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Research Article

Effect of pregabalin on postoperative pain after shoulder arthroscopy

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Abstract *Background:* Postoperative pain is difficult to be managed with the use of opioids analgesia alone, so multimodal pain management is a method to improve postoperative analgesia with minimal side effects. Pregabalin has an analgesic and opioid sparing effects in postoperative analgesia. The objective of the present study was to evaluate the effect of premedication with pregabalin on postoperative analgesia in patients undergoing shoulder arthroscopy.

Methods: Eighty patients ASA I-II and aged 18–60 years undergoing elective shoulder arthroscopy were randomized to receive two doses of either placebo or pregabalin 300 mg 12 h and 1 h before surgery. Anesthesia was induced with thiopental (3–5 mg/kg) and atracurium (0.5 mg/kg) and maintained with isoflurane with O_2. Patients were studied at 1, 4, 8, 12 and 24 h postoperatively for Visual Analogue Scale (VAS), nalbuphine consumption (was given when VAS > 4), satisfaction score and side effects of pregabalin.

Results: The VAS scores of the pregabalin group were significantly lower than the control group at 1, 4 and 8 h after surgery. The total nalbuphine consumption at 24 h postoperatively of pregabalin group (33.8 + 6.89) was highly significant lower than the control group (46.4 + 5.72) ($p < 0.001$). There were no significant differences between groups in somnolence-dizziness and nausea-vomiting. The satisfaction score was higher in the pregabalin group.

Conclusion: A 300 mg pregabalin administered 12 h and 1 h preoperatively is a safe and effective method in management of pain after shoulder arthroscopy.

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1. Introduction

Advances in surgical techniques have led to increasingly more procedures being performed on an outpatient basis [1–4] as shoulder arthroscopy. Postoperative pain is the most common reason for delayed discharge, and the main reason for unanticipated hospital admission [5]. Opioid medications have been still the mainstay of postoperative pain management, but these medications have serious adverse effects [6].

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Shoulder surgery often results in bone removal, extensive resection of bursal tissue, insertion of hardware, and soft tissue distension from irrigation fluid. Many patients are hospitalized overnight to control pain that results from this intervention. This may be because the postoperative pain is under-treated in the outpatient setting [7].

Pregabalin is the active S-enantiomer of racemic 3-isobutyl GABA [6] and binds to the alpha 2-delta (α2-δ) subunit of the presynaptic, voltage-gated calcium channels that are widely distributed throughout the peripheral and central nervous system [8–10]. The probable mechanism of action of pregabalin via, potent binding at this site reduces calcium influx at nerve terminals and therefore reduces the release of several neurotransmitters including glutamate, norepinephrine and substance P [11,12]. Pregabalin was used in the treatment of chronic pain conditions, but recently it has used in the treatment of acute postoperative pain [13–18], but there was not any research has been done to study its effect on acute postoperative shoulder pain. The aim of the study is to evaluate the efficacy and safety of preoperative pregabalin on acute postoperative pain in patients scheduled for shoulder arthroscopy.

