Comparison of intradermal Dexmedmotidine and subcutaneous Ketamine for post-surgical pain management in patients with abdominal hysterectomy

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Abstract

Hysterectomy after cesarean section is the second most commonly used surgery for women in the United States. One of the most common problem after hysterectomy is pain. We decided to compare the effects of dexmedmotidine or ketamine on pain in patients by a double blind randomized clinical trial on 126 female candidates for abdominal hysterectomy in three groups of 42 persons referred to Taleghani hospital in Arak. For the first group, 50 micrograms of intradermal dexmedmotidine were injected, while in the second group, patients were injected with 100 mg of subcutaneous ketamine and the third group received 5 cc normal saline. Data were next analyzed by SPSS version 19. The mean age and body mass index of the patients were not significantly different in the three groups. The mean scores of pain during recovery of patients in ketamine, dexmedmotidine and placebo groups were 4.2±0.77, 2.6±0.89 and 1.3±0.87, respectively (p = 0.001). Scores of pain in patients at 4 and 8 hours after surgery showed also significant differences. In conclusion, ketamine and dexmedmotidine significantly reduce the severity of pain, but ketamine has a lower effect.

Key Words: Post-surgical pain, abdominal hysterectomy, Dexmedmotidine, Ketamine.
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Hysterectomy is an operation to remove the uterus and, depending on the type of surgical procedures, accompanying organs including fallopian tubes, ovaries and cervix.[1] Hysterectomy is the second surgical procedure after caesarean section in the United States. Of the 650,000 operations performed annually, 75% are abdominal and 25% vaginal hysterectomies.[2] The highest number of hysterectomy is seen in women between the 40 and 49 years, to treat women that not responded to drug therapy.[3] Suitable hysterectomy indications include benign uterine diseases or symptoms such as dysfunctional uterine bleeding, pelvic pain, uterine enlargement and prolapse, uterine leiomyoma, infectious abortions. Benign uterine and ovarian diseases, in which the uterus is not initially involved, pelvic inflammatory diseases, pelvic endometriosis, ectopic pregnancy, and neoplastic diseases including cervical intraepithelial carcinoma, early invasive cervical cancer, endometrial adenocarcinoma, sarcoma, Gestational trophoblastic disease (GTD), fallopian tube and ovarian tube neoplasms, and malignancy of other adjacent organs. Endometritis.[3,4] Pain after abdominal surgery is one of the common problems for the patients and analgesic regimens can reduce the death toll surgery. Many studies show that analgesics reduce postoperative complaints,[3] Preemptive analgesia as a pain intervention method is harmful before provoking which can relieve postoperative pain by reducing peripheral and central sensitization.[5,6] However, in major abdominal surgeries, opioid analgesics are preferred but there are many unwanted side effects, such as nausea, vomiting, gastrointestinal symptoms and respiratory depression.[7-10] Many studies have been done to reduce postoperative pain through various techniques, including the use of local anesthetics,that has been considered as a cheap, low risk and easy method.[11-13] Local anesthetics are well tolerated and reduce risks of nausea and vomiting in patients. Local aanesthetics relief pain via spinal cord sensitization by activating glutamate and aspartate in N-methyl-D-aspartate receptors (NMDA).[14] This leaded to use of NMDA antagonists such as ketamine.[15,16] The use of low dose ketamine as an NMDA receptor antagonist not only reduces pain, but also reduces the need for systemic opioids.[17] Dexmedmotidine is a highly specific α2 adrenergic agonist that has both antidiarrheal and

sedative properties and has an antiadrenergic effect during operation and cardiovascular protection effect. It does not induce respiratory depression, being routinely used to calm down patients in day-care.[18,19] No studies compared the effects of ketamine and dexmedmotidine as appropriate opioid alternatives for treating postoperative pain after hysterectomy. The aim of this study is to investigate their effects in case of local administrationis.

Materials and Methods

This study was a double-blind randomized controlled trial on female candidates for abdominal hysterectomy who had resorted to Taleghani hospital in Arak, Iran. A total of 126 patients were randomly selected and divided into three groups according to the principles of randomized sampling method and table of randomized numbers. After obtaining informed consent, patients were enrolled in the study, but they were not informed about their group. The purpose of the study was explained to all enrolled persons and written consent was obtained from them. The information of all patients wa kept confidential by the trial organizesr. All ethical statements in the Helsinki Research Committee and ethics committees in Arak University of Medical Sciences were considered. This research was approved with the Code of Ethics 297. 1395 IR.ARAKMU.REC. The registration code at the Iranian Center for Clinical Trials was IRCT2016122520258N20.

