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Original article

Arthroscopic bankart surgery: Does gabapentin reduce postoperative pain and opioid consumption? A triple-blinded randomized clinical trial

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ABSTRACT

Background: The role of gabapentin as preemptive analgesia in managing acute pain following shoulder bankart arthroscopy is controversial and the studies addressing this issue are limited.
Hypothesis: The present study was undertaken to examine the effects of preemptive single dose of gabapentin on pain management and opioid consumption in patients undergoing arthroscopic bankart surgery.
Patients and methods: In the current triple-blinded randomized clinical trial, 76 eligible patients were randomly divided into two groups either taking gabapentin 600 mg (G group) or placebo (P group). The primary outcomes were pain intensity assessed based on Visual Analogue Scale (VAS) and secondary outcomes were opioid consumption and side effects, dizziness, sedation, nausea and vomiting at 6 h and 24 h follow-up visits.
Results: The pain intensity were not significantly different between the G and P groups ($P > 0.05$). The opioid consumption, however, was significantly reduced in G group at both 6 h and 24 h follow-up visits ($P < 0.001$). Dizziness and sedation were similar in both groups. Nausea and vomiting were significantly lower in G group only at 6 h visit but similar at 24 h follow-up visit ($P < 0.001$).
Discussion: The preemptive single dose of gabapentin 600 mg administered prior to arthroscopic bankart surgery does not decrease post-operation pain, but reduces opioid consumption. Gabapentin restrained postoperative nausea and vomiting for a short while (less than 6 h).
Level of evidence: Level I, treatment study.

1. Introduction

Arthroscopic methods for shoulder instability surgery are increasing mainly due to the early recovery, creation of small incision, and accessibility to the shoulder tendon [1]. However, moderate to severe acute pain may occur secondary to surgical interventions such as bone removal, resection of bursa tissue, insertion of surgical instruments into the joint and irrigation-induced soft tissue distension [2]. Such postoperative acute pain may go untreated or inadequately treated in 50% of all surgical procedures [3,4]. Up to two decades ago, despite their side effects such as respiratory depression and postoperative nausea and vomiting (PONV), opioids were the cornerstone for the treatment of postoperative pain [5,6]. Thus, multimodal analgesia, tended to target the routes of nerves and various neurotransmitters to inhibit hyperalgesia and nociception [7]. On the other hand, it has been demonstrated that such postoperative pains may not be pure nociceptive and may include inflammatory and neurogenic conditions [8,9].

In 1993, gabapentin was introduced as an anti-epileptic drug and it was subsequently administered for acute and chronic pain associated with different diseases such as post-herpetic neuralgia, diabetic neuropathy, trigeminal neuralgia and various headaches [10]. Gabapentin binds to the alpha2-delta-subunit of voltage-gated calcium channels and inhibits the release of

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nociceptive neurotransmitters including glutamates, P-substance and norepinephrine from presynaptic afferent neurons [11]. The anti-hyperalgesic feature of gabapentin may be the main reason for the reduction of pathologic postoperative pain [12]. Daul et al., in a systematic review, compared seven randomized clinical trials (663 patients) and demonstrated that gabapentin reduced pain significantly and decreased the need to opioids in 6 out of 7 studies [8]. However, In a systematic narrative review of 22 randomized clinical trial studies, 4 out of 10 studies using gabapentin as a single dose preemptive analgesia indicated that gabapentin did not reduce pain and opioid consumption [13,14].

The effectiveness of gabapentin as an adjuvant to analgesics has been addressed in several met-analyses [8,13,15–17], however its efficacy in relieving postoperative pain is still controversial and has been questioned in some studies [18–21]. While arthroscopic surgery, as a minimally-invasive procedure, has been increasing during the past decade, there are limited numbers of studies -particularly high quality RCTs-examining the effectiveness of gabapentin in arthroscopic surgeries, especially arthroscopic shoulder surgery [18,22,23]. In the present study, we examined the therapeutic effects of gabapentin as a preemptive analgesic in managing pain secondary to arthroscopic bankart surgery. We hypothesized that preoperative oral administration of 600 mg of Gabapentin to the patients undergoing arthroscopic bankart surgery will result in the reduction of pain and opioid consumption.

2. Materials and methods

2.1. Study design

The present study received the approval of vice chancellor of research and ethic committee of our University of Medical Sciences and was registered on the Registry of Clinical Trials. A triple blind randomized clinical trial study was designed and conducted in the academic hospital. Before recruitment, the patients were briefed about the pros and cons of the two treatment methods and signed the informed consent forms. The study was also in accordance with the ethical standards of Helsinki and Consolidated Standards of Reporting Trials (CONSORT) statement.

