

COMPARING THE EFFECTS OF CLONIDINE AND PREGABALIN ON POSTOPERATIVE SHIVERING AND PAIN IN PATIENTS UNDERGOING LAPAROSCOPIC CHOLECYSTECTOMY: A CLINICAL DOUBLE-BLIND STUDY

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ABSTRACT

Introduction: Controlling the pathophysiology of postoperative acute pain reduces stress responses, sympathetic tone, spinal reflexes and morbidity and mortality rates and increases patient satisfaction and the health-related quality of life. On the other hand, postoperative shivering increases oxygen consumption, intraocular pressure, intracranial pressure, the surgical site pain and cardiovascular supply-demand balance disorder. Therefore, this study investigated the analgesic and anti-shivering effects of oral consumption of clonidine and pregabalin in laparoscopic cholecystectomy.

Research method: In this randomized clinical trial, 67 candidates for elective laparoscopic cholecystectomy - aged between 18 and 85 years - were enrolled using the same anesthetic method. Before the administration of anesthetic medications and intubation, the first, the second and the third groups received clonidine (0.2 mg, oral), pregabalin (50 mg, oral) and vitamin C (100 mg, oral), respectively. The blood pressure levels and heart rate were recorded every fifteen minutes before the surgery, immediately after initiation of the surgery, after the surgery and in the recovery room. The levels of pain were recorded every 15 minutes, in the recovery room, when leaving the recovery room and 24 hours later. The amount of shivering, nausea and vomiting were recorded in the recovery room. The data were analyzed in SPSS 11, using T-test and ANOVA test.

Results: There was no significant difference between the three groups in terms of their blood pressure levels and heart rate before anesthesia, during the surgery and in the recovery room. There was no significant difference between the three groups in terms of shivering, nausea and vomiting. Clonidine significantly decreased pain at time 30 min [in the recovery room] compared with the other two groups; however, no significant difference was observed at other times. There was also no significant difference between the 3 groups in terms of pain levels, when leaving the recovery room. There was a significant difference between the clonidine and pregabalin groups and the vitamin C group in terms of pain levels, 24 hours after the surgery. Oral administration of both drugs reduced the pain levels compared with the vitamin C group, 24 hours after the surgery.

Conclusion: Clonidine and pregabalin both reduced the postoperative pain in patients undergoing laparoscopic cholecystectomy, without changing the hemodynamic state of the patients.

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Introduction

Gallstones are among the most common disorders in most countries [1]; as their incidence is 11-30% in autopsy reports [2]. This disease is more common in women than in men, as some studies have shown that 20% of women and 8% of men in the United States suffer from this disease, with an overall population of more than 15 million people [3]. More than 90% of patients with acute inflammation suffer from cholecystitis. Gallstones are made of solid materials in the bile. They are

