Original Article

Comparison of the Effect of Preoperative Oral Tizanidine and Pregabalin on Shoulder Pain in Laparoscopic Cholecystectomy Under General Anesthesia

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Abstract

Background: Shoulder pain is considered as the most important and relatively common postoperative cholecystectomy complications that often controls in recovery room by systemic narcotics that may have some side effects. The aim of this study was to evaluate the effect of premedication with oral tizanidine on shoulder pain relief after elective laparoscopic cholecystectomy.

Materials and Methods: In this double-blinded clinical trial, 75 adults of American Society of Anesthesiologist physiologic state 1 and 2 scheduled for elective laparoscopic cholecystectomy under general anesthesia were selected and randomly divided in three groups of T, P, and control groups. Ninety minutes before the induction of anesthesia, patients received either 4 mg tizanidine (T group), 100 mg pregabalin (P group), or orally in 50cc or the same volume of plain water as a placebo (control group). Then, the vital signs, pain intensity, and the need for analgesic were measured during 24 hours and then compared in the groups.

Results: There was no significant difference in patient characteristics, with respect to age, weight, gender, and duration of anesthesia and surgery between the groups ($P > 0.05$). The pain intensity and need for analgesic were significantly lower in tizanidine and pregabalin groups than the control group ($P < 0.003$) vs ($P < 0.001$). There was no significant difference in vital signs characteristics between the groups.

Conclusion: Oral administration of 4 mg tizanidine and 100 mg pregabalin 90 minutes before laparoscopic cholecystectomy significantly relive postoperative shoulder pain and analgesic consumption without any complication.

Keywords: Analgesia, laparoscopic cholecystectomy, pregabalin, shoulder pain, tizanidine

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Introduction

Laparoscopic cholecystectomy (LC) was introduced by Philip Mort in 1987 and is currently the gold standard method for the treatment of gallstones.[1] Pain after laparoscopic surgery usually appears as an acute pain.[2-4] Pneumoperitoneum during LC can cause changes in hypercapnia, hypoxemia, hemodynamic, and shoulder pain that is attributed to diaphragmatic stimulation as a result of residual carbon dioxide gas after LC. In fact, postoperative shoulder pain is a common side effect after

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laparoscopic procedures. It seems to have a multifactorial mechanism, but the most reported theory is carbon dioxide gas persistence between the right diaphragm and the hepatic dome. It appears mainly after patient verticalization and it may remain even after standard analgesic medications. General anesthesia (GA) enables the control of intraoperative pain and ventilation.[5,6] Postoperative pain can lead to increased heart rate, high blood pressure, and consequently, increased cardiac workload, nausea, vomiting, and ileus. Adequate control of postoperative pain is very important in accelerating the resumption of normal daily activity of the patient from the operation.[6] Pain and discomfort due to peritoneal traction, hemodynamic disorders, and ventilation changes resulting from gas entering the peritoneum during LC can further activate the body's stress response.[7] Intraoperative stress response can be reduced by using α-2 receptor stimuli.[8-10] The use of narcotics to control postoperative pain has many side effects, including respiratory weakness, drowsiness and sedation, postoperative nausea, and vomiting. Nonsteroidal anti-inflammatory drugs are also used to control postoperative pain in practice but they are associated with side effects, such as coagulation disorders, renal dysfunction, and gastrointestinal bleeding.[11-13] Alpha-2 stimulants are very important in the role of adjuncts to anesthetics and analgesic drugs.[14] In anesthesia, they are mostly used due to their sedative, antianxiety, and analgesic effects.[15] Tizanidine is an oral α-2 receptor stimulus and is used as a central muscle relaxant in painful muscle spasms with fewer cardiovascular side effects, which makes it a drug drawing attention for being used in anesthesia.[16] Pregabalin is an anticonvulsant drug that has been shown to be effective in treating central and peripheral neuropathic pain, including diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, and central neuropathic pain with spinal cord injury.[17] Due to the rapid onset of action, the pain usually subsides on the first day after treatment in an adult.[18] The most common side effects of pregabalin include dizziness and drowsiness.[19] Talakoub *et al*.[20] investigated the effect of oral tizanidine on pain relief after selective LC and found that it reduces postoperative pain and the need for opioid and thus stay in the recovery room without any side effects. Imai *et al*.[21] (2015) examined the effect of pregabalin in reducing shoulder pain after thoracotomy in patients with lung cancer. Their findings suggested a decrease in the severity of shoulder pain after surgery. In the present study, the effects of preoperative oral tizanidine and pregabalin on shoulder pain after selective LC were evaluated and compared.

