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COMPARISON OF THE EFFECTS OF DEXMEDETOMIDINE AND REMIFENTANIL ON RECOVERY CRITERIA FOR PATIENTS SUBJECTED TO TOTAL ABDOMINAL HYSTERECTOMY UNDER INTRAVENOUS ANESTHESIA WITH PROPOFOL

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ABSTRACT

Introduction: Postoperative pain and agitation are considerable postoperative challenges in post anesthesia care units. These complications prolong recovery period and increase patient morbidity and health care costs. The aim of this study was to compare the effects of dexmedmotidine and remifentanil on pain, sedation, nausea and vomiting, and duration of recovery period in patients undergoing hysterectomy under anesthesia with propofol.
Methods: This is a clinical trial study. In clinical trial, patients scaduled for total abdominal hysterectomy (TAH) under Intravenous general anesthesia at Firoozgar Hospital were entered the study. The patients were randomly divided into two groups: In group D, dexmedetomidine at a dose of 1 µg/kg was infused in 15 minutes and then continued at a dose of 0.2 µg/kg/min during the surgery. In group R, a continuous infusion dose of remifentanil with 0.1 µg/kg/min started from the beginning to the end of surgery. Data were analyzed by SPSS software version 22.
Results: The pain score according to the NRS criteria in patients receiving dexmedetomidine and remifentanil had mean and standard deviation of 1.55±1.5 and 3.9± 1.48 respectively, and this difference was significant (P <0.05). The sedation score in patients receiving dexmedetomidine was significantly higher than those receiving remifentanil (3.3± 0.8 vs 2.4± 0.68, P <0.05). There was no significant difference between the amount of nausea and vomiting in patients receiving dexmedetomidine and remifentanil during recovery (P >0.05). Recovery time was significantly higher in patients receiving dexmedetomidine than in patients receiving remifentanil (P <0.05).
Conclusion: The use of dexmedetomidine during surgery compared with remifentanil causes less pain score, but with more sedation and recovery time.

Keywords: Dexmedmotidine, Remifentanil, Propofol, Hysterectomy.

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INTRODUCTION

Hysterectomy is one of the most common surgeries in non-pregnant women. This surgery can be conducted by open or laparoscopic approach (1). The length of hospitalization in this surgery is affected by factors such as pain, nausea and vomiting, sedation and complications of the surgery itself. So, all these factors are effective on quicker discharge of patients (2 & 3). Physiologic response to stress and surgical injury involves secretion of cortisol, catechol amines, cytokines, ADH and glucagon. Some of the metabolic responses to surgery will lead to derangements in important physiologic states. on the other hand the delayed effects of anesthetic drugs per se may affect the natural ability of body in re-stabilization of physiological balance in post-anesthetic care unit (4) The purpose of management in post anesthesia care unit (PACU) is to awaken the patients steadily, and to recognize and treat any possible complications like airway obstructions, fluctuations in blood pressure or body temperature,and to alleviate postoperative complications such as pain , agitation or nausea and vomiting (5).

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In this regard many drugs have been studied and are frequently used to improve the quality of anesthesia and the recovery profile after surgery .in daily practice It is common to use opioids besides anesthetic drugs like propofol, but assuming the known side effects of opioids including respiratory depression and nausea/ vomiting , anesthetists often try to find better alternatives. One of the remarkable drugs is dexmedetomidine which is an elective alpha 2 receptor agonist, and it has both sedative and analgesic effects (6). This drug adjusts the activity of α2A central receptors. The central and peripheral effects of alpha 2 receptors are mediated by dexmedetomidine and depending on drug dosage these effects are manifested by decrease in systemic blood pressure, heart rate, cardiac output, and norepinephrine release. (7).
Remifentanil is a super-fast anesthetic drug of opiate category that is used when fast analgesic effects are needed before and during the surgery. Rapid metabolization of this drug has made it an appropriate choice to be used in anesthetic regimens for most of the major surgeries (8). Clinical experiences indicate that Remifentanil reduces the required dosage of anesthetic drugs significantly and when it is used as an auxiliary drug in anesthetic regimen, it can decrease blood pressure and heart rate (9,10). Since Postoperative pain is one of the most frequent complications of surgery and remifentanil lacks prolonged analgesic effects after discontinuation of its infusion and reducing the recovery time in PACU may decrease patient operating room costs (11) we decided to use dexmedetomidin intraoperatively and compare recovery profile of these two drugs especialy with regard to the postoperative pain ,sedation score and the time required for patient management in PACU before discharge. As we know many studies have evaluated the recovery conditions such as pain reduction, sedation and nausea and vomiting after infusion of dexmedetomidine and they have found various results.

