THE EFFECT OF TIZANIDINE ON POSTOPERATIVE PAIN MANAGEMENT AFTER LUMBAR FUSION SURGERY

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ABSTRACT

Lumbar fusion is one of the most commonly used surgical procedures to improve the pain and instability of the spinal vertebrae. After surgery, patients experience varying degrees of pain. The aim of this study was to determine the effect of tizanidine for the management of postoperative pain after lumbar spinal fusion surgery. This randomized clinical trial study was performed on 50 patients who were selected for spinal fusion surgery. Patients were randomly divided into two groups of 25 patients. Patients in the tizanidine and placebo groups received 4 mg oral tizanidine and placebo one hour before surgery and 24 hours after that. Severity of pain, presence of nausea, vomiting, pruritus, headache, vertigo, xerostomia, somnolence, bradycardia and excess opiate in the two groups were evaluated and recorded prior to exit from recovery and 2, 4, 6, 12, 24 and 48 hours after surgery. Data were analyzed by SPSS software version 24. There was a significant difference in pain score in tizanidine group at 24 and 48 hours after surgery compared with placebo (P <0.005). In the control group, the use of morphine sulfate was more than the tizanidine group. There was no significant difference in the incidence of side effects in the two groups (P> 0.05). Low dose tizanidine in postoperative pain management is effective without significant side effects. Due to its simpler administration, it is recommended to use for postoperative pain control after lumbar fusion surgery.

Keywords: *Tizanidine, lumbar fusion surgery, postoperative pain.*

INTRODUCTION

Lumbar fusion surgery is one of the most common selective neurosurgery procedures to relieve pain, instability or other symptoms by removing movement between the vertebrae (1-3). After all surgeries, patients inevitably feel pain to varying degrees. Despite increasing attention to the pain assessment program and the development of new standard methods of pain management, many patients still endure severe post-operative pain (4, 5). Patients undergoing spine surgery also experience moderate to severe postoperative pain (6, 7).

Postoperative pain can cause undesirable physiological effects such as inadequate breathing, failure to discharge respiratory secretions, atelectasis and other pulmonary complications, increased heart rate, hypertension, ileus and prolonged bed rest. This can eventually increase the incidence of deep vein thrombosis (8, 9). In addition, in patients undergoing vertebral surgery, postoperative pain can delay the onset of walking and physiotherapy, which may increase the length of hospital stay and ultimately the cost of surgery and changes the patient's sense of recovery and surgical outcome (6, 10).

Increasing evidence indicates that postoperative pain is not adequately treated (11). It is essential to treat pain with minimal side effects to increase rehabilitation and decrease postoperative morbidity (12). Side effects, such as prolonged hospital stays, delayed functional improvement, higher readmission rates, and increased health care resources are associated with inadequate pain management (13, 14). In addition, there is evidence that acute postoperative pain reduction may reduce the spread of chronic pain (15, 16).

Finding a way to get the most out of pain reduction and patient relaxation with minimal complications is one of the most important issues after surgery. Opioids, especially their injectable form, have been widely used as the first line of pain relief to relieve acute pain after surgery, including lumbar spine surgery (9, 17, 18). On the other hand, pain is a multifactorial phenomenon that is not completely controlled by monotherapy with opioids. In addition, Opioids use is associated with dose-related complications such as respiratory depression, nausea, vomiting, urinary retention, pruritus, drowsiness or postoperative ileus (19).

Tizanidine is a centrally-acting alpha-2 agonist with muscle relaxant, anxiolytic and sedative properties which has been widely used in the treatment of muscle spasms and more recently in the treatment of musculoskeletal pain (20). The use of tizanidine in anesthesia has been studied in several studies. According to these studies, oral tizanidine reduces the effect of hypertensive response during laryngoscopy and reduces the dose of midazolam induction. It also reduces the maintenance dose of propofol and MAC[1] of sevoflurane and can prolong spinal anesthesia (21-24). The role of postoperative analgesia of tizanidine on animal models (25) as well as in few human studies has been investigated (26).

