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Oral pregabalin for postoperative pain relief after third molar extraction: a randomized controlled clinical trial

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Title: Oral pregabalin for postoperative pain relief after third molar extraction: a randomized controlled clinical trial

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Abstract

Objectives The aim of this randomized controlled clinical trial was to evaluate the efficacy and safety of pregabalin administered pre- and post-operatively in patients with pain and swelling due to the surgical removal of impacted lower third molars.

Materials and Methods The final study sample comprised 60 volunteers (23 males and 37 females). Group 1 (n=30) received 75 mg oral pregabalin 1 hour before surgery and 1 hour after surgery. Group 2 (n=30) served as a control group and received no pregabalin. Postoperative pain intensity and swelling were measured using a visual analogue scale (VAS); pain relief experienced was reported using a four-point verbal rating scale (VRS); the rescue medication requirement, adverse effects, and global impression of the medication were also recorded.

Results No significant difference in pain intensity (VAS) was observed between the groups. However, fewer rescue medication tablets were needed by pregabalin-treated patients than by controls ($p=0.021$). The frequency and intensity of adverse effects were significantly higher in pregabalin-treated patients ($p<0.001$), although no serious adverse events occurred. No significant difference in the degree of swelling was observed in any measurement except that from mandibular angle to lip junction, which showed lesser inflammation in the pregabalin group at 24 h post-surgery ($p=0.011$). The global opinion on the medication received was more positive in the pregabalin group ($p=0.042$).

Conclusions Administration of pregabalin reduces the requirement for rescue medication after third molar surgery and results in a more constant pain level, with fewer peaks of pain intensity.

Clinical relevance These findings suggest that pregabalin may be useful to control acute postoperative pain. Adverse effects are known to be reduced at the low pregabalin dose used in our study.

Keywords: pregabalin; postoperative pain; acute pain; third molar; surgery

Introduction

Lower third molar extraction is one of the most common interventions in oral/maxillofacial surgery due to the highly frequent impaction of these teeth and the multiple associated diseases, mandating their extraction.[1–3]

Surgical removal is usually followed by a wide range of uncomfortable symptoms associated with various postoperative sequelae, including an inflammatory reaction characterized by pain, swelling, trismus, and functional discomfort of the oral cavity, which tend to appear during the first 24-48 h after surgery.[3, 4] Analgesic drugs are frequently assessed in the dental impaction pain model. This has become one of the primary models used to develop analgesic drugs because it provides a readily available healthy population and a relatively uniform surgical procedure confined to one area of the body.[5, 6]

The relief of pain has been described as a universal human right but is not always easily achieved.[7] Opioid analgesics are effective but their use is limited because they may have troublesome and serious side-effects, and their potential for abuse may lead to regulatory and logistical difficulties.[8] Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used drugs for postoperative pain after the extraction of impacted third molars because they have fewer regulatory restrictions; however, they also associated with some adverse effects, which are more likely at higher doses or with longer courses.[9] Despite numerous reports in the literature on the use of antiepileptic drugs for chronic pain control [10–13], few data are available on their administration for pain relief after oral surgery, and their usefulness to control acute pain remains unclear.

Pregabalin is a structural analogue of the inhibitory neurotransmitter γ-aminobutyric acid but is not functionally related to this acid. It binds to the α-2- δ

subunit of voltage-gated calcium channels, reducing the release of several excitatory neurotransmitters and blocking the development of hyperalgesia and central sensitization.[14–16] Pregabalin has similar anticonvulsant, anti-hyperalgesic, and anxiolytic properties to those of gabapentin [17, 18] but has a more favorable pharmacokinetic profile and is three- to ten-fold more potent, with fewer adverse effects.[19, 20]

Pregabalin is currently used against peripheral neuropathic pain and in the treatment of partial epileptic seizures and can also ameliorate different nervous conditions secondary to infections, lesions, diabetes, cancer, or AIDS.[21, 22] Pregabalin has been introduced as an adjuvant in the multimodal management of postoperative analgesia following reports of its effectiveness for acute postoperative pain in minor gynecological surgery [4], laparoscopic cholecystectomy [23, 24], tonsillectomy [25], and third molar surgery.[26] However, the limited amount of clinical trial data means that no consensus has been established on the timing, duration, or dosage of pregabalin in the treatment of acute postoperative pain.