MATERIALS AND METHODS

This double-blinded randomized clinical trial was first approved by ethical committee of Iran university of medical sciences (code: 130417) and registered at www.IRCT.ir database under the code: IRCT2017102731487N6. This study conducted in Firuzgar hospital affiliated to Iran University of Medical sciences. Based on previous studies and assuming alpha of 0.05 and with a power of 95% , sample size was calculated to be about 20 patients in each group (12) . at the beginning all patients candidated for elective total abdominal hysterectomy were entered the study . Patients lower than 70 years old and ASA I-II candidate for elective hysterectomy surgery were selected. After complete explanations to the patients written informed consent was obtained. Patients needed emergency surgery, patients with cardiovascular disease, renal disease, liver disease, diabetes, high blood pressure, excessive obesity, respiratory diseases, lactating women, patients with obstructive sleep apnea and patients with any psychiatric disorders were excluded from the study. For blind randomization method a special code was written in an enclosed envelop for each patient and it was opened just before anesthetizing the patient and just the researcher knew the patient's group. The results of hemodynamic changes and other variables in this study were recorded through a person unaware of the patient's group.In both groups in operating room, peripheral veins were taken and routine ASA monitoring including NIBP(noninvasive blood pressure), ECG(electrocardiography), ETCO2(end tidal capnography) and SPO2 (pulse oximetery) were done. In addition we evaluated and confirmed appropriate depth of anesthesia by BIS (bispectral index) monitoring. Before anesthesia induction, patients received isotonic saline 5ml per kilogram of body weight. For premedication, patients received midazolam with a dose of 25 µg/kg and fentanyl with a dose of 3 µg/kg. Induction of anesthesia started by propofol 2 mg/kg and atracurium 0.5 mg/kg.
After endotracheal intubation all of the patients underwent mechanical ventilation with a tidal volume of 10 cc/kg, respiratory rate of 10 breath per minute, Pmax of 35 H20 centimeter and I/E ratio of 1/2. In all patients, ETCO2 was maintained at about 35mmHg. Maintenance of anesthesia was conducted by propofol 100 to 150 µg/kg per minute according to appropriate BIS value(from 40 to 60) and atracurium 0.2 milligram per kilogram in every 30 minute intervals.Before starting of operation , patients in group D received dexmedetomidine 1µg/kg slowly infused intravenously over 15 minutes and then with a continuous infusion of 0.2 µg/kg per hour and patients in group R received continuous infusion of remifentanil at a dose of 0.1 µg/kg per minute from the beginning to the end of surgery. At every 60 minute intervals during the surgery, an intravenous bolus dose of fentanyl (50 micrograms) was given to the patients in each group.
It is noteworthy that in case of decrease in mean arterial blood pressure(MAP) of more than 20 percent of basic MAP at first the dosage of anesthetic drugs were reduced and the blood pressure was adjusted by infusion of crystalloids

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used during the surgery, and if the blood pressure was not improved, then 5 milligram of intravenous ephedrine was given and if the heart rate decreased to less than 50 beats per minute for more than 60 seconds, intravenous atropine (0.5 milligram) was given. On the other hand If the blood pressure increased to more than 20 percent of patient's own basic blood pressure (i.e. her blood pressure before induction of anesthesia), we increased the infusion rate of propofol by 20 percent of its basal rate at each 5 minute intervals until it reached to 150 µg/kg/min . At this point if the systolic blood pressure was still not controlled we assumed the infusion of nitroglycerine at a rate of 2-10 µg/min as rescue therapy.

Overall if the hemodynamic parameters were not corrected despite applying all the afformentioned measures then the patient was excluded from the rest of study. At the end of the surgery all drug infusions were hold and in case of stable hemodynamic conditions and after reversing of neuromuscular blockers and attaining good respiratory drive and swallowing reflex , patients were extubated and transferred to postanesthesia care unit (PACU).