Materials and Methods

This study was a double-blind randomized clinical trial conducted on 75 patients in the age group of 20 to 60 years with ASA I-II under selective LC after taking the approval of the Proposal Review Council and the University Ethics Committee in the operating room (A) of Imam Khomeini Hospital. Patients with hypertension, history of heart disease, renal and respiratory disorders, gastrointestinal disorders, mental health problems such as depression or obsessive compulsive disorder, and drug addicts and people treated with beta-blockers, Methyldopa, monoamine oxidase inhibitors, analgesics, and body mass index above 25 were excluded from the study. Preoperative drugs were prescribed by an anesthesia resident who was unaware of the patient classification form. The researcher was also unaware of which study group the patient belongs to. Patients in group (T) received 4 mg tizanidine, 100 mg pregabalin 90 minutes before anesthesia, and group (P) and control group (S) received placebo. Before entering the operating room, the patient was given a complete and sufficient explanation on how to use visual analogue scale scoring. After admission to the operating room, patients underwent standard monitoring of noninvasive sphygmomanometers, heart rate, arterial oxygen saturation (SPo_2), and electrocardiogram. Vital signs were recorded before the onset of anesthesia. For all patients, 10 mg of metoclopramide, 2 mg of midazolam, 100 μg of fentanyl were injected, and after 3 minutes of preoxygenation, 2 mg/kg of propofol-induced anesthesia was started and 0.5 mg/kg of atracurium was used to facilitate intubation. Anesthesia was continued with isoflurane 1 to 1.5% and nitrous oxide 50% with oxygen along with repeated doses of 50-100 μg fentanyl for maintaining heart rate and mean blood pressure as 20% before induction of anesthesia. After securing the airway and entering the gas into the peritoneal cavity, ventilation was continued to maintain end-tidal carbon dioxide ($ETCo_2$) between 35 and 40 mmHg. Pneumoperitoneum was created and maintained by carbon dioxide. For better visibility of gallbladder, the patient's bed was rotated for the head as 15 degrees downward and slightly turned to the left. Abdominal pressure was maintained at 12 to 15 mmHg. Finally, muscle relaxation residue was reversed through 0.04 mg/kg neostegmin and 0.02 mg/kg atropine. After ensuring the patient's ability to maintain airway and proper breathing quality and ventilation volume and follow the instructions, the endotracheal tube was removed. Vital signs were measured and recorded at the time of laryngoscopy, then they were measured and recorded every 5 to 30 minutes, and then every 10 minutes until the endotracheal tube removal. Tachycardia and bradycardia and increased and decreased blood pressure were referred to any change in these parameters 20% before the start of anesthesia. After removal of the endotracheal tube, patients were transferred to the postanesthesia care unit, and in recovery and after transferring the patient to the ward, the patient was asked about shoulder pain at 6, 12, and 24 hours after the operation and he/she showed the amount of pain through visual analogue scale scored from 0 to 10.[22] Patients were explained that the 0 would indicate no pain, 1 to 3 indicate low pain, 4 to 7 indicate moderate pain, and 8 to 10 scores indicate severe pain. Pentazocine 30 mg was used for patients with a pain score more than 4. The number of analgesia requests and the amount of analgesic drug were recorded and measured in all three groups. The information was recorded and collected in preprepared forms and statistically analyzed.

Results

Demographic factors showed no significant difference between the three groups [Table 1].

In the study of mean pain during recovery, 6, 12, and 24 hours after surgery, there was no statistically significant difference between the two groups of patients receiving tizanidine and pregabalin. These results were $P = .25$, $P = .79$, $P = .44$, and $P < .05$, respectively. However, in the study of the three groups, this difference was significant and the mean pain was significantly higher in the placebo group [Table 2].

The results of the present study showed that after transfer to the ward, there was a significant difference between the three groups in terms of drug demand, so that patients in the placebo group requested more analgesia compared to tizanidine and pregabalin groups ($P = .03$). There was no statistical difference in the amount of analgesic drug requested by tizanidine and pregabalin groups ($P = .84$) [Table 3].

