ORIGINAL ARTICLE

Placebo-controlled randomized double-blind comparison of the analgesic efficacy of lidocaine spray and etofenamate spray in pain control of rib fractures

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ABSTRACT

BACKGROUND: As far as we could detect, we could not find any study in literature on the analgesic efficacy of spray forms of lidocaine and etofenamate in rib fractures. In this study, our aim is to empirically compare the analgesic efficacy of etofenamate spray, lidocaine 10% spray and placebo spray in the management of pain secondary to trauma secondary to isolated rib fractures.

METHODS: The study was designed according to a single-center, prospective, randomized, placebo-controlled double-blind study model. About 30 sealed envelopes were prepared for each of the 3 groups and 30 patients were included in each group. A total of 84 cases were included in the study (three groups: 27, 28, 29).

RESULTS: Numeric rating scale (NRS) grades at admission and at 15-30-60-120 min were similar between the three groups (P>0.05). Analysis findings of NRS perception differences between the initial NRS level and the 15-30-60-120th min NRS difference at the 0–120th min showed more lidocaine spray organs, and it was not clearly perceived that these four parameters went between the 3 groups for the outline.

CONCLUSION: The analgesic efficacy of lidocaine 10% spray, etofenamate spray, and placebo spray used together with standard dexketoprofen 50 mg intravenous treatment in the pain management of rib fractures were similar to each other and although there was a difference at the 120th min, this difference was not statistically significant.

Keywords: Emergency department; etofenamate spray; lidocaine spray; pain; rib fractures.

INTRODUCTION

Chest traumas are seen at a rate of close to 15% among all trauma cases. It has been reported that rib fractures are seen in approximately 39% of chest traumas.[1] Although the incidence of rib fractures is high in chest trauma, it can cause severe and hard-to-tolerate pain.[2] These fractures are important because of conditions such as chronic pain and disability.[3] Conditions such as fractures or lung contusion secondary to trauma may cause severe chest pain and may limit the functions of patients such as coughing and deep inspiration and expiration.[2]

Treatment of patients without injury other than rib fracture; it consists of appropriate analgesia, stabilization of the ribs, restoring the physical function of the thorax, and mobilizing the patient as soon as possible.[4] In the past, standard treatment of rib fractures has included nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid group painkillers, transcutaneous electrical stimulation, and topical analgesics.[5]

Among these treatment modalities, the intercostal block method with lidocaine is one of the methods that provide effective analgesia, but it also has side effects such as pneu-

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mothorax or systemic toxicity.[6] In a literature review, no significant difference was found in analgesia efficiency compared to placebo in a study conducted with 5% lidocaine pach regarding pain (intercostal neuralgia) due to rib fractures.[7] Contrary to this situation, there is another study reporting that it has positive effects on patients' pain comfort and shortens the length of hospitalization.[1]

Today, topical NSAIDs are used in the treatment of osteoarthritis, back pain, and musculoskeletal pain, and many of the studies have proven to be superior to placebo. Etofenamate is also an NSAID with analgesic and antipiretic effects. It is one of the agents frequently used for topical application.[8]

As far as we could detect, we could not find any study in literature on the analgesic effectiveness of spray forms of lidocaine and etofenamate in rib fractures. In this study, our aim was to empirically compare the analgesic efficacy of etofenamate spray, lidocaine 10% spray, and placebo spray in the management of pain secondary to trauma secondary to isolated rib fractures.

MATERIALS AND METHODS

Study Design and Setting

The study was designed according to a single-center, prospective, randomized, placebo-controlled double-blind study model. Approval for the study was obtained from the Ankara City Hospital Ethics Committee No. 1 (E1-21-2188). All patients participating in the study were informed and their written consent was obtained. This study complies with the principles of good clinical practice of the Declaration of Helsinki.

Patient Selection

The study was carried out in the Emergency Medicine Service of Ankara City Hospital, an advanced training and research hospital. He was admitted to the emergency department with thoracic trauma, had an isolated rib fracture, was not injured in other organ systems and extremities, was hemodynamically stable, had no orientation and cooperation problems, and had no intrathoracic injury other than rib fracture (pneumothorax, hemothorax, tracheoesophageal injury, cardiac injury, and vertebral/spinal injury), patients older than 18 years of age, of both sexes, who agreed to participate in the study were included. Patients with bilateral rib fractures and patients with more than 4 rib fractures on one side were excluded from the study. Pregnancy, allergy to the drugs in the study, any contraindication to the use of these drugs, use of analgesic drugs in the last 6 h, mentally retarded and uncooperative, hearing impaired, and underlying organic neurological and psychiatric disorders were excluded from the study.

Sampling Size

Sample size analysis was performed using the data of the study of Ingalls et al. with Lidocaine patch.[7] According to this analysis, it was calculated that at least 26 cases should be included in each group with 95% power and 5% Type-1 error. For this reason, 30 sealed envelopes were prepared for each of the 3 groups, and 30 patients were included in each group. A total of 84 cases were included in the study (three groups: 27, 28, 29).