Acute postoperative dental pain is a common analgesic model, and the aim of this randomized controlled clinical trial was to evaluate the efficacy and safety of pregabalin administered pre- and post-operatively in patients with pain and swelling due to the surgical removal of impacted lower third molars under local anesthesia.

Materials and methods

Study design and patient selection

A single-centre randomized controlled clinical trial was undertaken. All participants signed their informed consent to participation in the study, which followed the Helsinki Declaration guidelines and was approved by the ethical committee of the University of

Granada. Out of the 68 Caucasian volunteers initially included in the study, 8 were excluded for failing to complete and return the data collection form. The final study sample therefore comprised 60 volunteers (23 males and 37 females) aged 18-30 yrs undergoing scheduled surgical extraction of impacted lower third molar at the Clinic of the School of Dentistry of the University of Granada (Spain) between October 2009 and September 2011. Study exclusion criteria were: age under 18 yrs, renal failure, pregnancy or breast-feeding, allergy to the study medication or related drugs, immunocompromised status, psychological disorder, epilepsy, receipt of medication with analgesic or anti-inflammatory properties less than 24 h before the surgery, preoperative inflammation and pain at the surgical site, and clinical or radiographic evidence of active oral disease.

A computer-generated random sequence was used to allocate participants to group 1 (pregabalin group) or group 2 (control group). Group 1 (n=30) received 75 mg oral pregabalin (Lyrica; Pfizer, Inc, New York, NY) 1 hour before surgery and 1 hour after surgery. Group 2 (n=30) served as a control group and received no pregabalin. As antibiotic treatment, all participants in both groups were administered with 875/125 mg amoxicillin/clavulanic acid or (in those with penicillin allergy) 300 mg clindamycin every 8 h for seven days plus 650 mg paracetamol every 8 h for two days. Treatment with 600 mg ibuprofen was permitted for patients not experiencing adequate pain relief after the paracetamol administration, but patients were strongly encouraged to wait for more than 1 h before taking this rescue analgesia to allow sufficient time for the paracetamol to exert its effects.

Surgical protocol

The surgeon and assistant were scrubbed and wore sterile gowns and gloves. Patients were fully covered with sterile drapes, and their lips and perioral facial skin were disinfected with 10% povidone iodine (Corsodyl, SmithKline Beecham, Brendford, U.K.). Immediately before surgery, patients rinsed their mouths for 2 min with 10 ml 0.12% chlorhexidine mouthwash (Perio-Aid, Dentaid SL, Barcelona, Spain), which was delivered using sterile injectors. All surgical procedures were performed by the same experienced surgeon (MVOG) under local anesthesia using 4% articaine with 1:100,000 epinephrine (Ultracain, Normon SA, Madrid, Spain). A releasing incision was made from the distal aspect of the second molar to its buccal sulcus, and a full-thickness flap was elevated to reveal the molar and adjacent bone.

Study variables

Study variables were classified as predictor variables or outcome variables.[27] Predictor variables were divided among those related to patients, teeth, and surgery.

Patient-related variables were: age, gender, presence of systemic disease (recording the diagnosis), and tobacco use (non-smoker, 1-10 cigarettes/day, 11-20 cigarettes/day, or >20 cigarettes/day).

Tooth-related variables were: extracted third molar (38/48); degree of extraction difficulty according to Pell and Gregory [28], using the Winter scale to classify it as mesio-angular, horizontal/transversal, vertical, or disto-angular; degree of molar eruption (semi-impacted/impacted); occlusal plane coincidence between third and second molars (position A: coincident, position B: third molar between occlusal plane and cervical line of the second molar, position C: third molar below cervical line of second molar); distance between mandibular ramus and distal aspect of the second molar (class I: adequate for the whole mesiodistal diameter of the third molar crown,

class II: smaller than the mesiodistal diameter of the third molar crown, class III: all or most of the molar is within the ramus).

Surgical variables were: surgery duration (min), incision type (linear/bayonet), ostectomy type (none, mesio-vestibular ostectomy, mesio-vestibular-distal ostectomy, mesio-vestibular-distal-occlusal ostectomy), coronal section (no/yes), and number of sutures.

Baseline inflammation was measured immediately before the surgery, using measurement landmarks from the mandibular angle to tragus, external corner of eye, ala nasi, lip junction, and pogonion.

