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ARAŞTIRMA / RESEARCH

Efficiency of topical and systemic flurbiprofen on pain and edema after impacted third molar surgery and comparison of gastrointestinal adverse effects

Topikal ve sistemik flurbiprofenin gömülü üçüncü molar cerrahisi sonrası ağrı ve ödem üzerine etkilerinin ve gastrointestinal yan etkilerinin karşılaştırılması

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Abstract

Purpose: The aim of this study was to evaluate the effects of systemic and topical nonsteroidal anti-inflammatory agents on postoperative pain and edema and also gastrointestinal side effects after impacted third molar surgery.

Materials and Methods: In this clinical study, 100 healthy patients with mandibular impacted third molar teeth in a similar position were included. After the operation, patients were divided into two groups, one group received Flurbiprofen tablets and the other group received Flurbiprofen 0.25% Oral spray. The pain was assessed postoperatively by Visual Analog Scale (VAS). The edema evaluation was measured on preoperative and postoperative 2nd and 7th days. Gastrointestinal adverse effects related to the use of nonsteroidal anti-inflammatory drug such as nausea, heartburn, dyspepsia, vomiting, and diarrhea were recorded according to information received from patients.

Results: There was a statistically significant difference between the groups with regard to Visual Analog Scale levels at 6th, 8th, 12th, 24th, and 48th hours. 2nd-day edema measurements of the systemic nonsteroidal anti-inflammatory drug group were found to be statistically lower than the local-topical nonsteroidal anti-inflammatory drug group.

Conclusion: Although the efficacy of topical nonsteroidal anti-inflammatory drugs on pain and edema is lower than systemic nonsteroidal anti-inflammatory drugs, it may be preferred because it has less gastrointestinal side effects.

Keywords: Pain, edema, third molar teeth, flurbiprofen, nonsteroidal anti-inflammatory agents

Öz

Amaç: Bu çalışmanın amacı, gömülü üçüncü molar diş cerrahisinden sonra sistemik ve topikal nonsteroid antiinflamatuar ilaçların postoperatif ağrı ve ödem üzerine etkileri ve ayrıca gastrointestinal yan etkilerin değerlendirilmesidir.

Gereç ve Yöntem: Bu klinik çalışmaya, benzer pozisyonda mandibular gömülü üçüncü molar dişe sahip 100 sağlıklı hasta dahil edilmiştir. Operasyon sonrasında hastalar iki gruba ayrıldı, bir gruba Flurbiprofen tablet uygulanırken, diğer gruba da Flurbiprofen 0.25% Oral spray uygulandı. Ağrı, postoperatif olarak Vizüel Ağrı Skalası (VAS) ile değerlendirildi. Ödem ölçümü preoperatif ve postoperatif 2. ve 7. günlerde yapıldı. Mide bulantısı, mide yanması, dispepsi, kusma ve ishal gibi nosteroid anti-inflamatuar ilaç kullanımına bağlı gastrointestinal yan etkiler hastalardan alınan bilgilere göre kaydedildi.

Bulgular: Gruplar arasında 6, 8, 12, 24 ve 48. saatler arasında Vizüel Ağrı Skalası düzeyleri açısından istatistiksel olarak anlamlı fark vardı. Sistemik nonsteroidal antienflamatuar ilaç grubunun 2. gündeki ödem ölçümleri lokal topikal nonsteroidal antiinflamatuvar ilaç grubuna göre istatistiksel olarak daha düşük bulundu.

Sonuç: Topikal kullanılan nonsteroid anti-inflamatuar ilaçların ağrı ve ödem üzerine etkinlikleri sistemik nonsteroid anti-inflamatuar ilaçlara göre daha düşük olmasına rağmen, daha az gastrointestinal yan etkiye sahip olduğu için tercih edilebilir.

Anahtar kelimeler: Ağrı, ödem, üçüncü molar diş, flurbiprofen, steroid olmayan antienflamatuar ajanlar

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INTRODUCTION

Impacted tooth extraction is one of the most common procedures in oral surgery and routine dental practice[1]. Impacted third molar surgery has similar complications with other surgical procedures on intraoperative and postoperative such as pain, edema, trismus, ecchymosis[2-5].