Immediately after admission to PACU, the patient's sedation score was determined according to Ramsay sedation score then patients were evaluated every 5 minutes until the aldrete score reached to 9. Pain severity was evaluated by numerical rating scale (NRS) by asking the patients to determine their pain degree (from zero to 10) on a scaled ruler (13). The amount of Postoperative Nausea/vomiting was measured according to a 4 scored rating method (designed as : 1=no nausea, 2=mild or just nausea feeling, 3= moderate or one or two episodes of gag reflex provoked by nausea 4= severe or any episode of vomiting (14) . the time required from admission to PACU until calculated aldrete score had reached to 9 was measured and recorded as the recovery time. All data were analyzed by SPSS V22. First, the normality of quantitative variables was assessed based on Kolmogorov-Smirnov test and was not confirmed. Therefore, to compare quantitative variables in two groups, t_ independent or U_ Mann–Whitney test was used and to compare qualitative variables in two groups' chi-square or Fisher exact test was used. $p<0.05$ was considered significant.

RESULTS

In this study, 49 patients scaduled for total abdominal hysterectomy (TAH) in Firoozgar Hospital in 2017 were entered the study. From these populations 9 patients were excluded from the study. Two patients due to surgical plan change, 4 patients due to deficiency in hospital file documents, 1 person due to hypertension disease , 1 person due to receiving morphine and 1 person due to receiving ondansetron during intraoperative period , and the rest of them (40 people) remained in the study .Twenty (50%) of patients were in Dexmedetomidine group and 20 (50%) in Remifentanil group. It is noteworthy that 2 patients in the Dexmedetomidine group suffered from bradycardias that were treated with 0.5 mg of atropine. Also, 2 patients in the Remifentanil group and 3 patients in the Dexmedetomidine group received triglyceride (TNG) due to hypertension.

There was no significant difference in age and weight of patients between two groups ($P>0.05$) (Table 1)

Variable	**Group**		**p_value**
	Dexmedetomidine	Remifentanil	
Age (year) Mean±SD	49.44±7.92	45.93±9.86	0. 14
Weight (year) Mean±SD	74.21±12.81	75.12±8.58	0.506

There was significant difference between pain scores (NRS scale) in patients undergoing hysterectomy in two groups ($P<0.05$) (Table II).

Variable	**Group**		**p_value**
	Dexmedetomidine	Remifentanil	
pain score No pain (0)	6 (30%)	2 (10%)	

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Mild (1-3)	11 (55%)	2 (10%)	<0. 001
Moderate (4-6)	3 (15%)	16 (80%)	
Severe (7-10)	0 (0%)	0 (0%)	

There was significant difference between sedation (Ramsay sedation score) in patients undergoing hysterectomy in two groups (P<0.05) (Table III).

Variable	Group					P.value
	Dexmedetomidine		Remifentanil			
sedation						
1	1	(5%)		2	(10%)	
2	0	(0%)		8	(40%)	
3	12	(60%)		10	(50%)	0. 001
4	6	(30%)		0	(0%)	
5	1	(5%)		0	(0%)	

There was no significant difference between nausea and vomiting in patients undergoing hysterectomy in two groups (P>0.05) (Table IV).

Variable	Group				P_value
	Dexmedetomidine		Remifentanil		
nausea and vomiting					
No (0)	1	(5%)	1	(5%)	
Mild (1-3)	19	(95%)	15	(75%)	0. 215
Moderate (4-6)	0	(0%)	3 (15%)		
Severe (7-10)	0	(0%)	1	(5%)	

There was significant difference between recovery time in patients undergoing hysterectomy in two groups (P<0.05) (Table 5).

Variable	Group		P_value
	Dexmedetomidine	Remifentanil	
Recovery time (minute)			
Mean±SD	34±7.53	26.25±8.71	0. 009

DISCUSSION

According to the most important results of this study, based on NRS criterion the pain score in patients after hysterectomy surgery under intravenous anesthesia with propofol receiving dexmedetomidine was less than the patients receiving remifentanil in recovery period. Based on Ramsay criterion, the sedation score in patients receiving dexmedetomidine was more than patients receiving remifentanil in recovery period. The rate of nausea and vomiting in patients receiving dexmedetomidine was less than those receiving remifentanil, but this difference was not significant. Moreover, the recovery period in patients receiving dexmedetomidine was longer than those receiving remifentanil.

