



Controlling Post-operative Pain Intensity in Patients Undergoing Tibia Fracture Surgery: Pregabalin vs. Clonidine

**Amir Sobhani Eraghi¹, Seyedehsan Daneshmand^{2*}
and Seyed Mohammad Malakooti²**

¹*Department of Orthopaedics Surgery, Rasoul-E- Akram Hospital, Iran University of Medical Sciences, Tehran, Iran.*

²*Bone and Joint Reconstruction Research Center, Rasoul-E- Akram Hospital, Iran University of Medical Sciences, Tehran, Iran.*

Authors' contributions

This work was carried out in collaboration among all authors. Authors participated in draft, design, interpretation, and the analyses of the study and wrote the manuscript. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2019/v31i630366

Editor(s):

(1) Dr. Syed A. A. Rizvi, Department of Pharmaceutical Sciences, Nova Southeastern University, USA.

Reviewers:

(1) Preksha Barot, GMERS Medical College, India.

(2) Arthur N Chuemere, University of Port Harcourt, Nigeria.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/53677>

Original Research Article

Received 20 October 2019

Accepted 25 December 2019

Published 27 December 2019

ABSTRACT

Introduction: The goal of this study was to compare the effect of two drugs (pregabalin and clonidine) on pain intensity within 24 hours after surgery in patients undergoing tibia fracture surgery is a step forward to choose the right drug.

Methods: In this randomized clinical trial, 64 candidates for elective tibia fractures were selected based on a randomized table. The patients were divided into two groups of those treated with clonidine (group C) and those treated with pregabalin (group P). Clonidine is given to patients in the first group one hour before surgery at a dose of 0.1 mg/kg and one hour after surgery at a dose of 0,1 mg / kg. Patients in the second group received pregabalin one hour before surgery at a dose of 200 mg and one hour after surgery at a dose of 200 mg orally. Then the variables are 6,12 and 24 hours. Finally, by using SPSS software, qualitative variables were compared according to their

*Corresponding author: E-mail: ehsanehsan30@gmail.com;

percentage using Chi square test, and for quantitative variables, the mean of each group was calculated and t-test was used to compare the means.

Results: The visual analog scale (VAS) scores were significantly lower in the pregabalin group compared with the clonidine group at .7 and 70 hours after surgery. A statistically significant analgesic effect was seen in the clonidine treated group compared with pregabalin.

Conclusion: Our data suggested that pregabalin improves pain relief after surgery, but it has less analgesic effect than clonidine.

Keywords: Tibia fracture; postoperative; clonidine; pregabalin; surgery.

1. INTRODUCTION

Nowadays, the treatment of tibial fracture is as large number of difficulties. According to health statistics reference (NCHS), 490 thousand persons are victims of tibial fractures in America annually [1,2], and the annual incidence of this condition is 1 per 2000 persons [3]. Anterior-Median face of tibia stands beneath the skin and is the main cause of its vulnerability to fractures instead of other long bones. Tibia is the most common bone that undergoes open fractures, and the main cause is vulnerability of tibial zone skin and connective tissue [4]. Fracture in the body of tibia is more common in young adults and may result in unemployment and other economic activities for the patient. At a greater scale, it can cause irreversible and important difficulties for countries' health system. Stimulation caused by surgery increases internal hypersensitivity and irritability in surgery site and may also develop so much pain afterward. Central inhibition in nervous system with pain killers may have so many advantages such as: reducing the pain just after surgery, improving the recovery and quality of life and reducing the chronic pains [5]. Preemptive analgesia by central desensitization in surgical incision sites is used for pain killing purposes during surgery [6]. Numbness and efficient anti pain effects can reduce the patient's stress reactions such as hyper-metabolism, water and sodium retention, hypertension, tachycardia and wound healing latency [7,8]. On the other hand, deep calmness can prevent harmful consequences such as pneumonia, vascular thrombosis and decreased blood pressure [9-11]. Clonidine is an alpha-2 agonist that is used for relaxant and pain killer effects [12-14]. Unlike other pain killers such as opioids this drug has comparatively less side effects and may cause a little bradycardia or hypotension [15].