2.2. Inclusion and exclusion criteria

The patients diagnosed with shoulder bankart lesion, candidates for arthroscopic surgery, were registered for the study with the following inclusion criteria: aged between 18–75, types I or II in American Society of Anesthesiology (ASA) physical status, operation duration time less than one hour and no concomitant lesions diagnosed during arthroscopy. The exclusion criteria were the presence of any accompanied cartilage lesions, any known allergy to gabapentin, having previous history of epilepsy, hepatic, renal or psychological disorders, alcohol and/or drug abuse and daily consumption of analgesics, corticoesteriods or anticonvulsants.

The eligible patients were randomized based on random block design receiving either gabapentin 600 mg (G group) or identical placebo (P group). The placebo capsules were produced in the form identical to the active counterparts manufactored by the same company. The capsules were administered randomly to the patients two hours prior to the operation by one the author who was not involved in the rest of the research design. The rest of the researchers were blinded to the design of the study till the end of the final analysis. None of the patients received other opioids or analgesics perioperatively. The pain intensity was preoperatively measured using Visual Analog Scale (VAS) (0 = no pain and 10 = unbearable pain). All the patients underwent general anesthesia. Anesthesia was induced with Fentanyl 2 μg/kg and thiopental (4 mg/kg) and maintained with 0.8–1.5% Isoflurane and N_2O and O_2 in ratio of 50%. Atracurium (0.5/mg/kg) was applid for intubation. The patients were also required to receive 7–10cc/kg crystalloid and to be under surveillance with standard monitoring for capnometry, pulse oximetry and non-invasive blood pressure. The first author of the study performed the bankart lesion repair using three titanium anchor sutures via standard anterior and posterior portals.

To control postoperative pain, pethedine (0.5 mg/kg) was injected on demand and opioid consumption was recorded in the patient's questionnaire. The primary and secondary outcomes were evaluated at 6 h and 24 h postoperative visits by another author who was blinded to the study groups.

2.3. Therapeutic outcomes

Pain intensity as measured by (VAS) and opioid consumption were considered as primary outcomes and incidence of side effects (nausia, vommiting, dizziness and sedation score) as secondary outcomes. All the patients were evaluated for nausea and vomiting (level one: nausea, level two: vomiting, level three: vomiting requiring medical intervention); sedation score (a: fully aware; b: aware but drowsy; c: drowsy but capable of following the verbal orders; d: drowsy without the ability to respond to tactile stimulus; e: drowsy unresponsive to any stimulus) and dizziness. Sedation was defined as somnolence or drowsiness and dizziness as light headedness and/or vertigo. The physician aware of which capsule the patients had received coded the questionnaires but without any indication of the type of group and sent them to the study statistician for final statistical analysis.

2.4. Statistical analysis

The sample size required to compare the changes of pain intensity and opioid consumption between the two groups was calculated in accordance to a recent study [22] to be 34 cases in each group providing 80% power with a confidence of 95% with the help of two-sided test. Chi^2 or Fisher exact test was used to compare qualitative variables. Mann Whitney-*U* test was applied to assess the categorical variables and non-normally distributed continuous variables. Student *t*-test was used to evaluate normally distributed quantitative variables. SPSS software (ver.19) for Windows was applied for statistical analyses and $P < 0.05$ was considered to be significant.

3. Results

Out of 113 eligible patients referred to our clinic between May 2011 to May 2013, seventy six patients were randomly assigned to either of the following groups: gabapentin (38 patients) or placebo (38 patients). There were no significant differences between the demographic characteristics (age, gender and BMI), the operation duration time and pain intensity between the two groups prior to the study (all $P > 0.05$) (Table 1). One patient from G group and four

Table 1
Baseline assessments: the demographic characteristics and operation duration time for both groups.

	Group G	Group P
Number, *n*	38	38
Age (mean ± SD)	30.2 ± 5	28.3 ± 4.4
Gender (Female/Male)	11/27	8/30
Operation time (Mean ± SD)	46.9 ± 10.7	43.9 ± 9.5
Weight (Kg)	68.2 ± 1.8	67.4 ± 11.3
BMI	23.3 ± 1.8	24.1 ± 3.4

P was not significant in all the analyses, $P > 0.05$. SD: standard deviation; BMI: body mass index.