Randomization

Detailed information was given about these drugs, along with the list of drugs to be administered to the patients selected according to the inclusion criteria, and signed informed consent was obtained. After the patients were identified and enrolled, they were divided into one of three groups using a computer-based randomization method (www.randomizer.org). The separation ratio was determined as 1:1:1. Prenumbered papers identifying the drug group were packaged and placed in dark envelopes to conceal the patient's identity information. In this way, the randomly selected drug was administered by the study nurse in accordance with the group in the envelope. The nurse who administered the drug then left the patient's treatment and follow-up. The researcher and the patient were blind to the drug administered. In the study, the patient's follow-up and numeric rating scale (NRS) evaluations were performed by a different physician who did not know the drugs to be administered.

Treatment Protocol and Groups

NRS was used to measure the level of pain and the scores of the patients were recorded. NRS markings on the case report forms prepared for the study before (0. min) and during (15., 30., 60., 120. min) were made by the patient himself, regardless of the previous sign. Again, together with the drug number applied on the same form, the patient's file numbers, age, gender, trauma mechanisms, rib fracture numbers, region, depleted–nondeplete distinction and numbers, the application date and time of the drugs, whether they used analgesics before coming to the emergency department, if any, how many recorded hours ago. Pain scores were recorded at the bedside at 0, 15, 30, 60, and 120 min.

Our treatment protocol was an intravenous rapid infusion of 50 mg dexketoprofen (Arveles® 50 mg) in 150 mL 0.9% NaCl at 0 min and 5 puffs spray (5 puffs of lidocaine 10%: 50 mg; 5 puffs of etofenamate: 90 mg; 5 puffs of placebo: 0.9% NaCl) applied to each patient at a distance of approximately 5 cm from the pain point. In order not to spoil the blind, the drugs were prepared in a single-type bottle with black tape around it and numbered. If relief did not begin at 30 min or if the pain score was 5 points or higher at 60 and 120 min, a rescue treatment protocol was initiated. The rescue treatment protocol was

planned to be administered tramadol hydrochloride 100 mg (Contramal® 100 mg ampoule) in 500 ml 0.9% NaCl in 30 min.

Statistical Analysis

Statistical analyzes of the study were performed with the IBM SPSS Statistics for Windows, version 20.0 (Armonk, NY: IBM Corp) package program. Intergroup comparisons of categorical data were performed with Pearson Chi-square and fisher's exact tests according to suitability. Distribution analysis of continuous data were performed with the Shapiro–Wilk test. Median comparisons between multiple groups of continuous variables that did not fit the normal distribution were made using the Kruskall–Wallis test. Results are expressed as the median and interquartile range (IQR). Bonferroni correction was made in the P-value for subgroup analyses in multiple group comparisons. P<0.05 was used for the statistical significance level in the analyses.

RESULTS

After 6 patients who dropped out of follow-up or did not want to continue the study, 84 patients were included in the study, including 27 (32.1%) placebo, 28 (33.3%) etofenamate, and 29 (34.5%) lidocaine group. Trauma mechanisms, 53 (63.1%) of whom were male patients, included "31 (36.9%) traffic accidents, 27 (32.1%) falls, 5 (6.0%) assaults, and 21 (25.0%) was calculated as other." The median age was 51 (IQR: 38.5–73). The comparison of age, gender, height, weight, trauma mechanism, symptom onset duration, rib fracture number, location, displacement characteristics, analgesic use, 112 emergency services use, rescue medication, and undesirable effect parameters in the three groups are presented in Table 1. Time from symptom onset to admission and rates of displaced fractures were different between the three groups (Table 1). The difference in the displaced fracture rate is due to the difference between the etofenamate

Table 1. Demographics

Variables	Main groups						P-value
	Placebo		Etofenamat		Lidocaine		
	Median (25-75%)	n (%)	Median (25-75%)	n (%)	Median (25-75%)	n (%)	
Age (year)	51 (34-64)		49.5 (38.5-78.5)		51 (44-73)		0.435
Gender							
Male		17 (63)		17 (60.7)		19 (65.5)	0.932
Female		10 (37)		11 (39.3)		10 (34.5)	
Height	170 (160-175)		169 (160-175)		170 (160-173)		0.886
Weight	72 (60-85)		75 (64-78)		75 (67-84)		0.474
Mechanism							
Traffic accident		10 (37)		14 (50)		7 (24.1)	-
Assault		3 (11.1)		1 (3.6)		1 (3.4)	
Fall		13 (48.1)		7 (25)		7 (24.1)	
Others		1 (3.7)		6 (21.4)		14 (48.3)	
Symptom time	2 (2-2)		3 (2-6)		4 (3-5)		<0.001
Rib fracture side							
Right		12 (44.4)		11 (39.3)		17 (58.6)	0.317
Left		15 (55.6)		17 (60.7)		12 (41.4)	
Rib number	2 (1-3)		3 (2-3)		2 (2-3)		0.215
Displaced		13 (48.1)		23 (82.1)		21 (72.4)	0.021
Analgesic drug use		3 (11.1)		2 (7.1)		2 (6.9)	0.790*
EMS use		20 (74.1)		26 (92.9)		23 (79.3)	0.170
Rescue drug use		11 (40.7)		10 (35.7)		5 (17.2)	0.131
Side effect		0 (0)		1 (3.6)		0 (0)	-

Kruskal Wallis test; Pearson Chi-square test. *Fisher's exact test, **Symptom time: The placebo group differs from the other two groups (Bonferroni correction).

spray and placebo groups. The time from symptom onset to presentation was significantly higher than placebo in both the drug groups [Bonferroni correction: P<0.016; Table 1]. The maximum number of broken ribs was determined as 4 in the placebo and etofenamate spray group and 3 in the lidocaine spray group.