In this study, we tried to compare the effect of two drugs, namely pregabalin and clonidine on the amount of post-operative pain in patients

undergoing tibia fracture surgery within 70 hours. This is a step forward to choose the right drug. Given the fact that tibial fracture and its surgery is so difficult for patients and clinical improvement takes a considerable amount of time, choosing the right drug between pregabalin and Clonidine 42 hours after surgery in patients who have undergone tibial fracture could be a way to better reduce the pain and improve their quality of life.

2. METHODS

2.1 Study Design and Drug Groups

In this randomized clinical trial, 25 patients who were going to undergo elective tibial fracture surgery were chosen according to a randomized table. They were divided into 2 groups: Group C was those treated with Clonidine and Group P were those treated with pregabalin (Table1). Then, according to their surgery date, they underwent surgery. Patients who had surgery on odd days received pregabalin, while those who had surgery on even days took clonidine. Inclusion criteria: male and female between 18 and 50 years old with 1 or 2 ASA class having tibial fractures. Exclusion criteria: patients over 50 years old or younger than 18, overweight people [BMI> 20%], history of pregabalin or Clonidine sensitivity, alcohol or drug abuse, medical disease such as asthma, hypertension, diabetes, history of chronic pains, dysfunction of liver and kidney, use of pain killers 6 hours before going for surgery, and duration of operation of more than 3 hours. Clonidine was used one hour before operation at the dose of 0.1 mg per kg and 1 hour after operation at the dose of 0.1 mg per kg in Group C. On the other hand, pregabalin was used one hour before operation at the dose of 200 mg and 1 hour after operation at the dose of 200 mg oral. Variables were assayed 6, 12 and 24 hours after operation. We used a checklist based on visual analog scale [VAS] score, post-operative nausea and vomiting [PONV], heart rate, blood pressure,

Table 1. Demographic comparison between C and P groups

	Group C [treated with clonidine]	Group P [treated with pregabalin]	p- value
Age mean [Standard deviation]	31,8 years [SD: 6,7]	32,6 years [SD=6,7]	0,2
Weight mean [Standard deviation]	54,26 ± 7,64	54,35±6,83	0,6
Height mean [Standard deviation]	167,04±0,87	164,48 ± 4,45	0,4
Surgery duration mean[Standard deviation]	105±15,2 min	108±14,8 min	0,96
PR mean[Standard deviation]	91,66 ± 13,7	92,17±13,9	0,141
MAP mean[Standard deviation]	65,39±13,7	65,1±13,26	0,765

sedation score, duration of painkiller need after surgery, and the whole amount of pain killer that cases had been used All checklists were filled by the researcher. Finally, we used SPSS and entered 22 to 25 cases and we have figured the qualitative variability with counting amplitude percentage and comparison with CHI square and to find quantitative variables, we used mean score and T test. Cases Information showed by checklists based on variables and in the end it will be published by results analysis.

Finally, we used SPSS and entered 22 to 25 cases and we have figured the qualitative variability with counting amplitude percentage and comparison with CHI square and to find quantitative variables, we used mean score and T test. Cases Information showed by checklists based on variables and in the end it will be published by results analysis.

Based on Prasad et al., study, the mean pain score in two groups that took Clonidine and pregabalin after operation was 3,58± 0,98 and 4,55 ± 1,03. With Confidence coefficient of 0.05 and the power of 90%, sample size in each group is 25 and totally is 50 people. Written informed consent was obtained from individuals to enter the study. Information about all individuals was kept by the researchers. The study imposed no financial burden on the patients.

2.2 Statistical Analysis

Final results for quantitative variability count by mean ± standard deviation and for qualitative variability's counts by percentages. Comparison

between quantitative and qualitative variables was made by t-test or if they had normal distribution; otherwise, Mann-Whitney U test was used. Comparison between qualitative variables is made by Chi Square test or Fischer test. The correlation between quantitative variables was investigated by Pearson correlation coefficient and Spearman rank correlation test. in the determining the difference of Study Indicators in Patients and in presence of Basic features of patients as study confounding factors, Multivariate logistic regression analysis will be used and the results will be expressed as Odds Ratio [30% Confidence Interval]. SPSS version 46 and SAS version 3.6 were used for statistical analysis. Significance level is considered below 0.05.