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usually very diverse in shape, size and composition. These stones are rarely observed in young children and adolescents and they gradually prevail in individuals 40 years old and older [4]. The incidence of gallstones is predicted to rise to such extent that 50% of people over 70 and 50% of those over 80 will suffer from this disease [5]. Common risk factors include: age, gender, race, pregnancy (especially multiple pregnancy), undesirable nutrition, Crohn's disease, gastric surgery, spherocytosis and thalassemia, sickle cell disease, spherocytosis, cystic fibrosis and diabetes mellitus. Biliary colic is the most significant clinical manifestation of symptomatic gallstones that increases within 0.5-1 hour and decreases within a few hours [6]. The pain is in the top of the abdomen or upper abdomen and typically radiates to the right shoulder or between the two scapulae. It is often accompanied by nausea and sometimes vomiting. During examination and in the presence of pain, epigastric tenderness usually occurs; however, it may not be observed in the absence of pain [7]. An important predictor in causing chronic pain is the lack of proper control of acute postoperative pain. Another issue in chronic pain syndrome is the role of the sympathetic nervous system. A sudden discharge from silent neuromas originating from nerve ending proliferations after an injury could induce neuropathic pain [8]. Approximately, 700,000 people need gallbladder surgery annually and 80-90% of them are candidates for laparoscopic cholecystectomy [9]. Recent studies have shown that over 500,000 people in the U.S. undergo laparoscopic cholecystectomy each year [10]. Cholecystectomy is the most common abdominal surgery [11]. Since the introduction of laparoscopic surgeries in the 1970s, significant progress has been made in surgical procedures and techniques to reduce patient trauma, mortality and hospitalization time. The homeostasis of patients is better maintained in laparoscopic surgeries [12]. However, it has been shown that there is no significant difference between open and laparoscopic cholecystectomy in terms of the rate of endocrine response, catecholamine and cortisol concentrations and anesthesia needs [12]. Surgery and its consequent tissue injury results in the release of histamine and inflammatory mediators, such as peptides (bradykinin), lipids (prostaglandin), neurotransmitters (serotonin), and neurotrophins (nerve growth factor) [13]. These inflammatory agents activate pain pathway through stimulating the nociceptors [14]. The stimulation of the pain receptors and transmission of pain to the central nervous system (CNS) causes neuroendocrine stress response and activates the hypothalamic-pituitary-adrenal axis. This increases sympathetic tone, catecholamine concentrations, and secretion of catabolic hormones, such as cortisol, antidiuretic hormone, glucagon, renin and angiotensin II and reduces anabolic hormones [15]. Eventually, this situation will lead to increased oxygen consumption and negative nitrogen balance and this subsequently delays the recovery period [15]. Due to the spinal reflexes, postoperative pain reduces respiratory function by reducing cough and deep breathing [16] which subsequently prolongs the recovery period. Controlling the pathophysiology of postoperative acute pain reduces stress responses, sympathetic tone, spinal reflexes and morbidity and mortality rates and increases patient satisfaction and the health-related quality of life [16]. On the other hand, postoperative shivering can increase oxygen consumption to 100%, depending on the intraoperative heat loss rate [17]. Postoperative shivering also increases intraocular pressure, intracranial pressure, the surgical site pain and cardiovascular supply-demand balance disorder [18]. Several medications such as clonidine, pregabalin, tramadol and physostigmine are used for the treatment of postoperative pain and shivering [14]. Pregabalin is an anticonvulsant drug that is usually used to treat neuropathic pains. There is still no agreement on the dose and the exact timing of postoperative oral administration of pregabalin [20]. Pregabalin effectively reduces pain through modulation of calcium channel conductance and controlling the entry of calcium into the nerve cells as well as the GABA receptors [19]. As a central alpha-2 agonist, clonidine is a symptomatic drug that is effective in controlling blood pressure, anxiety disorders, headache, alcohol withdrawal syndrome and some pains [21] and improves cardiovascular stability around the surgical site [22]. It has been shown that preoperative consumption of clonidine reduces hemodynamic responses of laryngoscopy and laparoscopy [23]. Also, preoperative consumption of clonidine, at a proper dose has had beneficial analgesic effects on postoperative pain of children [24]. Sara Katsianou et al. (2013), in their study showed that administration of 300 mg of pregabalin at the night before the surgery and one hour before the laparoscopic cholecystectomy was effective in reducing postoperative pain and in reducing opioids used by patients; however, it exacerbates patient dizziness [20]. Arora et al. (2011) in their study reported that in laparoscopic cholecystectomy surgery, clonidine at a dose of 150 µg, one and a half hours before anesthesia improved hemodynamic stability during anesthesia and reduced intraoperative anesthesia needs as well as preoperative analgesic needs [25]. Therefore, considering the importance of controlling postoperative pain and shivering and due to the increasing prevalence of laparoscopic surgeries and on the other hand, because of beneficial effects of clonidine and pregabalin reported in various studies, this study investigated and compared the analgesic and anti-shivering effects of oral consumption of clonidine and pregabalin in laparoscopic cholecystectomy.