During the 24-h postoperative period, each patient completed a data collection form with the following outcome variables: postoperative pain intensity at 1, 2, 4, 6, 8, 12, and 24 h using a horizontal 100-mm visual analogue scale (VAS) with “no pain” and “worst pain imaginable” as end-points; pain relief experienced at 1, 2, 4, 6, 8, 12, and 24 h using a four-point verbal rating scale (VRS) (1 = none, 2 = a little, 3 = acceptable, 4 = complete); degree of postoperative swelling of the treated area using a horizontal 100-mm VAS with “no swelling” and “worst swelling imaginable” as end-points; requirement for 600 mg ibuprofen (no/yes) and, when needed, number of tablets. At the end of the 24-h period, all participants completed a questionnaire on possible adverse effects (nausea, vomiting, drowsiness, motion sickness, tremors, sweating, dyspepsia, diarrhea, bleeding, dizziness, and disorientation) and their intensity (mild/moderate/severe) and on their global impression of the medication (1 = poor, 2. = not very good, 3 = good, 4 = very good).

Patients returned to the clinic two days after the surgery for a postoperative follow–up visit, and questionnaire items were clarified when necessary.

Statistical analysis

The Shapiro Wilk test was used to check the normality of the quantitative data distribution. Normally distributed variables were analyzed with the Student-t test and non-normally distributed variables with the Mann-Whitney test. The chi-square and Wilcoxon tests were used for the bivariate analysis of two qualitative variables. The significance level was set at $p< 0.05$. IBM® SPSS® Statistics Standard GradPack 22 for Windows (IBM Corporation, Armonk, NY) was used for the statistical analyses.

Results

The mean age of the participants was 23.90±5.69 yrs in group 1 (pregabalin group) and 23.17±7.10 yrs in group 2 (control group); 23 participants were male and 37 female, and 7 participants had systemic disease. The remaining predictor variables are summarized in Table 1.

Pregabalin and control groups did not significantly differ in mean age ($p=0.123$), sex ($p=0.144$), medical history ($p>0.05$), or tobacco consumption ($p=0.877$). No intergroup difference was found in tooth-related or surgical variables, with the exception of a significantly larger number of molars in class I between mandibular ramus and distal aspect of the second molar in the controls than in the pregabalin group ($p=0.003$).

No significant difference in pain intensity (VAS) was observed between the groups (Table 2). It was higher in the pregabalin group initially but was similar to controls and more constant in this group after a few hours, with fewer peaks in intensity and no variations in measurements > 1.00 (VAS), whereas the control group showed variations of > 2.00.

Rescue medication was required by 56.7% of the patients in each group, i.e., 34 of the 60 participants (Table 3). However, fewer tablets were taken by the pregabalin-

treated patients than by the controls (p=0.021). Pain relief on day 1 was similar between the groups (Table 4) and was significantly influenced by the receipt of rescue medication (p=0.014) and the number of tablets (p=0.035).

The frequency and intensity of adverse effects were significantly higher in pregabalin-treated patients (Table 5), affecting 17 (56.66%) of them. In comparison to the controls, they reported a significantly higher frequency of drowsiness (p<0.001 and motion sickness p=0.021), the most common adverse effects. No serious adverse events occurred in this study.

There was no significant difference between the groups in the degree of swelling (VAS) at 24 or 48 hours post-surgery (Table 6) in any measurement except that from mandibular angle to lip junction, which showed lesser inflammation in the pregabalin group at 24 h post-surgery (p=0.011).

The global opinion on the medication received was more positive in the pregabalin group than in the control group (p=0.042).

Discussion

Contradictory findings have been published by the few studies on the efficacy and adverse effects of pregabalin in the treatment of acute postoperative pain, possibly due to differences in the dosage, dosing regimen, and nature of the surgery. The third-molar extraction analgesia model is robust and has been well validated, with NSAIDs as comparators [1], but there has been little research on pregabalin with this approach.

We found no significant differences in the intensity of pain (VAS) between pregabalin and control groups during the first 24 hours after surgery. Although higher values were reported by the pregabalin group initially, significance was not reached, and the pain intensity was similar between the pregabalin and control groups after a few

hours and was more constant in the former, with fewer peaks in intensity. We also evaluated the degree of third molar extraction difficulty, the surgery duration, type of incision, amount of bone removed, need for coronal section, and the number of sutures, because pain intensity is reported to increase with greater extent of surgical intervention.[29] There was no significant difference in these variables between the groups with the exception of a larger number of class I molars in the control group (p=0.003). Our findings are in agreement with the results of the meta-analysis by Zhang et al. [30], who concluded that perioperative pregabalin administration does not reduce pain intensity during the first 24-h period after surgery, although significant differences *versus* placebo were reported in some of the studies reviewed.