All surgical procedures are a major cause of pain. Pain is one of the most common sequelae in the postoperative period. After impacted third molar surgery, pain emerges after the impact of anesthesia disappears and it reaches its maximum level within the first 6-12 hours postoperatively and adversely affecting the quality of life of the patient[6].

Following impacted third molar surgeries, lymph drainage is reduced and intravascular venous pressure is increased due to the surgical trauma. As a result of the inflammation, postoperative edema occurs. Various anti-inflammatory medications are used with the aim of minimizing postoperative edema[7-8]. Many postoperative medication studies have been conducted in order to prevent complications following impacted teeth operations and to this end, different agents like non-steroid anti-inflammatory drugs, steroids, enzymes, and antihistaminic medications have been used[2-5].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications frequently used to prevent and to eliminate postoperative inflammatory complications such as pain, edema, trismus, infection, ecchymosis. The most important effects of NSAIDs in terms of therapy are their anti-inflammatory, analgesic and antipyretic effects[9].

Systemic and topical NSAIDs can be used postoperatively as a complementary treatment in preventing the development of pain and edema. However, as well as its therapeutic properties, the use of such drugs can cause discomfort in the gastrointestinal system[10]. Heartburn, dyspepsia, nausea, and abdominal pain may be the most common gastrointestinal adverse effects of NSAID and erosion, asymptomatic ulcer, perforation, ulcer, bleeding may be rare gastrointestinal complications. Topical NSAIDs have a moderate effect on pain relief, with efficacy similar to that of systemic NSAIDs, but with a much better safety profile because of the lower systemic absorption[11].

The target of this study is to compare the two forms of NSAIDs in relation to pain, edema and gastrointestinal adverse effects following impacted third molar surgery.

MATERIALS AND METHODS

This study was initiated following Karabük University Ethics Committee approval (Date: 25.01.2017, Decision no: 1/8) and conducted in line with Helsinki Human Rights Declaration and the relevant guiding principles. The study was carried out on 100 patients with impacted third molar in the same position (vertical) and in full bone retention who applied to the Oral and Maxillofacial Surgery Clinic of Karabük University Faculty of Dentistry. The ages of the patients ranged from 18 to 25 years (the mean age of patients = 23.98±4.43). Pregnant and nursing mothers, patients with infection at the operation site, known hypersensitivities, sensitivities, or reactions to NSAIDs and aspirin and patients with gastrointestinal disorders such as reflux disease, gastritis, gastric ulcer, gastric bleeding, dyspepsia, ulcerative colitis, hemorrhoids were excluded from the study. Detailed information was provided to all patients and patients gave consent for inclusion in the study via a consent form.

100 mandibular impacted third molar surgeries were performed in a hundred patients under local anesthesia. The number of patients to be included in the study was determined as the result of power analysis.

Surgical procedure

Surgeries of the impacted third molars were completed under local anesthesia (2 % Articaine hydrochloride with 1 : 100.000 adrenaline) with buccal guttering technique after sufficient height and impression of the buccal mucoperiosteal flap. Bone osteotomies and extractions of teeth were performed under irrigation of physiologic saline (0,9 %). The mucoperiosteal flap was repositioned and sutured.

After the surgery, patients were placed into two groups randomly in a double-blinded by surgery nurse and assistant physician. One group was prescribed Flurbiprofen 100 mg (Majezik, Sanovel, Turkey), 2x1 daily postoperatively for 7 consecutive days at the same time of day and Flurbiprofen 0.25% Oral spray (Majezik, Sanovel, Turkey) (local application) was prescribed 3x3 daily to the second group for 7 consecutive days at the same time of day. Additionally, for routine antibiotic prophylaxis, Amoxicillin Clavulanate 625 mg 2x1 (Augmentin

BID, Glaxo Smith Kline Drugs, Istanbul, Turkey) was administered to the patients. Also, 2% chlorhexidine gluconate (Klorhex Gargara 200ml, Drogsan Drug Industries, Turkey) was prescribed as at mouthwash.

