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## The effect of intraperitoneal ketamine, dexmedetomidine and bupivacaine on postoperative pain control in patients undergoing abdominal hysterectomy

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**ABSTRACT**

**Introduction:** Today, hysterectomy is one of the commonest types of surgery and is the one of the most prevalent surgical procedures in the United States after cesarean section (C-section). One of the important complications of hysterectomy is postoperative pain. To relieve this pain, various methods are used, including the use of analgesics such as intraperitoneal ketamine, dexmedetomidine and bupivacaine. Therefore, the present study is aimed to conduct a comparative study on the effect of intraperitoneal ketamine, dexmedetomidine and bupivacaine on postoperative pain control in patients undergoing abdominal hysterectomy. **Materials and Methods:** The present study is a randomized, double-blind clinical trial which performed on 105 patients during March 2019 to June 2020, undergoing abdominal hysterectomy who were randomly divided into three groups including D (dexmedetomidine), K (ketamine) and B (bupivacaine). The study groups were compared in terms of hemodynamics, postoperative pain score and amount of drug used after 24 hours after surgery, as well as duration of postoperative analgesia. The obtained data were statistically analyzed using Spss 22 statistical software using ANOVA and T test. **Results:** The results of this study revealed the effect of intraperitoneal dexmedetomidine, bupivacaine and ketamine in controlling the pain following abdominal hysterectomy, among which intraperitoneal ketamine was more effective in controlling postoperative pain, increasing postoperative pain relief, and reducing postoperative opioid use when compared with dexmedetomidine and bupivacaine. **Conclusion:** All three drugs, intraperitoneal dexmedetomidine, bupivacaine and ketamine, were detected to be essential in controlling postoperative pain in patients with complete abdominal hysterectomy. However, the effect of intraperitoneal ketamine was found to be greater than that of the other two drugs.

**Keywords:** Abdominal hysterectomy, intraperitoneal, dexmedetomidine, bupivacaine, ketamine.

## 1. INTRODUCTION

Hysterectomy is a very common surgical procedure. After C-section, the surgical procedure of hysterectomy is the second most common one. The most common hysterectomy is performed on women aged 40 to 49 years. Problems such as severe pelvic pain, bleeding, and irregular menstruation and uterine cancer can lead to surgical removal of the uterus (Salman et al., 2000). However, hysterectomy is more commonly used for the treatment of a group of gynecological diseases which have not responded well to medication. In addition, this method can be suitable for women who no longer intend to have children and use ineffective and numerous treatments for conditions such as uterine leiomyomas or fibroids, endometriosis, cervical dysplasia, menstrual disorders, uterine prolapse, cancer, and endometrial hyperplasia (Novak, 2007; Zohar et al., 2004). One of the most common problems among pregnant women is pain after abdominal surgery (Salman et al., 2000).

In medical practice of gynecology, one of the most prevalent surgical procedures is hysterectomy. Following hysterectomy, abdominal pain is one of the most prevalent types of symptoms that is complained among the patients who undergo hysterectomy (Novak, 2007; Zohar et al., 2004). Therefore, the use of certain types of analgesic regimens can reduce the complications and mortality around the surgical procedure (Kehlet and Holte, 2001). Local anesthesia has been considered as a cheap, low-risk, and easy method (Moiniche et al., 1998). Failure to control postoperative pain causes acute and chronic adverse effects, probably leading to increase of mortality and mortality (Williamson et al., 1997). Also, it increases oxygen consumption, blood pressure, heart rate, as well as a heart attack (Kehlet and Holte, 2001; Williamson et al., 1997; Klein et al., 2000). Appropriate analgesia may be capable of reducing many of the complications after the surgery (Ali et al., 1998).