As per the one-way analysis of variance (ANOVA) statistical test, there was a significant difference between the consumption of analgesics among the three groups ($P = .001$). However, Tukey's-b *post hoc* test showed that there was no significant difference between tizanidine and pregabalin groups in terms of analgesic consumption ($P > .05$), but placebo group consumed more analgesics compared with tizanidine group ($P = .001$) and pregabalin group ($P = .001$) [Table 4].

At different times of measuring mean arterial blood pressure, only in recovery there was a significant difference among the three groups. As per ANOVA test, this value was not significantly different between the tizanidine and pregabalin groups ($P = .92$). However, there was a significant difference between tizanidine group and placebo group ($P = .002$) and pregabalin group and placebo group ($P = .03$). This difference was not significant in other measured times [Table 5].

Mean heart rate in recovery showed three statistical differences between the three groups and was higher in the placebo group than the other two groups ($P = .002$). ANOVA test showed that there was no significant difference between the tizanidine and pregabalin groups ($P = .32$). In the rest of the measurement times, the mean heart rate did not show a significant difference between the studied groups [Table 6].

Table 1: Demographic characteristics of patients in three groups

Group	Gender	Mean age (year)	BMI (kg/m²)
Tizanidine			
Male	8 (32%)	10.56±41.88	24.50±3.54
Female	17 (68%)		
Pregabalin			
Male	7 (28%)	13.07±41.68	8.45±23.99
Female	18 (72%)		
Placebo			
Male	8 (32%)	11.89±38.56	23.33±3.21
Female	17 (68%)		
P	0.93	0.54	0.65

Table 2: Comparison of mean shoulder pain score of patients in three groups

Group	Variable	Recovery	6 h after surgery	12 h after surgery	24 h after surgery
Tizanidine	Pain	3.20±1.50	1.16±2.50	1.06±2.37	1.12±2.45
Pregabalin		0.88±2.96	1.36±2.45	0.89±1.60	0.52±1.55
Placebo		1.69±4.28	40.6±1.14	0.44±3.82	0.59±3.73
P		0.003	0.0001	0.01	0.001

Table 3: Comparison of the frequency of analgesia requests times)

Group	Frequency of analgesia requests			Total
	Once	Twice	Three times	
Tizanidine	6 (54.5%)	3 (27.3%)	2 (18.2%)	11 (100%)
Pregabalin	6 (66.7%)	2 (22.2%)	1 (11.1%)	9 (100%)
Normal saline	2 (14.3%)	3 (21.4%)	9 (64.3%)	14 (100%)
Total	14 (41.2%)	8 (23.5%)	12 (35.3%)	34 (100%)

Table 4: Comparison of drugs consumption in mg

Group	Mean and standard deviation of analgesia consumed (mg)	Between groups Comparison		*P*
Tizanidine	309.45±41.69	Tizanidine	Pregabalin	0.60
Pregabalin	30.05±291		Placebo	0.001
Placebo	7.10±416	Pregabalin	Tizanidine	0.60
P	0.001		Placebo	0.001
		Placebo	Tizanidine	0.001
			Pregabalin	0.001

Discussion

Adequate control of postoperative pain is one of the important factors for patients' comfort of being discharged from the hospital and its effect is very important in accelerating the resumption of normal daily activity of the patient after surgery. Patients should be adequately informed and educated about the amount of postoperative pain that awaits them, how to evaluate and measure it, and the methods used and interventions to reduce and treat postoperative pain. If patients be informed about the amount and type of postoperative pain, they will have a great benefit. For example, a separate explanation for the discomfort and vague pain in the shoulder after laparoscopy instead of severe pain and explaining that this pain is not related to the chest and heart will be necessary for the patient and will calm him.[23] This prospective study was performed over a period of one year in the operating room of Imam Khomeini Hospital in Urmia. Our findings suggest that pretreatment of tizanidine and pregabalin can be effective in reducing shoulder pain caused by LC. In this study, we used 4 mg of tizanidine and 100 mg of oral pregabalin 90 minutes before surgery.