In evaluating the post-operative pain, 100 mm Visual Analogue Scale (VAS) which was designed as 0 being no pain and 100 being the worst pain ever experienced, filled in by the patients on the post-operative 2nd, 6th, 8th, 12th, 24th and 48th hours and also on 3rd, 5th and 7th days was used. The edema evaluation was made at preoperative and postoperative 2nd and 7th days with using the methods of Üstün et al.[12]. Soft tissue points on the face were used for measurement of edema; eye cantus - angulus mandibula, tragus - corner of mouth and tragus - pogonion. The distance between these points was marked, measured and recorded. Gastrointestinal adverse effects related to the use of NSAID such as nausea, heartburn, dyspepsia, vomiting and diarrhea were recorded according to information received from patients.

Statistical analysis

'Minitab 17' statistical program (Minitab Inc., State College, PA, USA) was used to evaluate the research data. Shapiro Wilks test was run in order to test the normality distribution of the parameters. Student's t-test was used for between-group comparison of normally distributed parameters and the Mann-Whitney U test was used for between-group comparison of non-normally distributed parameters. Variance analysis was carried out for repeated measures in within-group comparisons. Significance value level was accepted as $p<0.05$ and $p<0.001$.

RESULTS

The study was conducted on 100 patients, 78 females (78%), 22 males (22%), aged between 18 and 25 years. The mean age of the patients was 23.98±4.43. years. There was no statistical difference between the groups in terms of age and gender. ($p>0.05$) (Table 1).

Table 1. Baseline characteristcs of two compared groups

	Systemic Group	Local Group	p
Age $_{Mean±SS}$	23.36±4.04	24.6±4.80	**0.268**
Gender$_{n,\%}$			
Female	38 (%76)	40 (%80)	0.673
Male	12 (%24)	10 (%20)	

Student t text

There was no statistically significant difference between the groups with regard to VAS levels on the 2nd hour, 5th and 7th days ($p>0.05$). However, 6th, 8th, 12th, 24th, 48th hour and 3rd day VAS levels of the systemic NSAIDs group were found to be statistically significantly lower than the topical NSAIDs group ($p<0.05$; $p<0.001$) (Table 2).

Table 2. Postoperative pain intensity values measured by VAS post surgery

VAS (mm)	Systemic Group	Local Group	p
	Mean±SS	Mean±SS	
2nd hour	21.2±23.86	14±18.25	0.216
6th hour	30.4±20.09	52.4±25.54	0.002**
8th hour	23.6±20.18	40.8±21.77	0.012*
12th hour	14±15.54	36.4±22.33	0.0001**
24th hour	10±11.90	28.4±20.14	0.0012**
48th hour	7.2±10.61	19.6±17.43	0.0024**
3rd day	4.4±9.60	12.8±15.41	0.035*
5th day	4±7.63	8±13.84	0.202
7th day	1.6±3.74	3.2±6.09	0.32
p	0.001**	0.001**	

Mann Whitney U text, * $p<0.05$, ** $p<0.001$

No statistically significant difference was found between the groups in preoperative, 2nd and 7th day mean scores of edema measurements between eye margin-angulus mandibula and tragus-pogonion anatomic points (p>0.05) (Table 3). The 2nd-day edema level (tragus-corner of mouth) of the systemic NSAIDs group was statistically lower than the edema level of the topical NSAIDs group (p<0.05) (Table 3). There was no statistical difference between the groups in the means of edema measurement on the preoperative and 7th day tragus-mouth corner anatomic points (p>0.05) (Table 3).

Table 3. Postoperative edema measurements in milimetres (eye cantus-angulus mandibula, tragus pogonion, tragus-corner of mouth) preoperatively, on the 2nd and 7th day

Eye cantus/angulus mandibula	**Systemic group**	**Local group**	**p**
	Mean±SS	Mean±SS	
Preop	101.56±483	103.32±6.71	0.304
2nd day	104.6±5.46	107.72±6.74	0.08
7th day	101.72±4.74	103.84±6.51	0.205
	p	p	
Preop-2nd day	0.042*	0.012*	
Preop-7th day	0.09	0.78	
2nd day-7th day	0.026*	0.02*	
Tragus/pogonion	Systemic group	Local group	
	Mean±SS	Mean±SS	
Preop	145.36±8.47	146.8±12.07	0.62
2nd day	149±8.38	152.88±13.05	0.21
7th day	145.6±8.37	148±12.35	0.403
	p	p	
Preop-2nd day	0.06	0.052	
Preop-7th day	0.46	0.36	
2nd day-7th day	0.07	0.09	
Tragus/corner of mouth	Systemic group	Local group	
	Mean±SS	Mean±SS	
Preop	111.88±5.77	115.44±9.02	0.139
2nd day	114.88±6.05	120.32±9.03	0.02*
7th day	112.12±5.67	116.24±8.78	0.08
	p	p	
Preop-2nd day	0.03*	0.03*	
Preop-7th day	0.88	0.75	
2nd day-7th day	0.02*	0.047*	