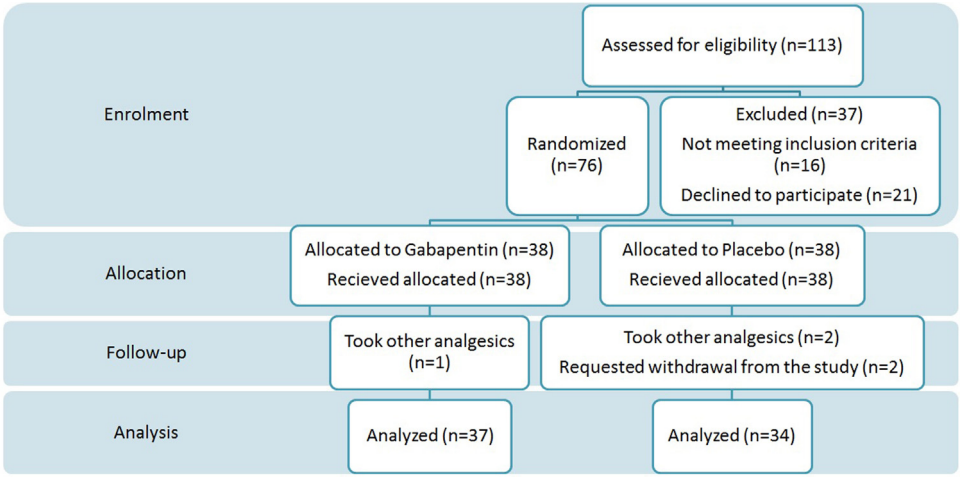

Fig. 1. Flowchart of the study design.

patients from P group took other analgesics or terminated their participation and thus, were excluded from the study (Fig. 1).

3.1. Pain intensity

At the first postoperative visit (6 h), the pain intensity means were 4.9 in G group (95% CI: 4.6–5.3) and 5.4 in P group (95% CI: 5.0–5.7), which were not statistically significant. At the second post-operation visit (24 h), the pain intensity means were 4.7 (95% CI: 4.3–5.2) in G group and 5.3 (95% CI: 4.9–5.6), which were again similar between two groups ($P > 0.05$).

3.2. Opioid consumption

Although the pain intensity was similar between G and P groups, the opioid consumption was significantly lower in G group both at 6 h and 24 h visits (Table 2).

3.3. Opioids side effects

Dizziness was similar in G and P groups both at 6 h and at 24 h follow-up visits. At 6 h follow-up visit, 6 patients (16%) from G group and 8 patients (24%) from P group and at 24 h follow-up visit, 5 patients (14%) from G group and 3 patients (9%) from P group reported dizziness, in that, the differences were not statistically significant (both $P > 0.05$). Sedation was also similar in both G and P groups at both follow-up visits, in that, administration of gabapentin did not increase sedation significantly ($P > 0.05$). At 6 h follow-up visit, 5 patients (14%) in G group and 4 patients (12%) in P group and at 24 h visit, 3 patients (8%) in G group and 2 patients (6%) in P group experienced sedation grade B and C.

Nausea and vomiting were significantly lower in G group at 6 h follow-up visit ($P = 0.001$), however, at 24 h follow-up visit, the difference between G and P groups was not significant ($P > 0.05$). Thus, at 6 h follow-up visit 1 patient (3%) in G group and 11 patients (32%) in P group and at 24 h follow-up visit, 1 patient (3%) in G group and 2 patients (6%) in P group experienced nausea and vomiting.

Table 2
Opioid consumption at 6 h and 24 h visits in both G and P groups.

	Visit			
	6 h		24 h	
	Group G ($n = 37$)	Group P ($n = 34$)	Group G ($n = 37$)	Group P ($n = 34$)
Pethedine consumption	20.5	40.3	18.4	40
Median	25	40	25	50
Mean Standard Error	2.1	1.6	2.4	4
95% CI	16.2–24.8	37–43.6	13.4 23.4	31.9–48.1
P-value	< 0.0001		< 0.0001	

95% CI: 95% confidence interval.

4. Discussion

According to the results of the study, administration of 600 mg gabapentin 2 h prior to surgery did not decrease pain intensity, but reduced opioid requirements for patients undergoing arthroscopic bankart surgery suggesting that patients taking gabapentin need less opioid for acute postoperative pain management. The results also indicated that administration of gabapentin decreased PONV at 6 h follow-up visit, but did not lead in reduction in dizziness or sedation scores.

The discrepancies in administration of gabapentin as a preemptive analgesic reported in several studies may be defined as the differences in gabapentin dosages, the time of the administration of gabapentin, being a single dose or multiple doses, study design and its quality, anesthesia method, the criteria for evaluating outcome measures and follow-up duration. Pandey argued that gabapentin should be administered at 600 mg dosage, which is more effective than 300 mg dosage and has the same effectiveness as higher dosages (900 and 1200 mg) in reducing pain intensity and total opioid consumption [24].

Ho et al., in a meta-analysis of 1151 patients (614 patients taking gabapentin in 16 RCTs) divided the studies into three categories according to the gabapentin dosages the patients had taken:

A. a single dose of 1200 mg;
B. a single dose less than 1200 mg;
C. multiple dose of less than 1200 mg.

In all three categories, the opioid consumption was significantly reduced postoperatively. In A and B categories, the patients taking gabapentin experienced significantly less pain than the placebo group. The pooled data analysis showed that patients in gabapentin group experienced significantly more sedation but less vomiting and pruritus [15].