Table 5: Comparison of mean arterial blood pressure in three groups (mmHg)

Group	During laryngoscopy	Recovery	6 h after surgery	12 h after surgery	24 h after surgery
Tizanidine	8.63±77.53	7.30±78.13	83/84±7/46	82.32±8.25	8.7±80.59
Pregabalin	7.08±79.07	9.72±79.47	82/58±9/06	8.03±81.05	83.25±9.58
Placebo	38/12±79.68	9.94±84.86	85.10±6.41	83.31±7.04	9.32±84.62
P	0.71	0.003	0.51	0.27	0.29

Table 6: Comparison of mean heart rate in three groups (number per minute)

Group	During laryngoscopy	Recovery	6 h after surgery	12 h after surgery	24 h after surgery
Tizanidine	10.43±77.20	8.94±75.24	8.03±81.48	83±5.30	5.17±84.40
pregabalin	7.53±75.84	8.63±76.56	10.19±84.40	84.60±10.17	8.44±83.68
Placebo	7.54±77.10	9.55±84.04	7.30±82.80	8.12±81.88	8.09±83.56
P	0.82	0.002	0.48	0.49	0.91

The results demonstrated a reduction in the mean pain score in recovery, 6, 12, and 24 hours after surgery in the tizanidine and pregabalin groups compared to the placebo group, and this difference was statistically significant. The rate of analgesia use and the frequency of requests for analgesia in the study groups were significantly lower than the placebo group. Mean arterial blood pressure and mean heart rate in the study groups were also lower than the placebo group. However, this difference was only statistically significant in recovery. The mean heart rate in the tizanidine group was lower than that of pregabalin, which may be attributed to the sedative and analgesic effects of tizanidine relative to pregabalin. Although this difference was not statistically significant,

Talakoub *et al*.[20] conducted a study on the effect of oral tizanidine in reducing pain after selective LC, postoperative pain, and the need for analgesics and the result showed a significant reduction of these two parameters in the study group compared to the placebo group. In the present study, use of 4 mg of tizanidine was also led to the similar results.

Imai *et al*.[21] conducted a study to evaluate the effect of pregabalin postoperatively on reducing shoulder pain after thoracotomy in patients with lung cancer. They used 150 mg of pregabalin postoperatively and concluded that the drug could be effective in reducing shoulder pain resulting from thoracotomy. Their findings are consistent with the results obtained in the present study. However, the type of surgery and the dose of the drug used are different in two studies.

Nutthachote *et al*.[24] at Bangkok University of Medical Sciences in Thailand studied the effect of pregabalin on relieving postoperative shoulder pain in gynecological diseases. 75 mg of pregabalin was administered 2 hours before surgery and then two doses of every 12 hours. There was a significant reduction in shoulder pain and the amount and use of analgesics after laparoscopic surgery. In our study, 100 mg of pregabalin was used as one dose 90 minutes before surgery and similar results were achieved. Although the type of operation was different, the mechanism of pain seems to be the same in both types of surgery.

Chang *et al*.[25] conducted a study at Konkuk University of Medical Sciences in South Korea to evaluate the effect of preoperative pregabalin on the prevention and relief of shoulder pain after LC. They used two doses of 300 mg pregabalin 12 hours before surgery and concluded that the drug could be effective in reducing shoulder pain resulting from laparoscopic surgery. The results were similar to our findings. However, the dose used in our study was 100 mg and a single dose.

Wei LA *et al*.[26] conducted a study at the University of Colorado, Denver, USA and found that pregabalin was effective in reducing pain after ocular plastic surgery compared with the placebo group. A study by Matsutani *et al*.[27] (2014) at University of Medical Sciences in Tokyo, Japan indicated that pregabalin is significantly effective for neuralgia developed after thoracotomy. These studies showed that this drug can be effective in reducing postoperative pain.

Numerous hypotheses have been put forward about the cause of shoulder pain after laparoscopic surgery, including overstretching of the diaphragm muscle fibers, rapid filling of the peritoneum with localized gas, and acidosis due to the conversion of carbon dioxide to carbonic acid, which can irritate the diaphragm muscle. These factors cause phrenic nerve stimulation and shoulder pain.[28] This study showed that the use of tizanidine and pregabalin can be effective in reducing the shoulder pain after LC.

Conclusion

Considering the results of the previous studies and the present research, it seems that separate or combined use of these drugs can be effective in reducing or controlling the postoperative pain with common analgesics that are currently used after surgery, including narcotics and noninflammatory analgesics, and reducing the dose of these drugs is associated with lower side effects and providing higher quality of life. The abovementioned points indicate that further research is required in this regard with more diverse drugs and doses to better control these side effects.

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Conflicts of interest
There are no conflicts of interest.

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