The effects of tizanidine on pain management after lumbar disc and lumbar fusion surgery have not been studied. Only there is few clinical trials in databases that have been conducted on the effect of tizanidine in pain management in other surgeries (26-28). On the other hand, a significant portion of postoperative pain is due to surgical position as well as muscle spasms, which has received less attention than the pain of incisions and operation.

Therefore, in view of the above, and the importance of pain relief in patients after surgery, including spinal surgery, as well as the few studies to determine the analgesic effects of tizanidine and its potential positive effects on pain control, this study was designed to determine the effect of preoperative oral tizanidine on the severity of pain after lumbar fusion surgery.

METHOD AND MATERIALS

Ethical considerations

Permission was obtained from the research department of the faculty to initiate the project. The information from this research and the responses of the individuals were collected in a confidential and anonymous manner. Subjects participated in the study with informed consent.

Design of study

This study is a double blind randomized controlled clinical trial.

Protocol of study

The study population consisted of patients undergoing elective lumbar fusion surgery referred to Imam Khomeini medical center in Sari. The sample comparison method was used to determine sample size. In addition, based on the study by Ahiskalioglu et al. (26) and according to the sample size calculations, taking into account the 80% power, the 95% confidence level was equal to 20 persons, which was determined to be 25 in each group, given the possible loss of participants. To conduct the study, 50 patients aged between 35-60 years with Class 1 and 2 Anesthesia (ASA) candidates for laminectomy with selective lumbar fusion surgery with 1. Discopathy of more than two lumbar spaces 2. Lumbar spondylolisthesis 3. Multiple lumbar canal stenosis, were selected as available. Initial selection was based on the condition of the study units. Inclusion criteria included: 1- Confirmation of diagnosis by physical examination, CT scan and MRI 2- Patient's willingness to participate in the study and obtaining informed consent 3- Candidate for non-emergency lumbar fusion surgery 4- age between 35 to 70 years old and 5- No

[1] Monitored Anesthesia Care

history of tizanidine hypersensitivity 6- lack of bradycardia (HR <60) 7- No CNS disease 8- No previous lumbar surgery. Exclusion criteria were as follow: 1- Patient's unwillingness at any time to continue the study 2- Opioids use 24 hours prior to intervention 3- Alcohol or drug abuse 4- Incidence of any uncommon side effects during surgery. Selected patients according to the inclusion criteria then were divided into groups A and B using permuted block randomization. Before surgery, patients were provided with detailed instructions on how to determine the severity of pain, nausea, vomiting, and postoperative pruritus using the visual analog scale (VAS) and how to use a PCA pump. Patients in group A received a single oral 4 mg tizanidine tablet (manufactured by Jalinous pharmaceutical company) and patients in group B received an oral placebo one hour before surgery and 24 hours after that. Anesthesia protocol was performed including premedication; midazolam at dose of 0.01 mg/kg and fentanyl at dose of 2 mc/kg; Then induction with sodium thiopental at dose of 4-6 mg/kg/iv and atracurium at dose of 0.5 mg/kg/iv and intubation with armored tube No. 7.5-8 was performed. During surgery, morphine sulfate at dose of 0.1 mg/kg and atracurium at dose of 0.01 mg/kg iv were administered to patients and 50% nitrous oxide gas with oxygen and isoflurane inhalation anesthetic 0.5-1.5 MAC was used as a maintenance anesthetic.

After surgery and in recovery room, an PCA pump containing the same medicine composition as 30 mg morphine sulfate, 3 gram of acetaminophen and the remainder up to 80 cc (total pump volume) of normal saline were applied for all patients. The pump setting specification was as follows: bolus rate of 0.5 cc and 15 min of Lock interval and 2 cc background infusion per hour.

