RESEARCH ARTICLE

Is Gabapentin Effective on Pain Management after Arthroscopic Anterior Cruciate Ligament Reconstruction? A Triple Blinded Randomized Controlled Trial

Mardani-Kivi M, MD; Karimi Mobarakeh M, MD; Keyhani S, MD; Hashemi Motlagh K, MD; Saheb Ekhtiari Kh, MD

Research performed at Guilan University of Medical Sciences, Rasht, Iran

Received: 21 July 2013 *Accepted: 21 August 2013*

Abstract

Background: Acute pain is common after arthroscopic surgeries and it is one of the most important causes of patient dissatisfaction, admission time and increased morbidity . Gabapentin with anti-hyperalgesic effects can play a critical role in pre-emptive analgesia methods. The aim of this study was to assess the efficacy of gabapentin in pain management after surgery and the rate of drug consumption in patients who are candidate for anterior cruciate ligament (ACL) reconstruction arthroscopic surgery.

Methods: In this randomized, triple blind clinical trial, 114 patients who were candidate for arthroscopic ACL reconstruction were divided into two groups of gabapentin (G) and placebo (p), with 57 patients in each group. The intervention group received gabapentin 600 mg and a placebo was administered in control group. Patients received on-demand pethedine for pain management. The primary outcome was pain intensity according to the visual analogue scale (VAS) and the secondary outcome was the amount of opioid consumption and incidence of side effects (including: dizziness, sedation, nausea and vomiting) at 6 and 24 h visits.

Results: The mean pain intensity in G group at both the 6 and 24 hour visits was significantly lower than the control group (Both $p<0.0001$). Also, patients in the gabapentin group consumed less opioid at both visits in comparison to the placebo group ($p<0.001$, $p=0.032$). The incidence rate of sedation, dizziness, nausea and vomiting was similar in both groups.

Conclusion: In arthroscopic ACL reconstruction, administering a preoperative single dose of 600mg gabapentin may decrease both pain intensity and opioid consumption.

Keywords: Gabapentin, Anterior cruciate ligament, Pain intensity, Opioid consumption, Randomized clinical trial.

Introduction

Seventy five percent of those 73 million patients who annually undergo a variety of surgeries in the Unites States complain about acute postoperative pain (1). Moreover, anterior cruciate ligament tear is one of the most common problems of knee joint and arthroscopic ACL reconstruction, which is accompanied by moderate to severe postoperative pain (2, 3).

The lack of optimal pain management may cause decreased patient satisfaction, impaired quality of life, increased length of hospitalization and overload on the socioeconomic burden (4, 5). At present, there is a wide variety in pain management after arthroscopic ACL reconstruction to create an appropriate analgesia with lower doses of analgesics (6). Opioids, despite of their side effects such as nausea, vomiting, and drowsiness, are still the main cornerstone in managing acute postoperative pain (7). Modern approaches have been proposed to reduce postoperative pain and opioids side effects (6, 8, 9). Preventing the pain before it starts by desensitizing the central nervous system is the main mechanism of the preemptive analgesic method and gabapentin is one of the applicable drugs in this field. However, in several clinical trials, systematic review and meta-analysis anti-allodynic and anti-hyperalgesic effects of gabapentin on acute postoperative pain have been challenged (10-17). In a meta-analysis of 12 different RCTs done on 896 patients (449 gabapentin and 447 placebo cases), it was shown that the administration of gabapentin is significantly associated with a decreased postoperative pain score and opioids consumption but it results in increased incidence of drowsiness (14). However in two recent trials, it was shown that the administration of gabapentin has no effect on pain or opioid consumption reduction after thoracotomy surgeries and total knee ar-

***Coressponding Author*:** Mardani-Kivi Mohsen, Orthopaedic Department, Guilan University of Medical Sciences, Rasht, Guilan, Iran.
Email: Dr_Mohsen_mardani@yahoo.com

AB&JS THE ONLINE VERSION OF THIS ARTICLE ABJS.MUMS.AC.IR

throplasty (18, 19).

There are a few articles related to preemptive gabapentin in arthroscopic surgery (1, 15, 19-23) and just one study (21) has evaluated the efficacy of gabapentin in arthroscopic ACL reconstruction. Hence in this clinical trial we address the efficacy of gabapentin on pain intensity and opioid consumption and the incidence of side effects following arthroscopic ACL constructions.