Research Method

This clinical double-blind study was conducted in Kerman Afzalipour Hospital, Iran. The Ethics Committee approval of Kerman University of Medical Sciences (IR.KUM.REC.1395.80). 67 candidates for elective laparoscopic cholecystectomy - with cholecystitis or symptomatic gallstones, aged between 18 and 85 years - were enrolled. The exclusion criteria included pregnancy, history of heart, renal and hepatic failure, allergy to anesthetic agents, taking steroids, uncontrolled hypertension, endocrine disease and body mass index (BMI) over forty. Participants were enrolled with similar demographic conditions and were randomly divided into three groups and the same anesthetic method was used. Initially, 0.05 mg/kg midazolam and 2 µg/kg fentanyl were administered. Anesthesia began with 2 mg/kg propofol and 0.5 mg/kg atracurium besilate. Before

the administration of anesthetic medications and intubation (about ten minutes before the surgery) the first, the second and the third groups received clonidine (0.2 mg, oral), pregabalin (50 mg, oral) and vitamin C (100 mg, oral), respectively. Before the anesthesia induction, all the patients received 5 ml/kg of Ringer's solution. A mixture of nitrous oxide and oxygen, isoflurane and atracurium besilate were used every half hour to maintain anesthesia. The blood pressure levels and heart rate were recorded every fifteen minutes before the surgery, immediately after initiation of the surgery, after the surgery and in the recovery room. If the case of increase of heart rate above 100 beats per minute and increase of the mean arterial pressure above 20%, fentanyl was administered at a dose of 50 µg. In the recovery room and after consciousness, a single dose of diclofenac (50 mg suppository) was prescribed for those scored 4 to 6 and for those scored 7 to 10, a single dose of diclofenac (100 mg suppository) was prescribed. At the end of the recovery process and after completing the questionnaire, in case of pain, 20 mg intravenous pethidine was administered. To homogenize the data, the length of patients' stay in the recovery room [the recovery time] was determined as 45 min. The variables of pain, shivering, nausea and vomiting were checked up to 24 hours after the surgery. Levels of pain were re-checked and recorded, 24 hours after the surgery. Visual analogue scale (VAS) was used to measure pain. The scale ranged from 0 to 10 and the patients were asked about the level of their pain. In this study, 0 and 10 represented no pain and very severe pain, respectively. Different types of shivering [chills, tremor, fasciculation or none] were recorded on the basis of observations in the recovery room. The data were analyzed in SPSS 11, using T-test and ANOVA test.

Results

The participants included 56 (83.6%) female and 11 (16.4%) male and the mean age of the participants was 45.8 ± 13.1 years. The blood pressure levels and heart rate were recorded and compared before the surgery, during the induction of the anesthesia and during the surgery at times 15, 30, 45, 60, 75 and 90 minutes (Tables 1 and 2). There was no significant difference between the groups in hemodynamic variables of heart rate and blood pressure. The frequency of fentanyl injection during the surgery was $1.2 \pm 0.8\%$ times in the vitamin C group, 1 ± 0.5 times in the clonidine group and 1 ± 0.7 times in the pregabalin group and no significant difference was observed. At the arrival of the patients to the recovery room, their blood pressure levels and heart rate were recorded at times 0, 15, 30 and 45 minutes and no significant difference was observed between the groups. In the recovery room and at times 15, 30 and 45 minutes, the VAS values were recorded and scored by asking the patients. In the vitamin C group, the VAS values at times 15, 30 and 45 minutes included 5.2 ± 2 , 5.5 ± 1.9 and 4.9 ± 2.2 , respectively. In the clonidine group, the VAS values at times 15, 30 and 45 minutes included 4.6 ± 2.1 , 3.9 ± 1.6 and 4 ± 0.8 , respectively. In the pregabalin group, the VAS values at times 15, 30 and 45 minutes included 5 ± 2.1 , 4.9 ± 1.9 and 4.3 ± 1.6 , respectively. Based on the results, clonidine reduced pain at time 30 minutes and it had a significant difference with other two drugs, in this regard ($p < 0.01$). In the recovery room, 8 of the vitamin C recipients (38%), 11 of the clonidine recipients (44%) and 6 of the pregabalin recipients (28.5%) had nausea and there was no significant difference between the groups in this regard. One of the vitamin C recipients (4.7%) and 2 of the pregabalin recipients (9.5%) vomited during their stay in the recovery room; however, no vomiting was observed in the clonidine group and there was no significant difference between the groups in this regard (Table 3). Among the vitamin C recipients, 11 individuals (52.4%) experienced fasciculation, 3 individuals (14.3%) experienced tremor and 7 individuals (33.3%) experienced no symptom. Among the clonidine recipients, 11 individuals (44%) experienced fasciculation, 3 individuals (12%) experienced tremor and 11 individuals (44%) experienced no symptom. Among the pregabalin recipients, 7 individuals (33.3%) experienced fasciculation, 3 individuals (14.4%) experienced tremor and 11 individuals (52.3%) experienced no symptom. In total, there was no significant difference between the three groups regarding the variable of shivering (Table 3). At the of time of leaving the recovery room, the VAS values for the vitamin C group, clonidine group and pregabalin group were 4.4 ± 1.6 , 3.4 ± 1.2 and 3.8 ± 1.9 , respectively and no significant difference was observed between the three groups. 24 hours after the surgery, the VAS values for the vitamin C group, clonidine group and pregabalin group were 5.4 ± 2 , 3.5 ± 1.6 and 2.8 ± 1.7 , respectively and there was a significant difference between the clonidine and pregabalin groups with vitamin C group (p value = 0); however, no significant difference was observed between the clonidine and pregabalin groups in this regard.