Student t text, Analysis of Varience, * p<0.05, ** p<0.001

Table 4. Gastrointestinal adverse effects of systemic and topical flurbiprofen

Gastrointestinal adverse effects	Systemic Groups Mean ± SS	Topical/Oral Groups Mean ± SS	p
Nausea	0.14±0.35	0.02±0.141	0.027
Vomiting	0.06±0.239	0.02±0.141	0.312
Heartburn	0.16±0.37	0.04±0.19	0.046
Dyspepsia	0±0	0±0	0
Diarrhea	0.04±0.197	0.02±0.141	0.56

Student t text, Analysis of Varience, p<0.05.

There were no statistical differences between the groups in terms of gastrointestinal adverse effects such as diarrhea, dyspepsia and vomiting ($p>0.05$) (Table 4). But, when assessed for adverse effects such as nausea and heartburn; a statistically significant difference was found between the groups. Adverse effects such as nausea and stomach burning were less common in patients in the group using topical NSAIDs ($p<0.05$) (Table 4)

DISCUSSION

Medical treatment and management of complications after impacted third molar surgeries are very important for the patient's quality of life. These complications such as pain, edema, trismus can be treated with NSAIDs and these medications are often preferred for the treatment of these complications[13]. However, there are no studies in the literature evaluating the effects of topical and systemic NSAIDs on postoperative complications and gastrointestinal side effects after impacted third molar surgery. In our study, we evaluated the efficacy of topical and systemic NSAIDs in the treatment of these complications after impacted third molar surgery and compared gastrointestinal side effect levels.

Akinbade et al. and Seymour et al., reported that female patients experience more pain than male patients after impacted third molar surgery, in their studies[14,15]. Parry et al. reported that females felt more postoperative pain than males[16]. Contrary to the results of the studies, there was no statistically significant difference between pain level and gender, in the present study. We attribute this to the fact that the age of the patients is close to each other. It was thought that pain thresholds might be close to each other because of the narrow age range, all of the patients were young and all operations do not have difficulty.

Kaplan et al., administered single use Tenoxicam, Diclofenac and Flurbiprofen to their patients before the impacted third molar surgery and performed postoperative pain, edema and trismus evaluation[17]. In the present study Flurbiprofen was used for treatment of pain and edema after the impacted third molar surgery because Flurbiprofen has an effective analgesic effect and not every NSAID has a topical form.

Isola et al., used Lornoxicam, Flurbiprofen and placebo for pain control after impacted third molar surgery, in their study. They reported that the peak pain level in the flurbiprofen group was 12 hours[18]. In our study, tablet and spray form Flurbiprofen was used for pain control after impacted third molar surgery. The peak pain level occurred in the postoperative 8th hour in patients taking both forms of medication. The reason for this is that the half-life of flurbiprofen used in the study is 6 hours and the most severe postoperative pain occurs after the first 6-8 hours. This result is in parallel with the studies in the literature[19].

Isola et al., evaluated the efficacy of Lornoxicam, Flurbiprofen and Placebo on pain and edema after impacted third molar surgery and found that flurbiprofen was less effective than lornoxicam in the first 24 hours on pain, however, reported that all medicine group was equally effective on edema[18]. In our study, systemic and topical flurbiprofen form was used for postoperative pain and edema control after the third molar surgery. It was found that flurbiprofen in tablet form used systemically was more effective than topical flurbiprofen on pain but, two drug forms were found to have a similar effect on edema.

Tiso et al. evaluated systemic and topical NSAIDs used for knee pain in the short term and they didn't find any statistically significant difference between them on pain[20]. The present study investigated the efficiency of systemic and topical NSAID (Flurbiprofen) on pain in impacted third molar surgery and found that systemic NSAID was more efficient in the short term on pain. However, there are no studies in the literature evaluating the effects of topical and systemic NSAIDs on postoperative complications after third molar surgery, this study is compared with a limited number of studies.