Mathiesen et al., in a systematic review of 23 RCTs conducted on 1529 patients, reviewed the analgesic effects of gabapentin on postoperative pain in different surgical interventions and demonstrated that pain intensity during rest and physical activity, and opioid consumption were significantly reduced in all 5 studies associated with hysterectomy and 4 studies with spinal surgery

Table 3
Literature review: gabapentin administration for postoperative pain in shoulder arthroscopy.

Author, year (reference)	Demographic data Sample size (no.) Age (mean ± SD) Sex (M/F)		Gabapentin dosing	Anaesthesia Intra- and postoperative analgesics	Follow-ups	Results		
	G	P				Pain	Opioid	Side effects
Adam et al., 2006 [18]	*n* = 27 Age: 43 ± 18 Sex: 18/9	*n* = 26 Age: 47 ± 15 Sex: 18/8	800 mg 2 h preoperative	ISB block and GA Intra-operative: remifentanil 1 μg/kg at induction Postoperative: ketoprofene 150 mg (Bid) and acetaminophen 400 mg + dextropropoxyphene 30 mg (Qid) as needed	2 times on surgery day and 4 times on the first postoperative day	NS	NS	NS (Except for headache in Placebo group)
Bang et al., 2010 [22]	*n* = 23 Age: 56 ± 8 Sex: 9/14	*n* = 23 Age: 59 ± 6 Sex: 8/15	300 mg 2 h preoperative	GA Intra-operative: fentanyl 1 μg/kg at induction Postoperative: at PACU: PCA fentanyl 0.15 g/mL in a total volume of 100 mL + fentanyl 1 g/kg, if patients required pain relief At general ward: fentanyl 1 g/kg + pethidine 0.5 mg/kg or ketorolac 30 mg if VAS > 3	2, 6,12, and 24 h postoperative	Reduced significantly in gabapentin group at 2, 6 and 12 h postoperative	NS	NS
Spence et al., 2011 [23]	*n* = 26 Age: 31 ± 10 Sex: 22/4	*n* = 31 Age: 31 ± 9 Sex: 22/5	300 mg 1 h preoperative and for 2 days	ISB block and GA Intra-operative: fentanyl with sequence of 1 to 3 μg/kg Postoperative: at PACU: fentanyl up to 500 μg and meperidine up to 50 mg At home: oxycodone 5 mg and acetaminophen 325 mg Qid as needed	2 times at PACU, 2 times on 1st and 2nd postoperative days	NS	NS	NS

[17]. In this review, only in one [25] out of five [18,25–28] studies associated with orthopedic and musculoskeletal surgeries, the pain intensity was significantly reduced among patients taking gabapentin as compared to placebo group, but in other four studies [18,26–28], opioid consumption was reduced significantly at 24 h follow-up visit. In all reviewed studies, the side effects were similar except in one study [25], in which patients reported an increase in dizziness rate following administration of gabapentin.

To our knowledge, only 3 studies [18,22,23] examine the analgesic effect of gabapentin on postoperative pain in shoulder arthroscopy (Table 3). In 2 out of the 3 studies, interscalene brachial plexus block was performed and there were no significant differences between the G and P groups [18,23]. Gabapentin failure may be related to the administration of interscalene brachial plexus block, in that, lack of central sensitization due to nerve block may inhibit the analgesic effect of gabapentin on pathologic pains associated with hyperalgesia. However, this explanation needs further studies. In addition, longer follow-up time and more sample size are recommended.

In conclusion, gabapentin as a preemptive analgesia at least may result in either pain relief, lower opioid consumption or less side effects. Since the maximum plasma concentration occur 2–3 h after the injection [29], it is recommended to administer gabapentin 2 hours preoperatively to have maximal plasma concentration peak during the operative trauma; and since gabapentin has no hepatic metabolism, is excreted without change through the kidneys with first order kinetic mechanism and has no special medicinal intervention [29], it can be used in different surgical interventions. The dosage higher than 600 mg of gabapentin does not necessarily lead to additional analgesic benefit or additional decrease in opioid consumption. However, the repeated multi-doses of gabapentin will result in an increase in side effects especially sedation.

5. Conclusion

Administration of gabapentin 600 mg 2 h prior to arthroscopic bankart surgery may reduce opioid consumption, but does not manage postoperative pain. The side effects such as postoperative nausea and vomiting are also reduced as a result of administration of gabapentin but not dizziness and sedation.

Ethical Statement

Guilan University of Medical Sciences Ethics Committee approved the study (reference number: 1910051508) and it was registered on the Iranian Registry of Clinical Trials (IRCT no.: IRCT201205217274N5).

Disclosure of interest

The authors declare that they have no competing interest.

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