Each group consisted of 42 patients. For the first group, 50 micrograms of intradermal doses of dexmedetomidine were injected, in the second group 100 mg of ketamine were subcutaneously injected, in a volume 5 ml. The third control group was subcutaneously injected with 5 ml of normal saline. Patients entered the operating room after anesthesiologist's confirmation. A full examination was subsequently performed and after recording the heart rate and the percentage of oxygen saturation, they received 3-5 cc/ Kg of crystalloid. Subsequently, they were placed under supine position and general anesthetics were provided. After surgery, the local drugs were injected according to the random identification of the patients, Finally, average duration of pain relief and the pain score in patients was recorded using a Visual Analog Scale (VAS) ruler at 2, 4 and 8 hours after surgery. If scores of pain were more than 5 or equal to 5, at 2, 4 and 8 hours after surgery, 25 mg of pethidine were used to control pain of patients; two other doses were repeated if petients did not respond. Patients who received more than 100 mg pethidine were excluded from the study. Furthermore, to determine the average duration of anesthesia in patients, time of the first analgesic request was also recorded. The average amount of opioid consumed during 24 hours in these patients and the complications caused by the drugs and the vital signs of the patients, including blood pressure and heart rate, were recorded every 5 minutes during surgery. Colleagues who completed the questionnaire and scoring of patients pain based on the pain VAS was also not aware of the study groups, therefore, double-blind trial was conducted. All information was recorded in the questionnaire and the data were analyzed by y SPSS version 19, ANOVA, T-test and Chi square.

Inclusion criteria

1: Abdominal hysterectomy candidates with intent to participate in the study. 2: All patients undergoing general anesthesia. 3: Patients aged between 30 and 65 years. 4: Duration of surgery with a maximum of 120 minutes. 5: All patients were candidates for abdominal hysterectomy with Anesthesia Society American (ASA) Class I and II. 6: All surgeries are performed by a surgeon. 7: Lack of allergy to dexmedetomidine and ketamine. 8: Lack of underlying diseases of the heart, lungs, coagulation disorders and infectious diseases.

Exclusion criteria

1: a known allergy to dexmedetomidine or ketamine. 2: The lack of informed consent to participate in the study. 3: having surgery that lasts more than 120 minutes. 4: Patients outside the age range of 30-65 years. 5-: Having definitive contraindication for general anesthesia; 6: patient with ASA class above II. 7: Patients with underlying cardiovascular, pulmonary, coronary, and infectious diseases. 8: All surgeries lasting more than 120 minutes. 9. Patients undergo surgery other than abdominal hysterectomy. 10:The presence of several surgeons for surgery.

Sampling method

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (S_1^2 + S_2^2)}{(\mu_1 - \mu_2)}$$

$Z_{1-\frac{\alpha}{2}}$1 1.96 = μ2 62.7 = μ44.4= $S_1$13= $S_2$14= βz1-2.33= N = 42 in each group - Total number 126

A probability sampling method was used in which 126 patients were randomly divided into three equal groups of 42 persons (ketamine, dexmedetomidine, and placebo groups) using a table of randomized numbers.

Results

In this study, there was no significant difference between the mean age of the patients in the trhee groups, averaging to 46.5 years. There was no significant difference also in terms of Body Mass Index (BMI) (Table 1). As reported in Table 2, there was no significant difference between the two experimental groups in terms of mean blood pressure in patients during operation, indeed the mean blood pressure in the three groups was approximately 72.5 ($p \geq 0.05$). Furthermore, no significant difference was found between the three groups in terms of mean heart rate of patients and in the mean oxygen saturation between the three groups ($p \geq 0.05$). On the

Table 1. Mean age and mean BMI in patients with abdominal hysterectomy

Groups	Dexmedetomidine	Ketamine	Placebo	p value
Average age	46.9±2.7	46.4±4.9	47.1±3.9	p≥0.05
Average BMI	26.8±1.6	27.1±2.1	26.3±1.9	p≥0.05

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Table 2. Mean blood pressure, heart rate and oxygen saturation during surgery in patients with abdominal hysterectomy

Groups	Dexmedetomidine	Ketamine	Placebo	p value
Mean blood pressure	72.6±10.8	72.9±9.9	73.1±7.8	p≥0.05
Average heart rate	76.8±11.1	77.1±9.1	76.6±8.4	p≥0.05
Mean oxygen saturation	98.5±3.2	98.8±2.1	98.1±4.1	P≥0.05

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Table 3. Mean duration of analgesia (in minutes) in patients with abdominal hysterectomy

Groups	Dexmedetomidine	Ketamine	Placebo	p value
Analgesia duration (min)	111.8±10.1	178.2±12.3	60.6±8.5	p=0.01

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Table 4. Average narcotic drug consumption during 24 hours after surgery (in mg)

Groups	Dexmedetomidine	Ketamine	Placebo	p value
Average drug in 24 hrs	207.6±22.4	151.7±19.8	246.4±20.1	p=0.01

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Table 5. Pain scores in patients with abdominal hysterectomy at recovery and 2, 4 and 8 hours after surgery

Groups	Dexmedetomidine	Ketamine	Placebo	p value
VAS Recovery	2.6±0.89	1.3±0.87	4.2±0.77	p=0.001
2 hour after VAS	5.2±1.3	4.2±0.98	5.9±1.1	p≥0.05
4 hour after VAS	3.7±0.86	2.9±0.95	5.4±1.2	p=0.01
8 hour after VAS	3.7±1.1	2.8±0.77	6.02±1.3	p=0.001

other hand, there was a significant difference between the three groups regarding the mean duration of analgesia, as shown in Table 3. The level of analgesia was significantly higher in the ketamine group , while it was significantly greater in the dexmedetomidine group compared with the placebo group (p = 0.01). Table 4 shows that no significant difference were found between the three groups in terms of drug use in the 24 hours after surgery. On the other hand the amount of consumption in the ketamine group was significantly lower than what was revealed in the in the other two groups, where it was found to be lower in the dexmedetomidine group than in the placebo group (p = 0.01). Table 5 confirms that there was a significant difference between the three groups in the mean pain scores in the postoperative period. in the ketamine group pain scores were significantly lower than in the other two groups and pain in the dexmedetomidine group was lower than in the placebo group (p = 0.001). Differences of pain scores were not significant only at 2 hours after surgery (p≥0.05).

