulate phase 2 hyperalgesic responses by contributing to the development of central sensitization since it is known that both has GABA-A receptor activity effect. However, according to the results obtained in the current study, only propofol had preemptive analgesic effect.^[22] Nevertheless, according to our findings, propofol had more desirable preemptive analgesic effect than remifentanyl and

Table 5: Means VRS in the three groups 0, 2, 6, 12 and 24 h after recovery

VRS	Remifentanyl mean±SD	Propofol mean±SD	Ketamine mean±SD	P value
Immediately after recovery	1.57±1.16	3.31±0.66	3.30±0.72	0.001<
2 h after recovery	1.61±0.99	2.76±0.69	3.07±0.67	0.001<
6 h after recovery	1.65±0.65	2.03±0.63	2.44	0.001<
12 h after recovery	1.57±0.79	1.62±0.62	2.04±0.71	0.034
24 h after recovery	1.71±1.03	1±0.66	1.26±0.66	0.453
P value		0.002		

VRS=Verbal rating scale



Consort flow diagram

ketamine in some cases. In another study, analgesic effect of propofol was reported.^[23]

In a clinical trial in 2009, prescribing, ketamine combined with remifentanil had a great preemptive analgesic effect in post-operative pain control. This could be explained by combination of the two medications, especially for ketamine effect against opioid-induced hyperalgesia.^[24] Based on the findings of the present study, preemptive analgesic effect of remifentanil is greater than that of ketamine.

In a clinical trial to compare the preemptive analgesic effect of sufentanil with remifentanil, it was reported that V.A.S was significantly higher in remifentanil 2 h after extubation. It was also observed that the time interval between recovery and administration of the first analgesic dose was longer in sufentanil while the post-operative opioid dose required was higher in remifentanil group.^[25] In the current study, remifentanil, compared to the two other drugs has the least VAS 2 h after anesthesia. The three groups were not significantly different with regard to the time of administration of the first analgesic dose. However, the lowest post-operative opioid dose belonged to propofol and then to remifentanil.

In another clinical trial carried out in 2004, it was shown

that performing preemptive analgesia during the surgical operation by ketamine leads to a desirable anesthesia after recovery. However, the duration is not sufficient (about 1 h); it also enhances the post-operative analgesic effect of tramadol.^[26] Regarding the findings of the present study, ketamine had the lowest analgesic effect within the first 12 h after anesthesia.

In a clinical trial, combination of remifentanil and ketamine was administered in laparoscopic cystectomy. The most desirable preemptive analgesic effect was observed in patients who received 0.75 µg/kg remifentanil after anesthesia induction up to the suture time and 100 µg/kg ketamine from induction to 6 h after anesthesia.^[27]

CONCLUSION

A low dose of remifentanil (0.25 µg/kg) immediately after induction of general anesthesia provide better post-operative pain relief in comparison with ketamine (0.3 mg/kg) or propofol (0.25 mg/kg) in lower abdominal surgery.

The principal limitation of this study was the specific setting for post-operative pain relief and the relatively low number of patients, so this observation should be replied in further surveys in a large number of patients and different setting and in our study median sleep score was different between

three groups in some times after the recovery; therefore, our findings about VAS and VRS are reliable in patients who were cooperative.

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