There are several ways to reduce pain after surgery, one of which is to inject pain killers such as ketamine, dexmedetomidine, and bupivacaine intraperitoneally, which are used by many surgeons as a way for reducing pain. Intraperitoneal local anesthesia plays a crucial role in controlling the postoperative pain in modern surgery (Fares et al., 2015). In this method, the material is injected directly into the intraperitoneal cavity, which significantly reduces postoperative pain in gynecological surgeries, laparoscopy and general surgeries (Narasimham and Rao, 2017). Ketamine as an analgesic and sedative plays a its inhibitory role on N-methyl-D-aspartate (NMDA) receptor, leading to reduction of the sensitivity of the central nerves to painful stimuli and the need for systemic opioids (Faiz et al., 2014; Jyothi et al., 2017). The use of alpha 2 adrenergic agonists is another way to reduce postoperative pain. Adrenergic alpha 2-agonists have been introduced to clinical anesthesia due to their sympatholytic and sedative properties as well as proper hemodynamic stabilization. Their main action is through alpha-2 ( $\alpha_2$ ) adrenergic receptor located in the locus corleus and the posterior horn of the spinal cord.

Dexmedetomidine is a potent selective  $\alpha_2$ -adrenoceptor agonist that binds to the G-Protein receptor in the brain and spinal cord, and affects central nervous system function and result in analgesia. It has recently been introduced to anesthesiologists as a dose-dependent anesthetic (spinal and supraspinal) without respiratory depression. This drug has analgesic and sedative properties as well as anti-adrenergic and cardiovascular effects (Sun et al., 2017; Xiao et al., 2017). Bupivacaine is a type of amide-type local anesthetic that has the potential to induce long-term anesthesia (Pati, 2017; Anand et al., 2014). Therefore, the present study is aimed to conduct a comparative study on the effect of ketamine, dexmedetomidine, and intraperitoneal bupivacaine in postoperative pain control in patients with abdominal hysterectomy.

## 2. MATERIALS AND METHODS

The present study is a double-blind clinical trial that was performed on patients who experienced abdominal hysterectomy in Taleghani Hospital during during March 2019 to June 2020, in Arak, Iran. After obtaining informed written consent, the patients who were candidate for hysterectomy and met the inclusion criteria was divided into three categories of bupivacaine, dexmedetomidine and intraperitoneal ketamine using block random sampling method.

Inclusion criteria were 1- Patients who are candidates for abdominal hysterectomy, 2- Patients with ASA class 1 and 2, 3- Having conscious satisfaction, 4- Age range 30-30 years

Exclusion criteria were 1- Patients with ASA class 3 and 4, 2- Out of the age range of 30-70 years, 3- All emergency patients, 5- Patients with allergies to dexmedetomidine, bupivacaine and ketamine.

According to the following formula, the number of samples in each group was calculated 35 individuals, which a total of 105 were registered in the study.

$$n = \frac{\left(z_1 - \frac{\alpha}{2} + z_1 - \beta\right)^2 + (\delta_1 + \delta_2)^2}{(\mu_1 - \mu_2)^2}$$

$$z_1 - \frac{\alpha}{2} = 1.96$$

$z_1 - \beta = 1.28$   
 $\delta_1 = 0.71$   
 $\delta_2 = 0.66$   
 $\mu_1 = 2.25$   
 $\mu_2 = 1.5$      $n = 35$

### Procedure

In this study, 1-2 mg midazolam, 1-2 cc fentanyl as premedication were given to all patients in the operating room, then 3-5 cc /kg crystalloid fluid as CVE was given to all patients. Patients were then treated with 2-3  $\mu$ /Kg fentanyl, 0.03-0.05 mg/kg midazolam, 2-3 mg propofol, and 0.5-0.75 mg/kg atracurium. Then all the patients underwent DRP and PRB surgery and were prepared for abdominal hysterectomy (TAH) surgery. After removal of the uterus and blood sampling, the patients were separate into three catagories randomly including dexmedetomidine (0.5-0.7  $\mu$ g /kg), bupivacaine (15-20 mg) and ketamine (50-75 mg). For blinding, the intraperitoneal injection volume was increased to 5cc for all three groups, and the syringes were labeled in the same shape and with the same appearance as A, B, and C.

### Data collection

After the operation, the questionnaire was completed by interne. The questionnaire included questions based on patients' demographic information, their hemodynamic symptoms, patients' postoperative pain score, the amount of drug used after 24 hours after surgery and the duration of patients' postoperative analgesia.

### Statistical analysis

The data obtained from the questionnaire were statistically analyzed using Spss-22 statistical software. Statistical Anova and T test were used for analysis and the results were expressed as tables and statistical charts (figures).