Materials and methods

The present triple-blinded randomized clinical trial was approved by the vice chancellor for research and ethics committee of the University of Medical Sciences. Information about the advantages and disadvantages of the two groups was given to the patients and informed consent forms were obtained prior to enrolment. All patients who were candidate for ACL reconstruction were evaluated for eligibility. Inclusion criteria included: age between 18-55 years, physical condition type I or II in ASA (American Society of Anesthesiology), operation duration time less than one hour, and no concurrent lesions identified during arthroscopy. Exclusion criteria included: associated tearing of other ligaments and or meniscii, presence of any chondral lesions, a known allergy to gabapentin, psychological disorders, alcohol or drug abuse, and regular consumption of analgesics, corticosteroids or anticonvulsants. Preoperative pain intensity was measured by using a visual analog scale VAS (zero= no pain, 10= unbearable pain). Randomizing eligible patients was performed by the random block method according to quaternary sequences. (group G: 600mg of gabapentin, group p: identical-looking placebo). The placebo was provided in identical form to the original capsule by the same pharmaceutical company. Medications were given according to the randomization schedule two hours pretreatment. No other sedatives or analgesics were given to the patients during the follow-up period. All the patients underwent general anesthesia. Anesthesia was induced with fentanyl 2µg/kg and thiopental (4mg/kg) and maintained with 0.8-1.5% Isoflurane and N2O and O2 in a ratio of 50%. Atracurium (0.5/mg/kg) was applied for intubation. In all cases, ACL was reconstructed by the first author of the study (M.M.K) using a four-strand hamstring tendon with the help of the two standard anterolateral and anteromedial portals. For graft fixation, absorbable interference screws and endo-buttons were applied on the tibial and femoral side respectively.

On-demand pethedine (0.5mg/Kg) was injected for patients' pain management in the first 24 h post-operation and total opioid consumption was recorded in the patient questionnaire. Patients were assessed by another physician (K.S.E), who was blinded to the patients' group allocation to the 6 and 24 h visits to determine pain intensity, pethedine consumption and the incidence of side effects (nausea, vomiting, dizziness, and sedation). Nausea and vomiting were studied in three levels: 1) nausea, 2) vomiting 3) vomiting requiring medical intervention. Sedation score is also considered in five modes: 1) completely conscious, 2) aware but sleepy, 3) drowsy but able to obey verbal commands, 4) drowsy with no response to tactile stimulation, and 5) sleep with no response to any stimulus. The questionnaires were isolated with an anonymous regimen and by the only researcher that was aware of the patient's grouping and finally were given to the statistical assessor (statistical consultant) for data analysis.

The sample size required comparing the changes of pain intensity and opioid consumption between the two groups, which was calculated according to a recent study (24), where in 52 cases in each group providing 80% power with a confidence of 95% with the help of the two-sided test. Chi squared test or Fisher's exact test were used to compare the qualitative variables. Ordinal variables and continuous non-parametric variables were evaluated by the Mann-Whitney-U test. Student's test was also used to compare the quantitative normally distributed variables of the two groups. Statistical analysis was performed using SPSS software ver.19 and the significance level was set at $p<0.05$.

Result

Of the 114 eligible patients whom were candidate for arthroscopic ACL reconstruction, 57 patients were randomized in each treatment arm. Demographic characteristics such as age, gender, body mass index, duration of surgery and preoperative pain intensity (Table 1) showed that there were no significant difference between the two groups ($P>0.05$) . Two patients in the gabapentin group and 4 patients in the placebo group received another sedative and so they were excluded from the study. The final data analysis was done on the remaining patients (55 patients in the gabapentin group and 53 patients in the placebo group).

Pre-operative pain assessment determined that both groups were similar; pre-operative pain in group G and P were 2.5 (95%CI: 2.2-2.8) and 2.7 (95%CI: 2.3-3) respectively ($P=0.71$). Again postoperative pain was evaluated after the first and second visit (6hr and 24hr). In both visits the mean pain intensity in group G was significantly less than group P ($P<0.0001$) (Table2).

Table1. Demographic characteristics such as age, sex, weight, body mass index and duration of surgery in two groups.

	Group G (N=57)	Group P (N=57)	P-value
Age (mean±SD)	32.2±9.3	30.5±10.2	0.35
Gender (m : f)	49 : 8	51 : 6	0.57
Surgery time (mean±SD)	40±10	36±7	0.43
Weight (mean±SD)	74.9±9.4	73.6±8.5	0.41
BMI (mean±SD)	24±2.2	23.5±2.8	0.26

Mean opioid consumption showed that the pethedine consumption in group G was significantly lower than patients in the placebo group at 6 and 24 hours (Table3).