Underwood et al., examined the impacts of oral (tablet) and topical ibuprofen in a 12-month period for pain management in 585 patients with chronic knee pain and found no statistical difference between two different forms on pain[21]. Different than the results of this study, our study revealed that while tablet form Flurbiprofen was more efficient than the topical form with regard to pain in third molar surgery.

Whitefield et al., examined the efficiency of topical and oral (tablet) ibuprofen on edema in a hundred patients with soft tissue damage and found no difference in the elimination of the edema[22]. Similarly, no statistically significant difference was

found in our study between the edema measurements in both drug groups. However, it was reported that only edema measurement means between tragus-mouth corner anatomic points on the 2nd postoperative day was lower in the systemic drug group.

NSAIDs have gastrointestinal adverse effects such as dyspepsia, diarrhea, hemorrhage, heartburn, nausea, vomiting. Several studies have been performed in attempts to identify agents that can be co-administered to prevent NSAIDs induced gastrointestinal complications[23]. In our study, we evaluated the efficacy of topical and systemic Flurbiprofen on postoperative complications and it has been reported that there are fewer gastrointestinal adverse effects in patients receiving topical Flurbiprofen.

Adverse effect levels of the orally (tablet) administered systemic NSAIDs are higher than the topical NSAIDs. For these reasons, topical/oral spray NSAIDs can be preferred for pain management[21,24,25]. However, it is necessary to evaluate the efficiency of topical/oral spray NSAIDs for pain and edema. Similarly, our study was designed accordingly, and the results of the study indicated that the efficiency of the postoperatively tablet form Flurbiprofen for pain was found superior to the topical form. However, no statistically significant difference was found with regard to the edema. Moreover, gastrointestinal adverse effects were less common in patients using topical form Flurbiprofen.

In conclusion, although the effect of systemic form Flurbiprofen on pain was higher than the topical-oral spray form, it was found to have similar effects on edema. It is very well known that the adverse effects of systemic drugs are higher than topical drugs. In our study, it was determined topical form Flurbiprofen has less gastrointestinal system side effects than systemic form. Therefore, it is considered that topical/oral spray NSAIDs after third molar surgery can be used alone or as an adjunct to systemic forms for postoperative pain and edema management.

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REFERENCES

1. Soylu E, Akcay H, Canakci G, Etoz OA, Alkan A. Comparison of pre-operative difficulty and postoperative morbidity in third molar extraction. Ann Clin Anal Med 2019;10:544-8.
2. Gorecki P, Rainsford K, Taneja P, Bulsara Y, Pearson D, Saund D, et al. Submucosal diclofenac for acute postoperative pain in third molar surgery: a randomized, controlled clinical trial. J Dent Res. 2018;97:381-7.
3. Landucci A, Wosny A, Uetanabaro L, Moro A, Araujo M. Efficacy of a single dose of low-level laser therapy in reducing pain, swelling, and trismus following third molar extraction surgery. Int J Oral Maxillofac Surg. 2016;45:392-8.
4. Kim JC, Choi SS, Wang SJ, Kim SG. Minor complications after mandibular third molar surgery: type, incidence, and possible prevention. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;102:e4–e11.
5. Sortino F, Cicciù M. Strategies used to inhibit postoperative swelling following removal of impacted lower third molar. Dent Res J (Isfahan). 2011;8:162-71.
6. Rashid H, Hussain A, Sheikh AH, Azam K, Malik S, Amin M. Measure of frequency of alveolar osteitis using two different methods of osteotomy ın mandibular third molar ımpactions: a double-blind randomized clinical trial. J Ayub Med Coll Abbottabad. 2018;30:103-6.
7. Vegas-Bustamante E, Micó-Llorens J, Gargallo-Albiol J, Satorres-Nieto M, Berini-Aytés L, Gay-Escoda C. Efficacy of methylprednisolone injected into the masseter muscle following the surgical extraction of impacted lower third molars. Int J Oral Maxillofac Surg. 2008;37:260-3.
8. Litkowski LJ, Christensen SE, Adamson DN, Van Dyke T, Han SH, Newman KB. Analgesic efficacy and tolerability of oxycodone 5 mg/ibuprofen 400 mg compared with those of oxycodone 5 mg/acetaminophen 325 mg and hydrocodone 75 mg/acetaminophen 500 mg in patients with moderate to severe postoperative pain: a randomized, double-blind, placebo-controlled, single dose, parallel-group study in a dental pain model. Clin Ther. 2005;27:418-29.