Table 1

Group	Systolic blood pressure (mmhg)						Diastolic blood pressure (mmhg)					
	15 min	30 min	45 min	60 min	75 min	90 min	15 min	30 min	45 min	60 min	75 min	90 min
Vitamin C	119.2 ±20.6	136.3 ±20.5	136.9 ±19.8	135.9 ±19.3	136.4 ±16.1	144.3 ±17.6	75.2 ±11.6	84.6 ±11.3	86.8 ±12.8	85.4 ±11.1	86.5 ±10.9	85.6 ±9.4

Clonidine	123.9 ±14.5	128.2 ±15.1	129.4 ±15.8	130.7 ±16.6	126.7 ±14.9	129.8 ±12.9	80.2 ±8.7	83 ±7.3	81.6 ±7.6	83.3 ±7.9	80.3 ±6	81.2 ±6.8
Pregabalin	126.8 ±25.1	132.2 ±24.1	131.7 ±23.3	131.9 ±22.2	138.2 ±15.1	136 ±14.5	78.1 ±15.4	82.5 ±14.4	82.5 ±10.6	83.5 ±9.9	80.4 ±15.1	80.7 ±12.8

Table 2

Group	Heart rate (b/min)					
	15 min	30 min	45 min	60 min	75 min	90 min
Vitamin C	82 ±11.2	85.8 ±10	84.9 ±11.4	84.9 ±12.2	85.5 ±12.7	84.6 ±9.6
Clonidine	79.6 ±9.2	79.4 ±10.8	78.9 ±10.8	78.9 ±9.3	79.4 ±10	80.5 ±9.2
Pregabalin	83.7 ±9.6	84.2 ±10	82 ±9.4	81.9 ±8.7	81.6 ±8.1	81.3 ±9

Table 3

Group	Vitamin C	Clonidine	Pregabalin	
Nausea	8 (38%)	11 (44%)	6 (28.5%)	
Vomiting	1 (4.7%)	0 (0%)	2 (9.5%)	
Shivering	None	7 (33.3%)	11 (44%)	11 (52.3%)
	Fasciculation	11 (52.4%)	11 (44%)	7 (33.3%)
	Tremor	3 (14.3%)	3 (12%)	3 (14.4%)
	Chills	0 (0%)	0 (0%)	0 (0%)

Discussion

Reducing stress responses and controlling sympathetic tone and sympatho-adrenal reflexes after surgery will reduce morbidity and mortality and will ultimately increase patient and caregiver satisfaction and will improve patients' postoperative quality of life after surgery [16]. One of the proposed techniques in this regard is using various analgesic drugs, as a premedication, to affect the cardiovascular system and to reduce postoperative shivering through reducing oxygen consumption and hemodynamic changes [14]. Various strategies have been so far investigated to reduce postoperative pain and shivering and to minimize hemodynamic changes and postoperative complications and each strategy has been accompanied with its advantages and disadvantages. Clonidine and pregabalin are two analgesic and sedative drugs. They affect the sympathetic and cardiovascular systems and they are today used along with anesthetic agents in different surgeries [14]. This study investigated and compared the analgesic and anti-shivering effects of oral consumption of clonidine and pregabalin in laparoscopic cholecystectomy. The results showed that patients who received pregabalin or clonidine