### Ethical considerations

In this study, the names and details of the subjects were kept confidential. No charges were imposed on the patient's family and hospital. Patients were trained with their consent and a written consent was obtained from the patients. At all stages of the research, the researchers were required to adhere to ethics in research approved by the Ministry of Health and the Helsinki Declaration. The ethical code is IR.ARAKMU.REC.1397.265.

## 3. RESULTS

The comparison of the mean pain score of patients with abdominal hysterectomy in recovery, 2, 4, 8, 12 and 24 hours following the surgery, in three groups of intraperitoneal dexmedetomidine, ketamine and bupivacaine are demonstrated in Table 1. According to Table 1, the mean pain score in the ketamine group at recovery times, 2 and 4 hours after surgery was lower than the other two groups ( $P = 0.03$ ), but following 8, 12 and 24 hours of the surgery, there was a significant difference between them. No pain was seen between the three groups in terms of score, indicating that intraperitoneal ketamine is more beneficial in decreasing postoperative pain in patients than the other two drugs. However, usually within 6-8 hours after the operation, the half-life of the mentioned drugs is over, so by receiving painkillers in all three catagories, the pain scores of the three catagories eight hours following the operation were not significantly different.

**Table 1** Comparison of mean pain score of patients with abdominal hysterectomy

| Group / average pain score            | Dexmedetomidine group | Ketamine group  | Bupivacaine group | P-value |
|---------------------------------------|-----------------------|-----------------|-------------------|---------|
| Average recovery scoreboard           | 3.1 $\pm$ 1.1         | 1.83 $\pm$ 0.98 | 3.3 $\pm$ 1.6     | P=0.02  |
| Mean pain score 2 hours after surgery | 5.3 $\pm$ 1.3         | 3.3 $\pm$ 1.7   | 4.8 $\pm$ 1.2     |         |
| Mean pain score 4 hours after surgery | 5.6 $\pm$ 1.9         | 3.9 $\pm$ 1.3   | 4.9 $\pm$ 1.1     |         |
| Mean pain score 8 hours               | 4.5 $\pm$ 1.7         | 4.7 $\pm$ 1.6   | 4.01 $\pm$ 0.98   |         |

|  |           |           |           |       |
|--|-----------|-----------|-----------|-------|
| after surgery                          |           |           |           | P=0.2 |
| Mean pain score 12 hours after surgery | 2.8±0.97  | 2.8±1.1   | 2.1±0.86  |       |
| Mean pain score 24 hours after surgery | 2.01±0.97 | 1.08±0.79 | 1.75±0.88 |       |

The mean vital signs of patients undergoing abdominal hysterectomy in recovery are listed in Table 2. The three studied groups were not significantly different in terms of mean arterial oxygen saturation, heart rate and blood pressure ( $P > 0.05$ ).

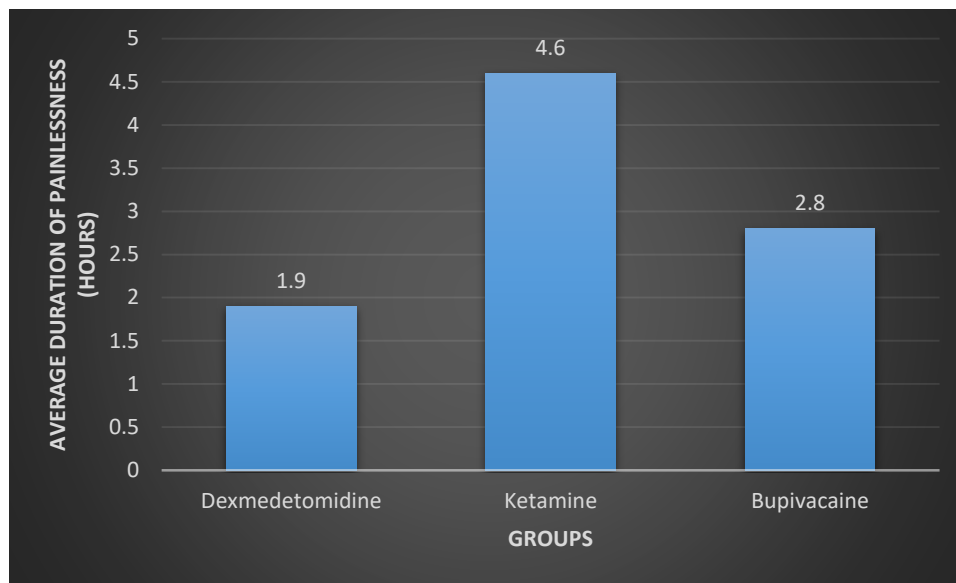
**Table 2** Comparison of mean vital signs of patients with abdominal hysterectomy in recovery