The severity of pain, nausea and vomiting, pruritus and opioids use of patients and other possible side effects including xerostomia, bradycardia, headache, dizziness and drowsiness in the two study groups after consciousness in recovery and then in neurosurgery ward at time 2, 4, 6, 12, 24 and 48 hours after surgery were evaluated and recorded. Morphine would administer intravenously at a dose of 3 mg if the patient has a pain score more than 5 (according to the VAS criteria for pain control). In case of nausea with the score more than 3 or vomiting, ondansetron 4 mg was given up to three doses in 24 hours. In addition, the amount of fentanyl consumed during anesthesia was also assessed and recorded. The primary outcome is the study of patients' pain intensity and opioids use and the secondary outcome is the presence of nausea and vomiting, pruritus, xerostomia, bradycardia, headache, dizziness and drowsiness. The evaluation was done by a project nurse who was unaware of the study groups and had received adequate training in this area. Patients' body mass index (BMI) was calculated and was recorded in the relevant form alongside with other information including age, education, duration of surgery, duration of anesthesia, the number of intervertebral space and number of vertebrae involved in fusion surgery and morphine intake at 48 hours and ondansetron administration at 48 hours (if VAS> 4) After surgery. It is noteworthy that the placebo required in the study was obtained from Sari School of Pharmacy. In addition, all surgeries were performed by a surgeon.

Data collection

Data was collected by field method using information questionnaire.

Statistical analysis

Data analysis was performed using SPSS version 24. The variables were described with percentage, mean, standard deviation, minimum and maximum. Repeated measure analysis of variance, independent and dependent t-tests were used to compare mean pain intensity between groups. Chi-square test was used to compare the frequency of nausea, vomiting, pruritus, xerostomia, bradycardia, headache, dizziness and drowsiness. The significance level was less than 0.05 available to university officials completely and unchanged.

RESULTS

In the present study, 50 patients were enrolled which divided into two groups of 25, one group receiving Tizanidine and the other placebo. In total of two groups were 30 (60%) female and 20 (40%) male. In intervention group 14 (56%) were female and 11 (44%) were male and in placebo group 16 (64%) were female and 9 (36%) were male. There was no significant difference between the two groups in terms of gender ($p = 0.821$).

Age distribution analysis showed that in the tizanidine group 36% were under 45 years old and 64% were over 45. In the placebo group, 44% were under 45 and 56% were over 45 years old. The results of chi-square test showed that the two groups were similar in age distribution, so that the mean age of the tizanidine group was 49.19 ± 9.80 years and the mean age of placebo group was 47.13 ± 11.31 ($p = 0.65$).

The results showed that there was no significant difference between the two groups in terms of other demographic data ($p> 0.05$) (Table 1).

The mean VAS severity measured at the time of recovery (zero hour) was 3.92 ± 1. 1.87 in the intervention group and 3.52 ± 1.78 in the placebo group but the difference between the two groups was not significant ($p= 0.442$). The mean VAS severity measured at 2 hours after surgery was 4.6 ± 1 in the intervention group and 4.52 ± 1 in the placebo group, with no significant difference between the two groups ($p= 0.802$). The mean VAS severity measured at 4 hours after surgery in the intervention group was 4.2 ± 0.91 and in the placebo group was 4.32 ± 0.9 which was not significant ($p= 0.620$). The mean VAS severity measured at 6 hours after surgery was 3.96 ± 1.27 in the intervention group and 3.96 ± 1.2 in the placebo group, which was not significant ($p= 0.992$). The mean VAS severity measured at 12 hours after surgery was 1.58 ± 3.8 in the intervention group and 1.55 ± 3.8 in the placebo group, but the difference between the two groups was not significant ($p = 0.897$). The mean VAS

severity measured in the 24 hours after surgery was 1.88 ± 1.39 in the intervention group and 2.84 ± 1.21 in the placebo group. The difference between the two groups was significant (p= 0.013). The mean VAS severity measured 48 hours after surgery was 1.28 ± 1.13 in the intervention group and 2.12 ± 1.39 in the placebo group. The difference between the two groups was significant (p= 0.024). (Figure 1 and 2).

Morphine sulphate intake during the 48 hours was 27.5 mg in the placebo group and 22 mg in tizanidine group, which was statistically significant ($p < 0.05$).