However, the post-operative administration of 300 mg pregabalin was found to provide a longer duration of analgesia in comparison to 50 mg pregabalin, 400 mg ibuprofen, or placebo, although it was associated with more frequent adverse effects and complications.[1] We administered lower pregabalin doses (75 mg 1 h before and 1 h after surgery) in an attempt to minimize these adverse effects. This dose (75 mg) was used in the study by Cheung et al. [26], who additionally reported a greater analgesic efficacy with the post-operative *versus* pre-operative administration of this dose. Our finding of no significant difference in pain relief between the pregabalin and control groups is also consistent with the observations of Cheung et al.[26] The same dose was selected by Kim et al.[11], who administered 75 mg pregabalin 1 h before surgery and 12 h afterwards and found that a perioperative dose of pregabalin was effective to reduce post-operative pain in patients undergoing mastectomy. Peng et al.[24] administrated 75 mg pregabalin, 50 mg pregabalin, or placebo at 1 h before surgery and then every 12 h after surgery for a total of three doses and reported lower pain scores in the 75 mg pregabalin group. In another study, analgesia after day-case gynecological

laparoscopic surgery was improved in patients preoperatively treated with 150 mg pregabalin and 800 mg ibuprofen in comparison to those receiving ibuprofen alone, although there was no reduction in analgesic consumption.[31] Perioperative administration of 75 mg pregabalin was recently found to reduce postoperative pain in patients undergoing mastectomy.[11]

Hence, although there is some evidence that 75 mg pregabalin appears to be effective for acute postoperative pain relief, further studies are required to establish the optimal regimen. One study found no statistically significant differences in opioid consumption or pain scores between single and multiple pre-operative dosing with ≤75 mg pregabalin, suggesting that repeated doses of the drug may offer no significant advantage.[32] Given that the value of 5.5 half-lives of pregabalin is approximately 27 hours, a single preoperative dose of pregabalin should be sufficient to cover peak postsurgical pain.[33]

Interestingly, although no differences in pain intensity were observed, the number of rescue tablets taken to ease the pain was significantly lower in the pregabalin group. The consumption of analgesics can be considered a valid measure of treatment efficacy as long as the test and control groups have similar pain scores, as in the present study.[34] A meta-analysis and systematic review on the efficacy of pregabalin against acute postoperative pain concluded that pregabalin did not reduce the pain intensity but that the opioid consumption during the first 24 h was lower.[30] Mishriki et al.[32] also observed statistically significant opioid-sparing effects after single and multiple doses of pregabalin ranging between 75 and 300 mg.

Pregabalin possesses anxiolytic as well as analgesic properties.[35] Jokela et al.[31] concluded that pregabalin at doses of 75 or 150 mg has the same anxiolytic effect as 5 mg diazepam. In the meta-analysis by Mishriki et al.[32] six of the ten

studies on preoperative anxiety reported that it was significantly reduced by pregabalin administration. This is especially relevant in oral/maxillofacial surgery, which is usually conducted under local anesthesia and can induce considerable anxiety in some patients on the day of surgery. In the present study, the anxiolytic effect of this drug may have played a role in the significantly more favorable view of their medication expressed by the pregabalin-treated patients than by the controls.

Although pregabalin is safer than other gabapentinoids, such as gabapentin, it should be administrated with caution due its possible adverse effects.[30] Drowsiness and motion sickness were more frequently reported by the pregabalin-treated patients than by the controls in the present study, although there were no serious adverse events. As noted above, Hill et al.[1] reported more frequent adverse events and complications in patients taking 300 mg pregabalin after dental surgery, and 100 mg pregabalin was observed to have significant side effects (e.g., dizziness and somnolence) in an outpatient population. As in the present study, Cheung et al.[26] found no serious adverse effects at a dose of 75 mg pregabalin, with dizziness being the most frequent effect. Mathiesen et al.[25] also reported an increase in dizziness with pregabalin treatment.

With respect to the degree of postoperative swelling, we cannot conclude from our data that pregabalin reduces the inflammation, given that the only significant difference was in the measurement from mandibular angle to lip junction, which showed significantly lesser inflammation in the pregabalin group at 24 h post-surgery.