Discussion

Hysterectomy is one of the most commonly used surgeries in women's medicine and abdominal pain after hysterectomy is also one of the most common complaints in patients undergoing surgery.[20,21] Therefore, the use of analgesics may reduce complications and deaths related surgery.[22] Dexmedetomidine is an α2-adrenoceptor agonist, that has sedative effects as a short-term sedative and can reduce hypertension.[23] It also has protective effects on postoperative cardiac injuries, reducing use of other sedative and analgesic drugs.[24,25] Ketamine, a

derivative of phencyclidine, is an antagonist of N-methyl-D-aspartate that has sedative and anti-nociceptive effects.[26-28] Ketamine not only reduces pain, but also the need for systemic opioids.[17] The aim of our study was to provide drugs that can be used subcutaneously and intradermally to control pain after abdominal hysterectomy. Subcutaneous or intra dermal compounds are important since they do not have the complications of intravenous compounds. Thus, we organized a randomized clinical trial to compare the effects of intradermal doses of dexmedetomidine and subcutaneous doses of ketamine in women undergoing abdominal hysterectomy. Our results show that both dexmedetomidine and ketamine were effective in controlling pain after abdominal hysterectomy, but ketamine had a better efficacy. Our results are in agreement with a series of previous studies suggesting a positive effect of ketamine and dexmedmotidine on postoperative pain after abdominal hysterectomy. Kamali et al. have conducted a study in 2016 to compare intra dermal and subcutaneous bupivacaine and cutaneous ketamine in controlling postoperative pain in patients undergoing abdominal hysterectomy under general anesthesia. In that study 99 female candidates for abdominal hysterectomy were randomly divided into 3 groups of ketamine, bupivacaine and placebo. The duration of analgesia in the placebo group was significantly lower than that of the two groups of ketamine and bupivacaine. However, there was no significant difference between the two groups of ketamine and bupivacaine in the mean duration of analgesia.[29] At the end of a laparoscopic hysterectomy surgery,[30] Chiruvella (2016) randomly divided patients into two groups, including ropivacaine plus normal saline recipients, and the other group receiving ropivacaine in conjunction with dexmedetomidine. The study showed that ropivacaine plus dexmedetomidine group had less pain than ropivacaine plus normal saline group.[31=30] Ülgey and colleagues evaluated the analgesic effects of Levobupivacaine with dexmedetomidine after abdominal hysterectomy. 50 candidates for abdominal hysterectomy were randomly divided into 2 groups of 25 patients. The first group received infiltration of the surgical area with levobupivacaine, while the second with levobupivacaine in combination with dexmedetomidine. Total meperidine consumption was significantly lower in the second group. Shukla and colleagues have evaluated the anti-nociceptive effects of dexmedetomidine and tramadol combined with bupivacaine to bupivacaine in 120 candidates for laparoscopic cholecystectomy. Their results revealed that the average narcotic drug and total score in the bupivacaine group in combination with dexmedetomidine had a better effect on pain management.[32] Another study comparered the analgesic effect of intraperitoneal dexmedetomidine or meperidine in combination with bupivacaine to intraperitoneal bupivacaine alone after laparoscopic gynecologic surgery in 60 women. The time to first request of analgesia and the dose of morphine consumed were significantly lower in the first group. In addition, the administration of intraperitoneal meperidine or dexmedetomidine in combination with bupivacaine tends to reduce the need for postoperative analgesia in women candidates for gynecological laparoscopic surgery.[18] Finally, a review of previous studies suggests that almost all of them indicated the beneficial effects of intraperitoneal, intradermal and subcutaneous administration of dexmedetomidine and ketamine, but none of them had compared intradermal and subcutaneous doses of dexmedetomidine and ketamine.[18,29-31] In conclusion, we here demonstrated that both subcutaneous ketamine and intradermal dexmedetomidine are effective in relieving pain after abdominal hysterectomy following general anesthesia and that subcutaneous ketamine provides a greater effects in comparison to intradermal doses of dexmedetomidine.

List of acronyms

ASA – Anesthesia Society American
BMI – Body Mass Index
GTD - Gestational trophoblastic disease
NMDA - N-methyl-D-aspartate receptors
VAS – Visual Analog Scale

Author's contributions

AK, ZZ, MS, SP, RSH equally participated in experimental design, data collection, writing and revision of the manuscript.

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Conflict of Interest

The authors report no conflicts of interests.

Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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