5 patients in the tizanidine group and 4 in the placebo group had nausea during the first 6 hours after surgery. No cases were reported at 12, 24 and 48 hours. There was no statistical difference between the two groups in terms of incidence and severity of nausea during different hours of operation ($p > 0.05$).

One person in both groups had vomiting, which was not statistically different between the groups. These two were given extra ondansetron. Considering the presence of one case of vomiting in both groups and the use of ondansetron, the mean of administered ondansetron was compared in both groups. Statistical calculations showed no significant difference between the two groups in terms of ondansetron intake.

2 patients in the placebo group and 1 in the tizanidine group had pruritus, which was not statistically significant. It also showed that there was no pruritus during the 4 hours after the operation.

According to Table 2, drowsiness in the tizanidine group was seen in 6 patients (24%) and in the placebo group was seen in 7 patients (28%), which was not statistically significant. Headache rate in tizanidine group was 4% and in placebo group 2 was 8% which the difference was not statistically significant. Also, dizziness was 12% in the tizanidine group and 4% in the placebo group, which was not statistically significant. Xerostomia in both groups was seen in 7 patients (28%), which was not statistically significant. Bradycardia hasn't occurred in none of the patients in both groups.

In overall, the results showed that the pain intensity was lower in the tizanidine group at 24 and 48 hours after surgery compared to the other group. There was no significant difference between the two groups in terms of possible complications such as nausea, vomiting, pruritus, headache, dizziness, xerostomia, bradycardia and drowsiness. Morphine sulfate intake was lower in the tizanidine group during 48 hours than in the placebo group and this difference was significant. However, the two groups did not differ in the amount of ondansetron intake.

Table 1. Demographic characteristics and clinical information of patients

Variable	Groups		P value
	Tizanidine (n= 25)	Control (n= 25)	
age	49.19 ± 9.8	47.11 ± 13.31	0.65
BMI (kg/m^2)	29.35 ± 3.98	30.88 ± 2.56	0.36
Operation time (minute)	232.46 ± 65.22	201.12 ± 78.71	0.74
Duration of anesthesia (minutes)	291.25 ± 56.41	261.32 ± 82.76	0.17
Number of fused vertebrae	3.20 ± 0.96	3.31 ± 1.17	0.96

Figure 1. The process of pain score changes within 48 hours after receiving the medications

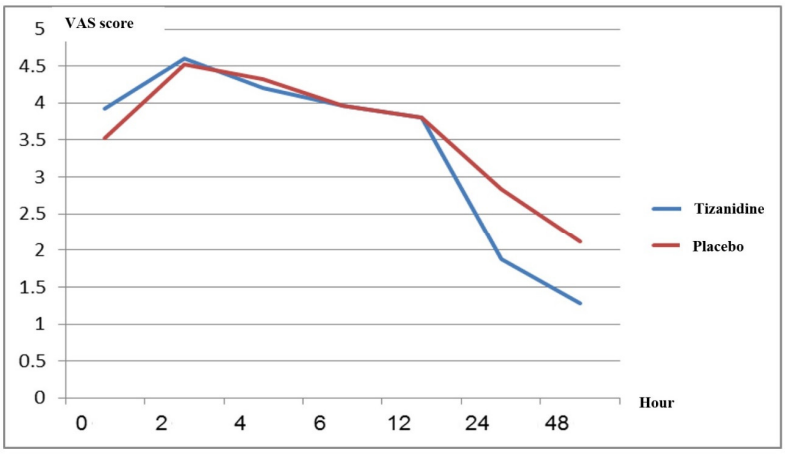


Figure 2. Comparison of mean pain score within 48 hours after medications administration