9. Al-Khateeb TH, Nusair Y. Effect of the proteolytic enzyme serrapeptase on swelling, pain and trismus after surgical extraction of mandibular third molars. Int J Oral Maxillofac Surg. 2008;37:264-8.
10. Van den Bekerom MP, Sjer A, Somford MP, Bulstra GH, Struijs PAA, Kerkhoffs GMMJ. Non-steroidal anti-inflammatory drugs (NSAIDs) for treating acute ankle sprains in adults: benefits outweigh adverse events. Knee Surg Sports Traumatol Arthrosc. 2015;23:2390-9.
11. Argoff CE. Topical analgesics in the management of acute and chronic pain. Mayo Clin Proc. 2013;88:195-205.
12. Ustun Y, Erdogan O, Esen E, Karsli E.D. Comparison of the effects of 2 doses of methylprednisolone on pain, swelling, and trismus after third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;96:535-9.
13. Bjørnsson GA, Haanaes HR, Skoglund LA. Ketoprofen 75 mg qid versus acetaminophen 1000 mg qid for 3 days on swelling, pain, and other postoperative events after third- molar surgery. J Clin Pharmacol. 2003;43:305-14.
14. Akinbade AO, Ndukwe KC, Owotade FJ. Comparative analgesic efficacy and tolerability of celecoxib and tramadol on postoperative pain after mandibular third molar extraction: A double blind randomized controlled trial. Niger J Clin Pract. 2019;22:796-800.
15. Seymour RA, Hawkesford JE, Weldon M, Brewster D. An evaluation of different ibuprofen preparations in postop- erative pain after third molar surgery. Br J Clin Pharmacol. 1991;31:83-7.
16. Parry M, Watt-Watson J, Hodnett E, Tranmer J, Dennis CL, Brooks D. Pain experiences of men and women after coronary artery bypass graft surgery. J Cardiovas Nurs. 2010;25:e9-e15.
17. Kaplan V, Eroglu CN. Comparison of the effects of daily single-dose use of flurbiprofen, diclofenac sodium, and tenoxicam on postoperative pain, swelling, and trismus: a randomized double-blind study. J Oral Maxillofac Surg. 2016;74:1946.e1-6.
18. Isola G, Alibrandi A, Pedullà E, Grassia V, Ferlito S, Perillo L et al. Analysis of the effectiveness of lornoxicam and flurbiprofen on management of pain and sequelae following third molar surgery: a randomized, controlled, clinical trial. J Clin Med. 2019;8:325.
19. Svensson CI, Yaksh TL. The spinal phospholipasecyclooxygenase-prostanoid cascade in nociceptive processing. Ann Rev Pharmacol Toxicol. 2002;42:553-83.
20. Tiso RL, Tong-Ngork S, Fredlund KL. Oral versus topical ibuprofen for chronic knee pain: a prospective randomized pilot study. Pain Physician. 2010;13:457-67.
21. Underwood M, Ashby D, CrossP, Hennessy E, Letley L, Martin J et al. Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. BMJ. 2008;336:138-42.
22. Whitefield M, O'Kane CJ, Anderson S. Comparative efficacy of a proprietary topical ibuprofen gel and oral ibuprofen in acute soft tissue injuries: a randomized, double-blind study. J Clin Pharm Ther. 2002;27:409-17.
23. Klinge SA, Sawyer GA. Effectiveness and safety of topical versus oral nonsteroidal anti-inflammatory drugs: a comprehensive review. Physic Sport Med. 2013;41:64-74.
24. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal antiinflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ. 2004;329:324.
25. Machen J, Whitefield M. Efficacy of a proprietary ibuprofen gel in soft tissue injuries: a randomised, double-blind, placebo-controlled study. Int J Clin Pract. 2002;56:102-6.