experienced less pain than those who received vitamin C, several hours after the surgery. One of the most remarkable results of this study was related to the VAS values in the recovery room and when leaving the recovery room. At these times, the clonidine recipients had less pain than the pregabalin recipients; however, at the end of the 24 hours after the surgery, the pregabalin recipients also experienced lower levels of pain compared to the control group (the vitamin C recipients). Previous studies have shown that gabapentin and pregabalin can reduce acute postoperative pain and opioid needs [27]. These studies have shown that using these drugs as a preoperative premedication will not only reduce intraoperative and postoperative pain; but, it may also play a role in preventing chronic postoperative pain, too [27]. Clarke et al. (2012) conducted a systematic review and a meta-analysis using the results of 8 studies on gabapentin and 3 studies on pregabalin. Based on their review, in four studies on gabapentin recipients and three studies on pregabalin recipients, the incidence of pain and the consumption of analgesic agents had reduced in the long run [26]. Consistent with previous studies, the results of the present study also showed that pregabalin, as a premedication, can reduce postoperative pain; however, in the recovery room, pregabalin had no significant effect on postoperative pain and shivering. Like gabapentin, pregabalin also acts as an anticonvulsant drug and exerts its analgesic effects through inhibition of voltage-dependent calcium channels [9]. Clonidine is also known as an alpha-2 adrenergic agonist, which reduces pain without causing respiratory depression [21]. Several mechanisms have been raised to explain the analgesic effects of clonidine. Clonidine may reduce pain through decreasing the activity of nociceptive neurons in the spinal cord. On the other hand, clonidine can cross the blood-brain barrier and affect the alpha-2 adrenergic receptors; therefore, it can exert its analgesic effects through decreasing the activity of supraspinal nociceptive neurons [21]. It has been also suggested that clonidine can have analgesic effects through the transmission of neurotransmitters at the delta and C pain fiber terminals [21]. Jarraya et al. (2015) showed that the spinal injection of clonidine and bupivacaine can increase the duration of postoperative analgesia [28]. Numerous studies have shown that gabapentin and pregabalin have effectively reduced postoperative pain [26]. However, it should be noted that studies with positive results have used higher doses of medications before the surgery and have continued them afterwards, too [26]. A systematic review also showed that preoperative administration of gabapentin was associated with a higher reduction in postoperative pain than the control group. It also decreased opioid dosages and associated complications [27]. The study of Sara katsianou et al. (2013) on preoperative administration of pregabalin in laparoscopic surgeries also confirmed its beneficial analgesic effects on postoperative pain [20]. During the surgery, the blood pressure levels and heart rate of the patients were recorded and no significant difference was observed between the groups. After the surgery and at the arrival of the patients to the recovery room, the blood pressure levels and heart rate were recorded, where there was no significant difference between the groups.

The administration of premedication was 10 minutes before induction, and this probably due to a no significant difference in the hemodynamic parameters between the three groups during the anesthetic and surgical procedures.

The present study concluded that clonidine cannot reduce hemodynamic responses and postoperative shivering, nausea and vomiting; however, unlike the results of this study, Parveen et al. (2016) showed that the administration of clonidine, as a premedication, reduces hemodynamic responses and the tracheal intubation stress during the surgery [29]. Arora et al. (2011) found that clonidine can effectively reduce postoperative analgesic needs and better hemodynamic stability [25]. The contradictions between this study and some previous studies on hemodynamic changes may be associated with the type of surgery, the depth of anesthesia, the dosage of the prescribed anesthetic or premedication drugs.

Conclusion

The results showed that clonidine and pregabalin both reduced the postoperative pain in patients undergoing laparoscopic cholecystectomy, without making a considerable change in the hemodynamic state of the patients. However, there were contradictions with some of the previous studies, especially regarding their effects on hemodynamic status of the patients during and after the surgery. To address these contradictions, further studies must be conducted on the effects of pregabalin and clonidine on postoperative pain and hemodynamic changes.

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