2. Methods

After approval from the local ethical committee of the Faculty of Medicine, Menoufiya University, written informed consents were obtained from the patients who were scheduled to undergo elective shoulder arthroscopy. Patients with the following characteristics were excluded from the study: age <18 years; age >60 years; pregnant; allergic and/or contraindicated to the study drugs; American Society of Anesthesiologists (ASA) score III and above; having drug and/or alcohol addiction, renal failure, diabetes mellitus or epilepsy; and currently using opioids for chronic pain and/or any of the drugs studied. A total of 80 patients, ASA I-II and aged 18–60 years were included in the study. Patients were randomly assigned to one of two groups using a closed envelope randomization schedule. The patients in Group I (placebo, $n = 40$) received 'placebo' two doses, 12 h apart prior to the operation (one 12 h and the other 1 h preoperative). Patients in Group II (pregabalin $n = 40$) received pregabalin 300 mg at the same time intervals as Group I patients. In the operating room, a crystalloid infusion was started through an IV cannula and the mean arterial blood pressure (MAP), heart rate (HR) and peripheral oxygen saturation (SpO2) were monitored. General anaesthesia was induced with thiopental sodium (3–5 mg/kg), fentanil (1 μg/kg) and atrachurium (0.5 mg/kg) and maintained with isoflurane and O2. Isoflurane concentration was adjusted to maintain adequate depth of anaesthesia. Before onset of surgery, intra-articular injection of 10 ml adrenalized 1:200000 bupivacaine 0.25% was performed to all study patients (adrenaline was giving due to its vasoconstrictor effect allowing reduction of bleeding at the operative field and better arthroscopic view). No other analgesic was administered during the surgery. After the end of surgery, all patients received intravenous diclofenac 75 mg as a routine analgesic. The patients were taught how to express the level of pain they experienced using a 10-point Visual Analogue Scale (VAS), with 0 indicating no pain and 10 indicating the worst possible pain. Incremental titrating doses of nalbuphine (4 mg/dose) were given when indicated (if VAS $\geqslant 4$) due to unavailability of PCA modality in our institute. Anxiety scores, vital signs, pain scores, Numeric Sedation Scores (NSS; 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep and not responsive to any stimuli), nalbuphine consumption and adverse effects such as nausea, vomiting, pruritus, urinary retention, somnolence, dizziness, vision abnormalities (double or blurred) and headache were recorded. Except for patient satisfaction score which was measured at 24 h postoperatively on a numerical score of 1–4 (1 = poor, 2 = fair, 3 = good, 4 = very good) and recorded only once before patient discharge from the hospital, all postoperative variables were recorded on the 1st, 4th, 8th, 12th and 24th hours after end of surgery.

2.1. Statistical analysis

A power analysis was performed using a power of 80% and an α value 0.05. We assumed that the difference between means of the two groups for VAS would be 0.77 with an average standard deviation 1.19. The sample size was calculated to be 38 patients, so we decided to include 40 patients in each group in the study. We used GraphPad Stat Mate version 2 statistics program for power analysis.

Statistical analysis was done using SPSS program. Descriptive statistics were expressed as mean + SD unless otherwise stated. Student's *t*-test was used for comparison of the means of continuous variables and normally distributed data. The Mann–Whitney *U*-test or Chi-square test was used otherwise. *P*-value < 0.05 was considered statistically significant.

3. Results

The two groups were comparable with respect to age, sex, weight, height and duration of surgery (Table 1). For VAS of pain at rest, there was a significant decrease in pregabalin group (group II) at 1 h, 4 h and 8 h postoperatively compared to placebo group (group I) and insignificant difference between the two groups at 12 h and 24 h after the end of surgery (Table 2). Also, nalbuphine consumption (Table 3) showed a significant decrease in pregabalin group at 1 h, 4 h and 8 h postoperatively compared to placebo group with a significant difference between the two groups in relation to total nalbuphine consumption during the whole 24 h ($P < 0.003$). The study showed a significant increase in NSS (Table 4) in pregabalin group at 1st and 4th postoperative hrs and insignificant increase at 8th, 12th and 24th postoperative hrs compared to placebo group. In relation to patient satisfaction to pain and

Table 1 Demographic data and duration of surgery.

	Group I	Group II
Age	42.15 ± 13.08	41.3 ± 14.7
Sex M/F	16/24	22/18
Weight	79.3 ± 7.88	75.2 ± 7.54
Height	170 ± 7.11	166.15 ± 6.38
Duration of surgery (min)	82.5 ± 15.52	77 ± 19.89

Group I: placebo, Group II: pregabalin, M: male, F: female. Data were expressed as mean ± standard deviation and number of patients.

Table 2 Visual Analogue Scale (VAS) for postoperative pain during 24 h.