3. RESULTS

Our sample included 92 patients aged between 34 - 50 who had a history of tibial fractures and were scheduled for elective operation. All the patients entered the study but after screening, 25 did not meet the inclusion criteria, 8 were excluded from the study because due to exclusion criteria, and finally 9 refused to cooperate and were excluded. Finally 50 [62,5%] individuals entered the study and were randomly divided into two groups, 25 each as described above. The average age in Group C was 32,6 [SD =6,4], and it was 31,8 [SD=6,7] in Group P, showing no statistically significant age differences. None of the patient had a history of medical diseases such as diabetes, hypertension, etc. Average duration of operations in Group C was 105±15, 2 minutes and it was 108±14/8 minutes in Group P, and there was no statistically significant, and also all patients

were hospitalized under identical physical conditions.

Means of pain severity are shown in Table 2. The VAS score in Group P was 7,26±0,31 after 6 hours and 7,02 ±0,32 after 12 hours and 7,26±0,36 24 hours after operation. VAS score in Group C was 7,12± 0,14 after 6 hours and 7,25±0,2 after 12 hours, and 7,35±0,1 24 hours after operation. The average severity of pain was lower in Group P than in Group C after 6 hours but it was not significant (p=0,07). Moreover, the average severity of pain in Group P was lower than that in Group C after 12 hours and it was significant (p=0,002). Finally, the average severity of pain in Group P was lower than that in Group C after 24 hours and it was significant [p=0,03]. Overall, regardless of the time parameter, severity of pain was lower in Group P compared to Group C, and it was statistically significant (P=0,025).

C group took 382 dosages of narcotics and p group took 346 dosages of narcotics in their treatment period. First time requirement for narcotics in Group C was 240±6,8 minutes and in Group P it was equal to 251,2±4,8. There was no statistically significant difference between the two groups. [P=0, 12] According to Table 3, the number of patients in group C who received 1 dose of opioids during the 12-24 hours after surgery was lower than that in Group P, which was not statistically significant [p = 0.4]. The number of patients in Group C who received 4 doses of opioids during the 6-12-24-hour period after surgery was smaller than that in Group P, which was not statistically significant [p = 0.07].

The number of patients receiving more than 4 doses of opioids during the 6-12-24 h postoperative period was smaller than that in Group P, which was statistically significant (P = 0.02). Overall, patients in Group C received a greater amount of pain relief than those in Group P, which was statistically significant. (p = 0.01).

According to Table 4, the Ramsay sedation score [RSS] was Table 4, 2 in both groups.

The results show the analysis within and between patients. Duplicate size revealed a significant improvement for all subscales of the questionnaire listing within the two combination groups through the 3 scores. [VAS: F = 155,17, p = 0,000, RSS: F = 27,26 p = 0,000, Heart rate: F = 32.62, p = 0,000, MAP: F = 48,82, p = 0.000, and members who need analgesic: F = 6,98, p =0,004].

Time-treatment interaction analysis also showed a greater and more significant effect for clonidine versus pregabalin over time showed a subscale of P = 0/002 [RSS] and P =0.000 [VAS]. There was no significant difference between the two groups in the other cases. As shown in Table 3, the mean changes in RSS score at the end of treatment among subjects in Group C [treated with clonidine] was significantly different from those in Group P [pretreated with gabaline] with a large effect size of 94., 5,38– mean difference [MD], 95% CI = -3.48, -1.59 to p = 0.000]. However, there was no significant difference between the two groups in the mean scores of

Table 2. VAS mean pain score comparison between P and C groups

	Group C	Group P	p- value
Mean pain score 6 hours after operation	7,12±0,14	6,35±0,31	0,07
Mean pain score 12 hours after operation	7,25±0,2	7,02±0,32	0,02
Mean pain score 24 hours after operation	7,26±0,36	7,35±0,1	0,03

Table 3. Comparison of the number of drug users between Groups P and C

	Group	after 6 hours after operation	after 12 hours after operation	after 24 hours after operation	p-value
1 dose	C	21 (84%)	17 (68%)	3(12%)	0,4
	P	22 (88%)	21(84%)	3(12%)	
2 doses	C	4 (16%)	8(32%)	15(60%)	0,07
	P	3(12%)	4(16%)	19(76%)	
More than 2	C	-	-	(14%)	0,02
	P	-	-	3(12%)	
Sum	C	25(100%)	25(100%)	25(100%)	0,01
	P	25(100%)	25(100%)	25(100%)	

the RSS subscale 64 hours postoperatively [P = 0.203]. Midpoint [MD, 30% CI = -6.02, -9.53 to -5.79] and endpoint [MD, 30% CI = -2.10, -7.67 to -4.64] However, there was a greater therapeutic effect at 42 h [d = 0.94] postoperatively than 24 h after surgery [d = 0.53] while tending to be significant [p = 0.051] for a higher effect. Clonidine versus pregabalin was present in the number of drug users at the end of post-operative 24 h.[MD, 95% CI = -0.74, -1.94 to 0.00] Comparison of response [p=0.026]. RSS rates between the two treatment groups showed a significant difference for the RSS subscale and the number of patients receiving the drug at 24 hours after surgery.