| Group / average pain score              | Dexmedetomidine group | Ketamine group | Bupivacaine group | P-value                  |
|---|-----------------------|----------------|-------------------|--------------------------|
| Mean MAP of patients in recovery        | 4.6± 82.7             | 4.3±89.4       | 3.4±82.4          | P=0.4<br>Non significant |
| Mean heart rate of patients in recovery | 82.5±4.2              | 86.6±5.2       | 81.4±3.9          | P=0.4<br>Non significant |
| Average SPO2 of patients in recovery    | 98.1±7.2 %            | 97.7±8.4 %     | 97.5±4.7 %        | P=0.6<br>Non significant |

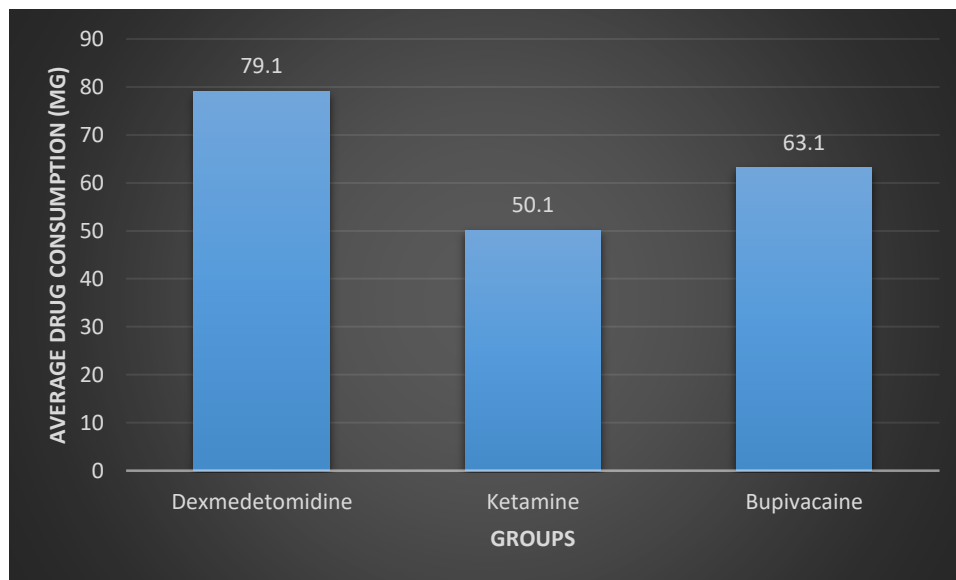
Table 3 show a comparison of the mean duration of pain in patients after abdominal hysterectomy and the amount of drug used in 24 hours following the surgery in three groups. According to Table 3, three studied groups were different in terms of duration of postoperative analgesia and the amount of drug used after surgery ( $P = 0.01$ ). Significantly, the duration of pain relief in the ketamine group was longer compared to the other two studied groups. The duration of analgesia was longer in the bupivacaine group compared to the dexmedetomidine group. Furthermore, the amount of drug used in 24 hours after surgery was lower in the ketamine group compared to the other two groups and less in the bupivacaine group compared to the dexmedetomidine group. In other words, ketamine is more effective than the other two drugs in decrement of postoperative pain, increasing their postoperative analgesia, and reducing opioid use in the 24 hours after surgery (Table 3, Figure 1 and 2).