In conclusion, although postoperative pain intensity is not directly affected by the administration of pregabalin, it may be useful to control acute postoperative pain, given the lesser requirement for rescue medication and more constant pain level in those receiving it, with fewer peaks of pain intensity. Adverse effects are known to be reduced

at the low pregabalin dose used in our study. However, further research is required on the efficacy of pregabalin in the control of postoperative dental pain and on associated adverse effects.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest statement

The authors declare that they have no conflict of interest

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Cover letter

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Table 1

Table 1 Summary of predictor variables: patient-related variables (n=60), tooth-related variables (n=60) and surgical variables

Variable	Pregabalin group	Control group	Variable	Pregabalin group	Control group
PATIENT-RELATED VARIABLES (N=60)			Position B	14 (46.6)	17 (56.7)
Age (yrs) [x**±s]**	23.9±5.69	23.17±7.10	Position C	5 (16.7)	3 (10.0)
Sex [n(%)]			**Distance mandibular ramus-distal M2** [n(%)]		
Male	9 (30.0)	14 (46.7)	Class I	5 (16.7)	14 (46.7)
Female	21 (70.0)	16 (53.3)	Class II	12 (40.0)	12 (40.0)
Systemic disease [n(%)]			Class III	13 (43.3)	4 (13.3)
No disease	25 (83.3)	28(93.3)	**SURGICAL VARIABLES**		
Cardiovascular disease	1 (3.3)	0 (0.0)	**Duration of surgery** (min) [x ±s]	31.20±18.47	34.10±17.66
Penicillin allergy	2 (6.7)	1 (3.3)	**Type of incision** [n(%)]		
Clavulanic acid allergy	1 (3.3)	0 (0.0)	Linear	19 (63.3)	16 (53.3)
Others	1 (3.3)	1 (3.3)	Bayonet	11 (36.7)	14 (46.7)
Tobacco use [n(%)]			**Osteotomy** [n(%)]		
No	23 (76.7)	24 (80.0)	No osteotomy	12 (40.0)	11 (36.7)
1 - 10 cig/day	6 (20.0)	3 (10.0)	Mesio-vestibular	1 (3.3)	4 (13.3)
11 - 20 cig/day	1 (3.3)	3 (10.0)	Mesio-vestibular-distal	16 (53.4)	12 (40.0)
>20 cig/day	0 (0.0)	0 (0.0)	Mesio-vestibulo-disto-occlusal	1 (3.3)	3 (10.0)
TOOTH-RELATED VARIABLES(n=60)			**Coronal section** [n(%)]		
Tooth extracted [n(%)]			No	19 (63.3)	15 (50.0)
38	18 (60.0)	12 (40.0)	Yes	11 (36.7)	15(50.0)
48	12 (40.0)	18 (60.0)	**Number of sutures**[x ±s]	3.87±1.22	3.97±1.13
Spatial relationship n(%)]					
Mesio-angular	12 (40.0)	20 (66.7)			
Horizontal-transversal	3 (10.0)	2 (6.7)			
Vertical	15 (50.0)	7 (23.3)			
Disto-angular	0 (0.0)	1 (3.3)			
Degree of eruption M3[n(%)]					
Semi-impacted	23 (76.7)	21 (70.0)			
Impacted	7 (23.3)	9 (30.0)			
Occlusal plane M3-M2 *[n(%)]					
Position A	11 (36.7)	10 (33.3)			

* M2 = second molar, M3 = third molar

Table 2 Pain intensity over time by group

VARIABLES	PREGABALIN GROUP (n=30)	CONTROL GROUP (n=30)	COMPARISON (*p value*)
Pain at 1 h	3.33±3.53	2.13±2.95	0.192
Pain at 2 h	3.50±2.70	3.41±3.20	0.724
Pain at 4 h	3.90±2.64	4.83±2.82	0.135
Pain at 6 h	3.36±2.44	4.20±2.80	0.214
Pain at 8 h	3.46±2.86	4.00±2.51	0.391
Pain at 12 h	3.46±3.23	4.03±2.90	0.380
Pain at 24 h	2.93±2.82	3.73±2.81	0.172
Mean pain during first 24 h	3.42±2.27	3.76 ±2.04	0.544