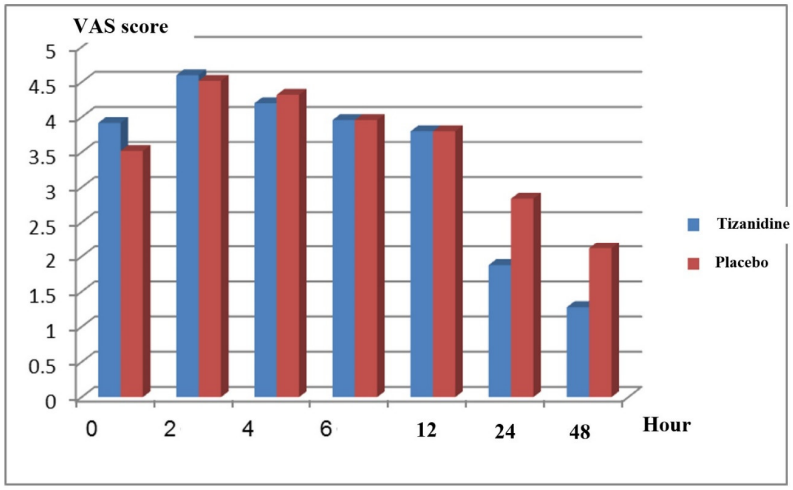


Table 2. Other qualitative variables and their comparison between intervention and placebo groups

Variables	Tizanidine group N (%)	Placebo group N (%)	Total N (%)	p value
Drowsiness	6 (24 %)	7 (28 %)	13 (26 %)	0.327
Headache	1 (4 %)	2 (8 %)	3 (6 %)	0.327
dizziness	3 (12 %)	1 (4 %)	4 (8 %)	0.35
Bradycardia	0	0	0	1.00
Xerostomia	7 (28 %)	7 (28 %)	14 (28 %)	1.00

* The date is expressed as frequency (percent)

DISCUSSION

Our study results showed that the VAS score was significantly lower in patients treated with low-dose tizanidine at 24 and 48 hours postoperatively than those receiving placebo. Postoperative morphine sulfate intake was significantly lower in the tizanidine group than in the placebo group. Earlier use of tizanidine or higher doses can lead to better and faster efficacy. Also, given prone position of patient in lumbar fusion surgery and long period of time which patient stays in this position, there may be muscle spasms consequently which tizanidine intake as prophylactic or therapeutic can improve the pain, due to its antispasmodic properties.

Clonidine is a prototype of a2-agonist. The role of clonidine in postoperative anesthesia is quite clear (29). Clonidine, when administered injectable, relieves post-operative pain and acts as a topical anesthetic. The pain then subsides and reduces the need for opioids during anesthesia. (7, 27) Clonidine and tizanidine were not previously compared in the terms of postoperative anesthesia, but the antinociceptive properties of tizanidine are weaker than clonidine and side effects of tizanidine are well tolerated (19, 28)

The sedative and hemodynamic effects of tizanidine and clonidine have been studied in healthy volunteers. Both medications have sedative and hypotensive effects and reduce salivary secretion, however; tizanidine effect is short-term. 4mg tizanidine decreased the SBP (systolic blood pressure) by 9% (30). Overall, adverse events were low with our pain management strategy; severity was mild and no treatment was required. Changes in heart rate and mean arterial pressure were within the prescribed range of operation and there was no required treatment and intervention in both groups.

In a study by Talakob *et al* on the effect of tizanidine on postoperative pain in patients undergoing laparoscopic cholecystectomy, 4mg oral tizanidine preoperatively reduced postoperative pain score during recovery hours 1, 2, 3, 6, 12 and 24, as well as opioids use duration of recovery in patients. While the reduction of pain score in our study was at 24 and 48 hours postoperatively and there was no significant difference between the study groups before that. In this study, 4 patients in the tizanidine group experienced drowsiness, which was statistically significant and other complications such as bradycardia, nausea and vomiting were not significant. However, in our study the incidence of complications was not significantly different between the two groups (27).

In the study of Rupani *et al*, the effects of oral Tizanidine on pain after anorectal surgery under spinal anesthesia were investigated. 60 minutes before admission to the operating room, placebo was given to control group and study group received 4 mg oral tizanidine. Pain onset and meperidine intake 24 hours after surgery and side effects were recorded. The mean duration of analgesia was 332.5 and 144 minutes, in the tizanidine and placebo groups, respectively, which was significantly longer in the tizanidine group than in the control group. Also, the mean dose of meperidine in the 24 hours after spinal anesthesia in the control group was 42.17 mg and 26.67 mg in the tizanidine group which was statistically significant. Same as our study, morphine sulfate intake levels were significantly lower in the tizanidine group at 48 hours postoperatively (28).