	Group I	Group II	*P*-value
1 h Postoperative	5.8 ± 1.32	4.65 ± 1.53*	0.015
4 h	4.5 ± 1.54	3.1 ± 1.02*	0.002
8 h	3.65 ± 1.27	2.6 ± 1.23*	0.011
12 h	2.75 ± 1.41	2.35 ± 0.99	0.306
24 h	1.95 ± 0.83	2.1 ± 0.79	0.562

Group I: placebo and Group II: pregabalin.
* $P < 0.05$ significant between two groups. Data were expressed as mean ± standard deviation.

Table 3 Nalbuphine consumption during 24 h.

	Group I	Group II	*P*-value
1 h	14.4 ± 1.01	10 ± 1.03†	< 0.001
4 h	11.6 ± 0.62	8.4 ± 1.28†	< 0.001
8 h	10.4 ± 1.01	8 ± 1.85*	0.015
12 h	5.6 ± 2.14	3.8 ± 1.52	0.133
24 h	4.4 ± 0.94	3.6 ± 1.21	0.25
Total (24 h)	46.4 + 5.72	33.8 + 6.89*	< 0.003

Group I: placebo and Group II: pregabalin.
† $P < 0.001$ high significant.
* $P < 0.05$ between two groups. Data were expressed as mean ± standard deviation.

Table 4 Numeric sedation score during 24 h.

	Group I	Group II	*P*-value
1 h	2.2 ± 0.82	2.75 ± 0.82*	0.042
4 h	2.1 ± 0.47	2.6 ± 0.99*	0.048
8 h	1.93 ± 0.92	2.45 ± 1.23	0.138
12 h	1.6 ± 0.82	2.0 ± 0.89	0.148
24 h	1.35 ± 0.49	1.65 ± 0.89	0.195

Group I: placebo and Group II: pregabalin. † $P < 0.05$ significant between two groups. Data were expressed as mean ± standard deviation.

surgery reported before patient discharge from the hospital (Table 5), there was an overall high significant increase ($P < 0.001$) in the pregabalin group compared to placebo group, as in group II (pregabalin group), 15 patients showed very good satisfaction (37.5%), 20 good (50%), 4 fair (10%) and 1 poor satisfaction (2.5%) in comparison with only 6 patients (15%) in placebo group showed good satisfaction, 20 fair (50%) and 14 poor satisfaction (35%). Table 6 showed the adverse effects reported during the study, as there were an increase in patients number suffering from dizziness, somnolence, headache and blurred vision and a decrease in patient number suffering from nausea, vomiting, urine retention and pruritus in pregabalin group compared to placebo group with insignificant difference between the two groups in all the above side effects. Postoperative shivering is significantly lower in pregabalin group than in placebo group ($P < 0.05$).

Table 5 Patient satisfaction.

	Group I	Group II†
Poor	14 (35%)	1 (2.5%)
Fair	20 (50%)	4 (10%)
Good	6 (15%)	20 (50%)
Very good	0 (0%)	15 (37.5%)

Group I: placebo and Group II: pregabalin.
† $P < 0.001$ significant between two groups. Data were presented as number of patients and (percentage).

Table 6 Adverse effects in both groups.

	Group I	Group II
Nausea	12 (30%)	10 (25%)
Vomiting	10 (25%)	6 (15%)
Dizziness	8 (20%)	10 (25%)
Somnolence	8 (20%)	12 (30%)
Headache	2 (5%)	4 (10%)
Blurred vision	0 (0%)	4 (10%)
Urine retention	14 (35%)	8 (20%)
Pruritus	16 (40%)	6 (15%)
Shivering	16 (40%)	2 (5%)*

Group I: placebo and Group II: pregabalin.
* $P < 0.05$ significant between two groups. Data were presented as number of patients and (percentage).

4. Discussion

The present study showed a significant decrease in pain score and nalbuphine consumption with an increase in sedation score during the 1st, 4th and 8th hrs postoperative in pregabalin group compared to placebo. During the later hours of study, there was no difference in the previous measures between the studied groups. These findings are in accordance with the pharmacokinetic profile of the drug as it has short elimination life (6–8 h) after a single dose [19,20].