Data analysis shows that the incidence of postoperative nausea and vomiting in two groups at both follow up visits

Table2. Pain intensity measures of both control and intervention studied groups at, 6 and 24 hours visits

Visits	6hr		24hr	
Group	G (n=55)	P (n=53)	G (n=55)	0.35
Mean pain intensity (VAS)	4.8	6.9	44	0.57
Median	5	7	4	0.43
Mean std. error	0.26	0.25	0.27	0.41
95%-CI	4.3-5.4	6.5-7.5	3.9-4.9	
P Value	<0.0001		<0.0001	

VAS: Visual analogue scale, 95%-CI: 95% Confidence Interval

did have any significant difference (both *P*>0.05). During the first follow-up, 5 patients in group G (9%) and 7 patients in group P (13%) had some degree of nausea and vomiting. In the second follow-up, 3 patients in group G and 4 patients (7.5%) in Group P complained about this side effect.

Incidence of dizziness was similar between the groups. At the first visit (6 h follow up), 7 patients in group G (13%) and 4 patients in group P (7.5%) and at the second visit (24 h follow up), 3 patients in group G (5.5%) and 6 patients in placebo group (11%) reported dizziness (both *P*>0.05).

Additionally. statistical analysis showed that the patients' sedation score in both groups were comparable at both visits (*P*>0.05). This means that gabapentin did not result in increased sedation scores. Of patients in group G and P, 6 cases (11%) and 3 cases (6%) respectively suffered from second and third degree sedation at their first visit. At the second visit, 2 patients in group G (4%) and 3 patients (6%) in group P had similar complains.

Discussion

This study indicated that the preoperative administration of gabapentin is significantly associated with pain intensity reduction and opioid consumption decrease as a pre-emptive analgesia method for anterior cruciate ligament reconstructions. In a similar study of 40 patients, Menigaux el al. randomly divided 40 patients requiring ACL reconstruction. In the intervention group they administered 1200 mg of gabapentin 1-2 hour before surgery (21). Pain intensity at rest and movement and the amount of opioid consumption at the first 48 h postoperative were in favor of the gabapentin group. The results of our study were consistent with this study. The most common side effects of gabapentin are drowsiness and dizziness (25). Since the incidence of gabapentin side effects is dose dependent, we only administered a single dose of gabapentin. However, the rate of patient drowsiness and dizziness at their first visit was a little more than te control group; but it did not reach statistical significance.

In a conducted meta-analysis, 16 RCTs related to preemptive gabapentin analgesia were divided into three categories: A) single dose of gabapentin 1200 mg, B) single dose of gabapentin less than 1200 mg, C) multiple dose of gabapentin. In all three groups, total opioid consumption was significantly reduced. Also, patients in group A and B significantly experienced less postoperative pain than the placebo group. In the light of the side effects, pooled data analysis showed that gabapentin was associated with more sedation, less vomiting and pruritus (26). In the present study, the rate of nausea and vomiting was somewhat lower in the gabapentin group, but it did not reach a significant amount.

In an RCT (19) on knee arthroplasty candidates to evaluate pre-emptive analgesia, a regimen of acetaminophen 1000 mg and ketorolac 15 mg was administered every 6 h accompanied by PCA morphine pump. In the intervention group, the pre-operative gabapentin 600 mg and the gabapentin (200 mg/TDS) were added for two days. Although clinical outcomes (pain intensity and opioid consumption) were in favor of the gabapentin group, again it did not reach a significant amount. However, in another study, Clark et al. randomized candidates for knee arthroplasty in four groups with different dosages of gabapentin and compared it with the control group (27). All patients received preoperative celecoxib 400 mg and postoperative celecoxib 200 mg every 12 h for four hours. Although the mean pain intensity was similar between the groups, morphine consumption and the incidence of pruritus in groups that had taken gabapentin both before and after surgery had a significant reduction compared to the control group and the one which received a single dose just before surgery. In another study in the same year, candidates for total hip arthroplasty were divided into three groups of 38 (1- pre-emptive gabapentin 600 mg, 2- post operative gabapentin and 3- control group). All patients received celecoxib 400 mg, dexamethasone 8 mg and acetaminophen 1 g. The treatment outcomes in the three groups were similar and there was no special precedence in the intervention groups when compared to the control group (28).

Patient characteristics, type of illness, selected surgical procedures and anesthetic techniques may all have a role in the reduction of pethedine consumption and efficacy of gabapentin as pre-emptive analgesia. For instance, in some reported studies, the pain rate on the mean morphine consumption of patients was not reduced following the administration of gabapentin (1, 16, 18, 20, 28, 29); However, there are studies that are in favor of gabapentin (23, 24,

Table3. Opioid (Pethedine) consumption in studied groups at two visits at 6 and 24 hours

Visits	6hr		24hr	
Group	G (n=55)	P (n=53)	G (n=55)	P (n=53)
Mean opioid consumption	20	34	25	37
Median	25	40	0	50
Mean std. error	3	2.8	3.1	3.4
95%-CI	18.9-31.3	28.5-39.8	14-26.6	30.4-44
P Value	<0.0001		0.032	

30-32).