Pain intensity (VAS) values are given as means ± standard deviation

Table 3 Summary of rescue doses

VARIABLES	PREGABALIN GROUP (n=30)	CONTROL GROUP (n=30)	COMPARISON (*p value*)
Receipt of rescue medication [n(%)]			0.603
No	13 (43.3)	13 (43.3)	
Yes	17 (56.7)	17 (56.7)	
Mean Nº of rescue doses [$\bar{x}$ ±s]	1.20± 1.29	1.67 ± 1.62	0.320
Nº of rescue tablets [n (%)]			**0.021**
0	13 (43.3)	13 (43.3)	
1	6 (20.0)	1 (3.3)	
2	4 (13.4)	4 (13.4)	
3	6 (20.0)	7 (23.3)	
4	1 (3.3)	5 (16.7)	

Table 4 Pain relief on first day

VARIABLES	PREGABALIN GROUP (n=30)	CONTROL GROUP (n=30)	COMPARISON (*p value*)
Pain relief after 1 h	2.53±1.00	2.76±1.22	0.339
Pain relief after 2 h	2.53±0.86	2.73±1.08	0.386
Pain relief after 4 h	2.63±0.76	2.43±1.04	0.439
Pain relief after 6 h	2.80±0.80	2.60 ±1.00	0.441
Pain relief after 8 h	2.80±0.88	2.73±0.69	0.725
Pain relief after 12 h	2.80±0.92	2.90±0.75	0.813
Pain relief after 24 h	2.96±0.92	3.03 ±0.80	0.872

Verbal rating scale values (range 1-4) are expressed as means ± standard deviation

Table 5

Table 5 Summary of adverse effects reported by study groups

VARIABLES	PREGABALIN GROUP (n=30)	CONTROL GROUP (n=30)	COMPARISON (*p value*)
Adverse effects [n (%)]			
No adverse effects	13 (43.3)	27 (90.0)	**<0.001**
Nausea	0 (0.0)	1 (3.3)	0.500
Vomiting	1 (3.3)	0 (0.0)	0.500
Drowsiness	11 (36.7)	1 (3.3)	**0.001**
Motion sickness	9 (30.0)	2 (6.7)	**0.021**
Tremors	2 (6.7)	1 (3.3)	0.500
Sweating	0 (0.0)	0 (0.0)	-
Dyspepsia	0 (0.0)	0 (0.0)	-
Diarrhea	1 (3.3)	0 (0.0)	0.500
Bleeding	0 (0.0)	0 (0.0)	-
Dizziness	0 (0.0)	0 (0.0)	-
Disorientation	1 (3.3)	0 (0.0)	0.500
Intensity of adverse effects [n (%)]			**<0.001**
No adverse effect	13 (43.4)	27 (90.0)	
Mild	10 (33.3)	2 (6.7)	
Moderate	4 (13.3)	1 (3.3)	
Severe	3 (10.0)	0 (0.0)	

Table 6

Table 6 Swelling intensity over time by group

	INITIAL SWELLING			SWELLING AFTER 24 HOURS			SWELLING AFTER 48 HOURS		
	PREGABALIN GROUP (n=30)	**CONTROL GROUP (n=30)**	**COMPARISON (*p value*)**	**PREGABALIN GROUP (n=30)**	**CONTROL GROUP (n=30)**	**COMPARISON (*p value*)**	**PREGABALIN GROUP (n=30)**	**CONTROL GROUP (n=30)**	**COMPARISON (*p value*)**
MA – ear	4.46 ± 1.13	4.68 ±0.83	0.185	4.99 ± 1.33	5.09 ± 1.10	0.833	4.98 ± 1.30	5.19 ± 1.27	0.603
MA – eye	9.81 ± 0.84	9.91 ± 0.58	0.755	10.34 ± 0.98	10.55 ± 1.10	0.750	10.34 ± 0.79	10.50 ± 1.07	0.661
MA – nose	10.00 ± 0.76	10.25 ± 0.67	0.138	10.47 ± 2.04	11.13 ± 1.06	0.093	10.77 ± 1.36	11.12 ± 1.04	0.110
MA – lip	7.98 ± 0.98	8.16 ± 0.66	0.360	8.92 ± 1.08	9.71 ± 1.24	**0.011**	8.90 ± 1.13	9.36 ± 1.31	0.141
MA - pogonion	9.80 ± 1.20	10.18 ± 0.89	0.170	10.57 ± 1.28	11.06 ± 1.46	0.105	10.62 ± 1.44	10.90 ± 1.37	0.463

Values are given as the mean ± standard deviation

MA = mandibular angle, ear = tragus, eye = external corner of eye, nose = ala nasi, lip = lip junction.

Influence of rescue medication intake on mean inflammation 1-24 h: $p = 0.104$