The probable mechanism of action of pregabalin via, potent binding at α2-δ subunit of the presynaptic, voltage-gated calcium channels that are widely distributed throughout the peripheral and central nervous system [8–10], this reduces calcium influx at nerve terminals and therefore reduces the release of several neurotransmitters including glutamate, norepinephrine and substance P [11,12]. Also, the sensitization of dorsal horn neurons has been demonstrated in acute pain models [21,22] and possibly plays a role in the development of chronic pain after surgery [23,24]. By reducing the hyperexcitability of dorsal horn neurons induced by tissue damage, pregabalin may have a role in postoperative pain management [25–27].

Pregabalin has been used in doses starting from 50 [28], 75 [29], 100 [13], 150 [15], 300 mg [30,31] and 600 mg [14]. The 300 mg dose of pregabalin used in our study was considered the basis in many studies [30,31]. This dose has been well tolerated except for minor side effects like dizziness and sedation [32].

Also, pregabalin in the present study had a high percentage and significant increase in patient satisfaction and significant decrease in total nalbuphine consumption in relation to placebo. These findings were combatable with the study was done by Ittichaikulthol and colleagues [30] who found 300 mg 1 h before surgery, significantly reduced pain scores and morphine consumption after abdominal hysterectomy. Hill and co-workers [16] found that 300 mg pregabalin to be more effective than

50 mg pregabalin or 400 mg ibuprofen in attenuating pain after dental extraction. Also, Kim and others [33] showed pregabalin 150 mg 1 h before surgery and repeated after 12 h was effective in reducing postoperative pain in patients undergoing robot-assisted endoscopic thyroidectomy. Peng and others [28] reported low-dose pregabalin (75 mg) had given 1 h before surgery and then every 12 h for three doses, significantly reduced pain scores in patients after doing laparoscopic cholecystectomy.

On the other hand, other studies were done by Paech and colleagues [13], Jokela and others [14] and White and colleagues [34] reported that preoperative administration of pregabalin 100, 300 or 75–300 mg, respectively, was ineffective in reducing postoperative pain and the need for opioid analgesic medication. This can be explained firstly by using low doses of pregabalin 75, 100 and 150 which are ineffective to produce satisfactory level of analgesia, secondly the type of surgical procedures which were minor and superficial surgeries and so they have been use small doses of pregabalin in the previous studies and thirdly only a single dose of the medication was administered before surgery, while in our study we used 300 mg pregabalin, twice doses 12 h apart preoperative for patients scheduled to a painful operation (shoulder arthroscopy). Pregabalin is generally well tolerated [35] and associated with transient mild to moderate adverse effects which are dose dependent.

Dizziness and somnolence are most frequently reported side effects of pregabalin (22–29%) [36]. The present study approved this as: dizziness and somnolence were the most common side effects, 25–30% respectively in pregabalin group with insignificant difference between it and placebo. The same results reported by Gajraj [19] who found that somnolence (29.2%) and dizziness (22.2%) and Ittichaikulthol and colleagues [30] who found the same results, dizziness and somnolence (34.21%).

Postoperative shivering is physiologically stressful and unpleasant effect and occurs in 6.3–66% of patients recovering from general anaesthesia [37]. The present study showed significant decrease in postoperative shivering in pregabalin group which may be due to anticonvulsive, anxiolytic and analgesic effects of gabapentinoids may partly reduce the incidence of shivering, but the exact mechanism of pregabalin in postoperative shivering is still unexplained. So many future studies will be needed to focus on the effects of gabapentoids on shivering.

In conclusion, the present study demonstrated that twice, preoperative doses of pregabalin 300 mg (12 h apart) in patients undergoing shoulder arthroscopy resulted in significant reduction in pain score, nalbuphine requirement and a significant increase in patient satisfaction in 24 h postoperatively without significant side effects. So, the study recommends twice, 12 h apart, 300 mg of pregabalin oral preoperatively is a safe, effective and opioid-sparing method for multimodal analgesia in postoperative pain after shoulder arthroscopy.

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