Interestingly, even when the type of performed surgery is the same, the results may still be different. In another study, 44 women who were candidates for cesarean delivery were compared in two random groups of gabapentin 600 mg and placebo in terms of pain intensity, opioid consumption, adverse effects and patient satisfaction (33). During their 24 h follow-up, patient pain in the gabapentin group was significantly lower; so they concluded that 600 mg of gabapentin reduces pain after cesarean delivery and increases patient satisfaction. But in another randomized clinical trial, 126 women who were candidate for elective cesarean delivery were placed in three groups, gabapentin 300 mg, Gabapentin 600 mg and placebo and the significance level was the difference of more than 10 mm in VAS unit (17). The results revealed that neither of the intervention groups had any priority in terms of pain reduction when compared to the control group. Short et al. did not provide a definite reason due to underpowered findings.

Discrepancies among several studies related to gabapentin preemptive analgesia may be found in: difference in gabapentin dosage, administration time, and single or multiple doses, quality and design of the study, anesthetic technique usage, type of performed surgery, use of supplemental analgesics, criteria of clinical outcomes and follow-up time.

In this study, we applied on-demand pethedine as a pain reliever that could be replaced by morphine PCA pumps so that the patients could be satisfied with the exact dose of needed analgesic. Another limitation of this study is the lack of determination of other postoperative adverse effects. The strength of the present study is its triple-blinding design and acceptable sample size. However, this is just the preliminary step to definitely confirm gabapentin as a preferred preemptive analgesic for ACL reconstructions. Administration of a single dose of gabapentin 600 mg 2 hours before surgery for arthroscopic anterior cruciate ligament reconstructions results in reduced pain and opioid consumption.

Mohsen Mardani Kivi MD
Department of Orthopedic Surgery
Guilan Road Trauma Research Center, Guilan University of Medical, Sciences, Rasht, Iran.

Mahmoud Karimi Mobarakeh MD
Department of Orthopedic Surgery
Kerman University of Medical Sciences, Kerman, Iran.

Sohrab Keyhani MD
Orthopedic Research Center
Guilan University of Medical Sciences, Rasht, Iran.

Keyvan Hashemi Motlagh MD
Orthopedic Research Center
Guilan University of Medical Sciences, Rasht, Iran.

Khashayar Saheb Ekhtiari MD
Orthopedic Research Center
Guilan University of Medical Sciences, Rasht, Iran.

References

1. Spence D, Goff J, Mohan E, Bowen K, Osborne L, Maye J. Perioperative administration of gabapentin for shoulder arthroscopy: a prospective, randomized, double-blind, placebo-controlled study. AANA J. 2011;79(4 Suppl):S43-50.

2. Alentorn-Geli E, Lajara F, Samitier G, Cugat R. The transtibial versus the anteromedial portal technique in the arthroscopic bone-patellar tendon-bone anterior cruciate ligament reconstruction. Knee Surg Sports Traumatol Arthrosc. 2010;18(8):1013-37.

3. Dargel J, Schmidt-Wiethoff R, Fischer S, Mader K, Koebke J, Schneider T. Femoral bone tunnel placement using the transtibial tunnel or the anteromedial portal in ACL reconstruction: a radiographic evaluation. Knee Surg Sports Traumatol Arthrosc. 2009;17(3):220-7.

4. Bang SR, Yu SK, Kim TH. Can gabapentin help reduce postoperative pain in arthroscopic rotator cuff repair? A prospective, randomized, double-blind study. Arthroscopy. 2010;26(9 Suppl):S106-11.

5. Weinbroum AA. Non-opioid IV adjuvants in the perioperative period: pharmacological and clinical aspects of ketamine and gabapentinoids. Pharmacol Res. 2012;65(4):411-29.

6. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol. 2009;22(5):588-93.

7. White PF. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. Anesth Analg. 2002;94(3):577-85.

8. Elvir-Lazo OL, White PF. The role of multimodal analgesia in pain management after ambulatory surgery. Curr Opin Anaesthesiol. 2010;23(6):697-703.

9. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993;77(5):1048-56.

10. Al-Mujadi H, AR AR, Katzarov MG, Dehrab NA, Batra YK, Al-Qattan AR. Preemptive gabapentin reduces postoperative pain and opioid demand following thyroid surgery. Can J Anaesth. 2006;53(3):268-73.