4. DISCUSSION

Pain is the most common complaint of patients after surgery. Pain signals trigger a cycle of messages in the body's somatosensory system and enhance the stimulation of pain [9]. Clonidine is a 4-adrenoceptor agonist that induces anesthesia at the spinal and supraspinal levels. Oral clonidine is almost completely absorbed, with the highest plasma level occurring after 6 to 9 hours. It is fat soluble and can easily cross the blood-brain barrier. Pregabalin is a GABA analogue drug that prevents the release of many pain-related neurotransmitters. Having a half-life from 5.5 to 6.5, it is time-independent of dose and repetition [5].

We applied 655 mg of clonidine and pregabalin 6 hours before surgery and measured variables 42 hours after surgery. VAS and RSS at 64 and 42 hours postoperatively were significantly different between the two groups. Also, RSS was significantly higher in clonidine-treated subjects than in the pregabalin group, which may indicate that clonidine had a greater analgesic effect than pregabalin.

In a study by Montazeri and Ghobadian, similar to our study, the duration of anesthesia during spinal anesthesia with clonidine was increased [7]. In a study by Singh et al, patients were given

655 to 605 µg of clonidine 6-6.0 hours before spinal anesthesia, which significantly increased the duration of anesthesia among patients [9]. Partahusniajuto in his study showed that average anesthesia using 605 µg clonidine significantly increased in spinal anesthesia [10] Baidya et al. showed that post-operative analgesic requirement was reduced in patients treated with pregabalin [11]. In our study, the mean duration of anesthesia and VAS score were statistically different between the two groups. After pain relief, the duration of pain relief was significantly shorter in patients treated with pregabalin after 64 hours and 42 hours postoperatively, which may be effective in reducing postoperative pain in patients.

In another study by Ittichaikulthol et al., investigating the effect of pregabalin on postoperative morphine intake and abdominal pain in people undergoing hysterectomy, found that 955 mg of pregabalin one hour before hysterectomy significantly reduced morphine consumption. The study also suggests that pregabalin may be a postoperative analgesic alternative to morphine [12]. A review study by Clarke et al on preventing chronic postoperative pain using gabapentin and pregabalin, shows that the use of pregabalin and gabapentin relieves chronic postoperative pain. This study reviewed 474 articles, 11 of which were reviewed in the above article. In 9 case-control studies, there was a significant difference in the incidence of chronic postoperative pain in people who took gabapentin [13].

In another review study by Dauri et al. (2008), the use of gabapentin and pregabalin significantly reduced compared to the placebo group, and pain and drug use both decreased. Other treatment regimens have not been very effective. It was aimed to treat acute postoperative pain with gabapentin and pregabalin, which 37 articles have been studied [14]. A trial study by Akhavan Akbari et al aimed to evaluate the effect of oral pregabalin on postoperative pain in patients undergoing lower

Table 4. Comparison of RSS in Groups C and P

	Group C	Group P	p-value
RSS 6 hours after operation	RSS1: 13 (52%) RSS2: 12 (48%)	RSS1: 9 (36%) RSS2: 16 (64%)	0,23
RSS 12 hours after operation	RSS1: 7 (28%) RSS2: 18 (72%)	RSS1: 12 (48%) RSS2: 13 (52%)	0,05
RSS 24 hours after operation	RSS1: 11 (44%) RSS2: 14 (56%)	RSS1: 13 (52%) RSS2: 12 (48%)	0,03

extremity surgery, showing that a single oral dose of 605 mg preoperative pain effectively Postoperatively, it reduces the amount of pethidine used in orthopedic surgeries. The VAS score decreased throughout the study period compared to the placebo group. However, postoperative nausea and vomiting decreased by 4%. 2 hours and 6 hours postoperatively and pethidine intake in pregabalin group compared to placebo group has decreased [15].