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In the study of Rokhtabnak et al, on controlled hypotension during rhinoplasty both recovery time and sedation score in PACU were longer in patients received dexmedetomidin compared to patients received magnesium sulfate (15). In a study conducted by Park et al, in results consonant with the present study they found that the period of discharge from recovery in patients under cataract surgery is longer in a group received dexmedetomidine than in a group received remifentanil(16).

In a study consonant with our study, Pournajafian et al. perceived that the period required for recovery of patients under laparoscopic cholecystectomy is more in dexmedetomidine group than in remifentanil group (17).

In results of a study mismatching the present study, Salman et al. found that there is no difference between the amount of pain the recovery time (from admission to PACU to discharge) for receivers of dexmedetomidine and remifentanil in women's laparoscopic surgery. The amount of nausea and vomiting of dexmedetomidine receivers in women's laparoscopic surgeries is less than the receivers of remifentanil. However, at the end they reported that dexmedetomidine may be an alternative for remifentanil in outpatient surgeries (18).

In a study done by Elbakry et al. and in results matching our study, they found that the sedation score in patients with epilepsy surgery who receive intravenous infusion of dexmedetomidine and propofol is lower than that of the patients receiving intravenous infusion of remifentanil and propofol. The amount of nausea and vomit in patients receiving intravenous infusion of dexmedetomidine and propofol is less than those receiving intravenous infusion of remifentanil and propofol (19).

In a study by Ge et al., and in the results consistent with our study , they found that the pain score (both at rest and during body movement) in a 2-24 hours postoperative period after abdominal hysterectomy surgery under general anesthesia for receivers of dexmedetomidine + remifentanil + propofol is lower than the patients receiving remifentanil + propofol. In addition, there is no significant difference between severity of nausea and vomiting in patients under general anesthesia for receivers of dexmedetomidine + remifentanil + propofol and patients receiving remifentanil + propofol (20) in a study done by Rajan et al. and in the results matching the present study, they found out that based on VAS criterion, pain score in craniotomy surgery of patients in dexmedetomidine group is lower than that of the patients in remifentanil group (21).

In a study carried out by Rahimzadeh et al. and based on the results consistent with our study , they found out that pain score after posterior spinal fusion surgery who received infusion of dexmedetomidine is lower than those who received remifentanil intravenous infusion. As well, the period of discharge from recovery in patients receiving infusion of dexmedetomidine is longer than those receiving remifentanil intravenous infusions (22).

In a study conducted by Polat et al. they concluded that based on recorded pain scores and nausea/vomiting scores during the recovery period after nasal surgery , dexmedetomidine was better than remifentanil but in the results mismatching our study , remifentanil was better than dexmedetomidine based on agitation outbreak in recovery period.. This lack of consistency can be due to the difference of drugs used to preserve the anesthesia in two studies (23). Peng et al., found out that after cleft palate surgery in ediatrics conducted under anesthesia with propofol and remifentanil, agitation in dexmedetomidine group is less than placebo group (24).

In a study conducted by Hwang et al. and from the results consistent with the current study, theyfound out that after spinal surgery in patients under intravenous anesthesia with propofol, both the pain scores and nausea and vomiting scores in dexmedetomidine group were lower than remifentanil group (25).

regarding to the findings of previous studies and as well the present study, it seems that continuous infusion of dexmedetomidine in comparison to remifentanil is more effective in improving postoperative pain scores and sedation scores after hysterectomy surgery under intravenous anesthesia with propofol ,However there was no significant difference between severity of nausea and vomiting in receivers of dexmedetomidine and remifentanil. The recovery period in patients receiving dexmedetomidine was longer than those receiving remifentanil.

CONCLUSION

Based on the results of this study, the use of doxedetomidine during surgery compared with remifentanil leads to less pain score, but with more sedation and longer recovery time.

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