**Table 3** Comparison of the mean duration of analgesia in patients after surgery and the amount of drugs used in 24 hours after surgery

| Group / average pain score               | Dexmedetomidine group | Ketamine group | Bupivacaine group | Pvalue                    |
|--|-----------------------|----------------|-------------------|---------------------------|
| Average duration of painlessness (hours) | 1.9±0.89              | 4.6±1.2        | 2.8±1.1           | P=0.01<br>Significant     |
| Average drug consumption (mg)            | 79.1±8.4              | 50.1±8.2       | 63.1±7.8          | P=0.01<br>Non significant |



**Figure 1** Comparison of the average duration of painlessness (hours)



**Figure 2** Comparison of the average drug consumption (mg)

#### 4. DISCUSSION

Achieving the right combination drug is one of the specific goals of anesthesiologists and gynecologists for preventing postoperative pain in patients who undergo hysterectomy (Behaen et al., 2014). In the present study, the effect of three drugs ketamine, dexmedetomidine and bupivacaine intraperitoneally in postoperative pain control in patients undergoing hysterectomy were compared. The results of this study demonstrated that the pain score at 2 and 4 hours after surgery was significantly lower in the ketamine group compared to the other two groups. Moreover, the mean duration of analgesia in ketamine was higher than the other two groups, while the amount of drug used during the 24 hours following the surgery in the ketamine group was less than the other two groups, indicating a better and more effective effect of intraperitoneal ketamine than the other two drugs in controlling postoperative pain.

Our results were almost consistent with previous studies, so that in a study conducted by Kamali et al., (2019) on 126 candidate patients for hysterectomy, they compared the effect of intradermal (subcutaneous) dexmedetomidine and ketamine in postoperative pain control. The results of mentioned study showed that both intradermal dexmedetomidine and subcutaneous ketamine have significant role in controlling postoperative pain in patients but the effect of ketamine was greater than dexmedetomidine (Kamali et al., 2019). The results obtained in this study were completely consistent with our findings because

intraperitoneal ketamine was more effective than dexmedetomidine and intraperitoneal bupivacaine in controlling postoperative pain in our study.

Two studies in India compared the effects of intraperitoneal dexmedetomidine and bupivacaine in patients with gynecological surgery and abdominal hysterectomy (Pati, 2017; Anand et al., 2014; Behaen et al., 2014; Acharya et al., 2016). The results of these studies were almost consistent with our findings, where the effects of all three drugs, bupivacaine, ketamine, and dexmedetomidine were evident in postoperative pain control. Another study conducted by Smirit Anand et al., (2017) at the Institute of Anesthesiology in Punjab, India, conducted a study among patients undergoing laparoscopic cholecystectomy and compared the effects of intraperitoneal administration of bupivacaine, magnesium sulfate and their combination in controlling postoperative pain. Based on the results achieved from the present study it was observed that the combination of intraperitoneal bupivacaine and magnesium sulfate was effective in controlling postoperative pain in patients with laparoscopic cholecystectomy as compared with intraperitoneal bupivacaine and intraperitoneal magnesium sulfate alone (Anand et al., 2014). The findings of this study were almost consistent with our study because the effectiveness of intraperitoneal dexmedetomidine, ketamine and bupivacaine were seen in controlling postoperative pain in patients with abdominal hysterectomy.

The results of our study and previous studies almost all indicate the significant effect of intraperitoneal administration of bupivacaine, ketamine, and dexmedetomidine in postoperative pain control in patients with complete abdominal hysterectomy. In the mean time, many studies, such as ours, have reported a greater effect of intraperitoneal ketamine than other drugs, and therefore the use of intraperitoneal ketamine seems to be a good option for postoperative pain control in patients undergoing hysterectomy due to the relatively low side effects.

## 5. CONCLUSION

All three intraperitoneal bupivacaine, ketamine, and dexmedetomidine has a considerable role in controlling postoperative pain in patients with complete abdominal hysterectomy. But the effect of intraperitoneal ketamine was found to be greater in comparison with the other two groups.

### Consent for publication

All authors declare that they have Consent for publication

### Authors' contributions

All authors contributed to the design of the study, as well as data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

### Funding

The study did not receive any external funding

### Conflict of interests

The authors declare that there are no conflicts of interests.

### Data and materials availability

All data associated with this study are present in the paper.

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