5. CONCLUSIONS

The results of this study show that pregabalin relieves postoperative pain but has less analgesic effects than clonidine, and the most common complication of it is nausea and vomiting.

6. SUGGESTIONS

Evaluation of the efficacy of clonidine versus pregabalin in improving postoperative pain in this study can be a change in the relief of postoperative pain. This study can also be used as a basis for future studies with the following research questions:

1. Can the measurement of clonidine and pregabalin concentrations, be considered as a biomarker for pain relief?
2. Is pregabalin able to enhance the therapeutic effects of clonidine?
3. Can pregabalin be used to reduce clonidine's side effects in patients?

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Written informed consent was obtained from individuals to enter the study. Information about all individuals was kept by the researchers. The study imposed no financial burden on the patients.

ETHICAL APPROVAL

The study was confirmed by Ethics Committee of Iran University of Medical Sciences.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Watson JT. Treatment of unstable fractures of the shaft of the Tibia. *J Bone Joint Surg Am.* 1994;76:1575-84.
2. Bhandari M, Gordon H, Guyat T, Marc F, Swiont K, tornestta P, et al. Surgeons preference for the perative treatment of fracture of tibial shaft. *J Bone Joint Surg Am.* 2001;83:1746-52.
3. Milner SA, Davis TR, Muir KR, Greenwood DC, Doherty M. Long term outcome after tibial shaft fracture: is malunion important? *J Bone Joint Surg Am.* 2002;84:971-80.
4. Steven A, Sacramento O. Open fractures of the Tibia shaft. *J Bone Joint Surg Am.* 1997;79:334-41.
5. Carli E, Mayo N, Klubien K, Epidural analgesia enhances functional exercise capacity and healthrelated quality of life after colonic surgery: Results of randomized trial. *Anesthesiol.* 2002; 97:540-549
6. Vadivelu N, Mitra S, Schermer E, Kodumudi V, Kaye AD, Urman RD. Preventive analgesia for postoperative pain control: A broader concept. *Local Reg Anesth.* 2014;7:17-22.
7. Montazeri K, Ghobadian A. Oral clonidine as a premedication in spinal anesthesia: Effects on the duration of block and hemodynamic status a randomised double blind clinical trial. *J Res Med Sci.* 2002;7: 23-29
8. Martin J, Parsch A, Franck M, Wemecke KD, Fischer M, Spies C, Practice of sedation and analgesia in German intensive care units: results of a national survey. *Crit Care.* 2005;9:R117-23.
9. Singh H, Liu J, Gaines GY et al - Effect of oral clonidine and intrathecal fentanyl on tetracaine spinal block. *Anesth Analg.* 1994;79:1113-1116.
10. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous IV sedation is associated with

- prolongation of mechanical ventilation. Chest. 1998;114[2]:541-8.
11. Baidya DK, Agarwal A, Khanna P, Arora MK. Pregabalin in acute and chronic pain. J Anaesthesiol Clin Pharmacol. 2011;27: 307-14.
 12. Ittichaikulthol W, Virankabuttra T, Kunopart M, Khamhom W, Putarawuthichai P, Rungphet S. Effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without 36 salphingo - oophorectomy: A randomized, double-blind trial. J Med Assoc Thai. 2009;92:1318-23.
 13. Clarke H, Bonin RP, Orser BA, Englesakis M, Wijesundera DN, Katz J. The prevention of chronic postsurgical pain using gabapentin and pregabalin: A combined systematic review and meta-analysis. Anesth Analg. 2012;115:428-42.
 14. Dauri M, Faria S, Gatti A, Celidonio L, Carpenedo R, Sabato AF. Gabapentin and pregabalin for the acute post- operative pain management. A systematic-narrative review of the recent clinical evidences. Curr Drug Targets. 2009;10:716-33.
 15. Akhavan akbari G, Entezariasl M, Isazadehfar K, Mirzarahimi T. The effects of oral pregabalin on post- operative pain of lower limb orthopedic surgery: A double-blind, placebo- controlled trial. Perspect Clin Res. 2013;4:165-8.

© 2019 Eraghi et al.; This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Peer-review history:

*The peer review history for this paper can be accessed here:
<http://www.sdiarticle4.com/review-history/53677>*