In a study by Ahiskalioglu *et al*, the single-dose effect of 6mg Tizanidine preoperatively and bilateral cervical superficial block (BSCPB) comparing with the effect of BSCPB alone and placebo on postoperative total thyroidectomy pain was evaluated. In the tizanidine+BSCPB group, there was a significant difference in postoperative pain and opioid use compared to the placebo group. Fentanyl consumption was lower in the group 0-4 and 4-8 hours postoperatively than in the placebo group. Fentanyl consumption was also lower in the tizanidine+BSCPB group than in the BSCPB group alone during the first 4 hours postoperatively. Apart from the subgroup receiving tizanidine, occipital headaches and back pain were less common (28). In his study, a single 6mg dose of tizanidine significantly reduced pain in the PACU at 1, 2, 4, 8, 12, and 24 hours. However, in our study, there were significant differences in pain reduction at 24 and 48 hours. In their study, one person had xerostomia and one had drowsiness in the tizanidine group (n = 20) (26).

A study by Yazicioglu et al investigated the effect of tizanidine on acute pain after inguinal hernia surgery. The tizanidine group received 4 mg of tizanidine 1 hour before surgery and continued the treatment twice daily for one week, with the other group receiving placebo instead of tizanidine. The tizanidine group had lower pain scores at 6, 12, and 24 hours and 2, 3, and 4 days postoperatively, both at rest and during exercise. Excess analgesic consumption was also lower in the tizanidine group than in the control group. The return to normal activity and quality of life in the tizanidine group was also better than the control group (30).

Imanaga et al showed that 3 mg oral tizanidine as premedication can reduce the pain of infiltration and anesthetic diffusion due to epidural catheterization (31). In this study, the analgesic effects of tizanidine during epidural infiltration anesthesia was evaluated, but we studied its effect on postoperative pain in patients who underwent anesthesia.

Norouzi et al showed that premedication with 4 mg of tizanidine prior to lower extremity plaque removal surgery caused less pain during surgery and less opioid use after surgery, which in our study also reduced opioid use.

Side effects of tizanidine are dose dependent. Xerostomia and drowsiness are among the most common (26). In our study, there was no significant difference between the tizanidine group and placebo group in terms of side effects.

Several features of the study protocol require discussion. This was the first study to investigate the role of tizanidine in postoperative pain management of lumbar fusion surgery.

The effective dose and timing of tizanidine are not known in the field, so only a small dose of this medication intentionally was used. In addition to the low side effects of tizanidine, the low dose used in our studies and the timing of the first dose of tizanidine may be the cause of reduction in side effects incidence that we have encountered. One goal of using tizanidine is to avoid postoperative analgesic side effects by reducing their dose. In addition to impairing the patient's functioning, these side effects can interfere with the side effects of tizanidine. We believe that the low-dose side effects of tizanidine were similar in the two groups and were not significant.

The limitations of the study are as follows. Initially, two doses of 4 mg tizanidine were used in this study. More and more doses can have better analgesic effects, but may have more side effects. Second, the study protocol prevented the participation of patients who were prone to develop various side effects associated with pain management. Third, there were no fixed nursing staff at the time of hospitalization and there may be potential interference with information. In addition, patients were not assessed after discharge in terms of fatigue or sleep schedule, and it is unclear whether their pain score varied during the week following surgery.

CONCLUSION

Tizanidine has been shown to reduce postoperative pain in 24 and 48 hours after surgery and reduce analgesic administration without any significant side effects. Postoperative pain relief results in a faster return of patients to their normal daily activities. Obviously, the quality of life has also improved in terms of pain relief.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2013. Voluntary written and informed consent was obtained from the patient prior to enrollment in the study.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest regarding this manuscript.

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