11. Dahl JB, Mathiesen O, Moiniche S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of post-operative pain. Acta Anaesthesiol Scand.

2004;48(9):1130-6.
12. Dauri M, Faria S, Gatti A, Celidonio L, Carpenedo R, Sabato AF. Gabapentin and pregabalin for the acute postoperative pain management. A systematic-narrative review of the recent clinical evidences. Curr Drug Targets. 2009;10(8):716-33.
13. Dirks J, Fredensborg BB, Christensen D, Fomsgaard JS, Flyger H, Dahl JB. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. Anesthesiology. 2002;97(3):560-4.
14. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med. 2006;31(3):237-47.
15. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. J Neurosurg Anesthesiol. 2005;17(2):65-8.
16. Radhakrishnan M, Bithal PK, Chaturvedi A. Effect of preemptive gabapentin on postoperative pain relief and morphine consumption following lumbar laminectomy and discectomy: a randomized, double-blinded, placebo-controlled study. J Neurosurg Anesthesiol. 2005;17(3):125-8.
17. Short J, Downey K, Bernstein P, Shah V, Carvalho JC. A single preoperative dose of gabapentin does not improve postcesarean delivery pain management: a randomized, double-blind, placebo-controlled dose-finding trial. Anesth Analg. 2012;115(6):1336-42.
18. Kinney MA, Mantilla CB, Carns PE, Passe MA, Brown MJ, Hooten WM, et al. Preoperative gabapentin for acute postthoracotomy analgesia: a randomized, double-blinded, active placebo-controlled study. Pain Pract. 2012;12(3):175-83.
19. Paul JE, Nantha-Aree M, Buckley N, Cheng J, Thabane L, Tidy A, et al. Gabapentin does not improve multimodal analgesia outcomes for total knee arthroplasty: a randomized controlled trial. Can J Anaesth. 2013;60(5):423-31.
20. Adam F, Menigaux C, Sessler DI, Chauvin M. A single preoperative dose of gabapentin (800 milligrams) does not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery. Anesth Analg. 2006;103(5):1278-82.
21. Menigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg. 2005;100(5):1394-9, table of contents.
22. Turan A, Karamanlioglu B, Memis D, Hamamcioglu MK, Tukenmez B, Pamukcu Z, et al. Analgesic effects of gabapentin after spinal surgery. Anesthesiology. 2004;100(4):935-8.
23. Turan A, Kaya G, Karamanlioglu B, Pamukcu Z, Apfel CC. Effect of oral gabapentin on postoperative epidural analgesia. Br J Anaesth. 2006;96(2):242-6.
24. Waikakul W. Combination of gabapentin and celecoxib for analgesia after major orthopedic surgery: a randomized, controlled trial. Asian Biomedicine. 2011.
25. Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anaesthesiol. 2007;20(5):456-72.
26. Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain--a systematic review of randomized controlled trials. Pain. 2006;126(1-3):91-101.
27. Clarke H, Pereira S, Kennedy D, Gilron I, Katz J, Gollish J, et al. Gabapentin decreases morphine consumption and improves functional recovery following total knee arthroplasty. Pain Res Manag. 2009;14(3):217-22.
28. Clarke H, Pereira S, Kennedy D, Andrion J, Mitsakakis N, Gollish J, et al. Adding gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty. Acta Anaesthesiol Scand. 2009;53(8):1073-83.
29. Brogly N, Wattier JM, Andrieu G, Peres D, Robin E, Kipnis E, et al. Gabapentin attenuates late but not early postoperative pain after thyroidectomy with superficial cervical plexus block. Anesth Analg. 2008;107(5):1720-5.
30. Menda F, Köner Ö, Sayın M, Ergenoğlu M, Küçükaksu S, Aykaç B. Effects of Single-Dose Gabapentin on Postoperative Pain and Morphine Consumption After Cardiac Surgery. Journal of Cardiothoracic and Vascular Anesthesia. 2010;24(5):808-13.
31. Sen H, Sizlan A, Yanarates O, Emirkadi H, Ozkan S, Dagli G, et al. A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesth Analg. 2009;109(5):1645-50.
32. Srivastava U, Kumar A, Saxena S, Mishra AR, Saraswat N, Mishra S. Effect of preoperative gabapentin on postoperative pain and tramadol consumption after minilap open cholecystectomy: a randomized double-blind, placebo-controlled trial. Eur J Anaesthesiol. 2010;27(4):331-5.
33. Moore A, Costello J, Wieczorek P, Shah V, Taddio A, Carvalho JC. Gabapentin improves postcesarean delivery pain management: a randomized, placebo-controlled trial. Anesth Analg. 2011;112(1):167-73.