NRS scores at admission and at 15-30-60-120 min were found to be similar between the three groups (P>0.05). When the differences between the initial NRS level and the NRS levels at the 15-30-60-120th min were analyzed, the difference in NRS at the 0–120th min was higher in the lidocaine spray group, but no statistically significant difference was found between the 3 groups for any of these four parameters (Table 2). In addition, the rate of need for rescue medication was found to be lower for both drugs, especially for the lidocaine spray group. Although the difference was clinically significant for the lidocaine group, it was not statistically significant (Table 1). Side effects occurred in only 1 patient in the etofenamate group (redness).

DISCUSSION

The results of this study showed that in addition to dexketoprofen, topically applied lidocaine 10% spray, etofenamate spray, and placebo spray in the analgesic treatment of rib fractures did not make any difference in pain control and the other two sprays were not very effective in the treatment of pain associated with rib fractures compared to placebo, statistically equally in all three groups. indicates the need for rescue medication.

In the study conducted by Cheng, the mean age of the patients was 56.8±13.8 years.[1] At this stage, the mean age of the patients in our study was 55±21, but they were similar. In another study, it was stated that the gender percentage and mean age of the patients was 68.8% and 53%, respectively.[9] In addition, similar results were reported in another study.[10] In our study, 53 (63.1%) of the patients were male and had a close average age, which was similar to literature. In addition, in the study conducted by Cheng, it was reported that 31 (70.5%) of 44 patients had the left rib fractures and 13 (29.5%) had the right rib fractures.[1] In our study, 40 (47.6%) of 84 patients had a right rib fracture. In general, the trauma mechanisms of our patients are traffic accidents, falls, assaults, and other causes, respectively; were 36.9%, 32.1%, 25%, and 6%.

In general, intercostal nerve blocks with 2% lidocaine perform the task of blocking the intercostal nerves, especially in the affected area.[5]

In a study comparing lidocaine skin patch and placebo in pain control after thoracotomy, it was reported that there was a significant relief in the lidocaine group and the patients' need for morphine use was less.[11] In a study with isolated rib fractures where all patients received oral analgesics and one group used 5% lidocaine skin patch and another group used a placebo skin patch, it was also reported that the duration of hospital stay was shortened and analgesia was provided more effectively in the group using lidocaine skin patch after 4 days.[1] In the literature review, we concluded that analgesia treatments with topical agents for rib fractures are limited (lidocaine) and even nonexistent with topical sprays with etofenamate or other NSAID active ingredients.[1,7,11]

In one of the previous studies, they reported that the lidocaine skin patch did not have significant effects on the pain relief of the patients, and in the other two they reported that they had significant effects on the healing.[1,7,11] To pro-

Table 2. Pain scale

Variables	Main groups			P-value
	Placebo	Etofenamat	Lidocaine	
	Median (25-75%)			
NRS-0	8 (6-9)	8 (6.5-9)	8 (6-9)	0.997
NRS-15	6 (4-7)	6 (5-8)	6 (4-7)	0.536
NRS-30	4 (3-6)	5 (2.5-7)	5 (3-6)	0.606
NRS-60	3 (1-6)	3.5 (1.5-6)	4 (3-6)	0.696
NRS-120	3 (1-5)	3 (1-6)	3 (2-4)	0.973
Differences 0.15	2 (0-3)	2 (0-2)	2 (0-3)	0.750
Differences 0.30	3 (1-5)	3 (1-4)	3 (2-4)	0.643
Differences 0.60	4 (2-6)	4 (2-4.5)	3 (2-5)	0.828
Differences 0.120	4 (2-6)	4 (3-6)	5 (3-6)	0.835

Kruskal–Wallis test. NRS: Numeric rating scale.

vide topical analgesia in acute musculoskeletal injuries, there are studies that report that the gel with both capsaicin and ibuprofen active ingredient is superior to piroxicam versus piroxicam with capsaicin and ibuprofen gel.[12,13] In a review, it was stated that topical agents such as diclofenac, ibuprofen, and ketoprofen showed similar effects to oral NSAIDs and were significantly effective in relieving pain.[14] In addition, there are no studies on the pain control of rib fractures with topically applied analgesic spray with the active ingredient etofenamate.

In our study, lidocaine 10% spray, etofenamate spray, and placebo spray were used, but the analgesic superiority of the lidocaine spray group and the etofenamate spray group was not statistically superior at 0, 15, 30, 60, and 120 min, both over each other and placebo. Although the need for rescue medication in the treatment of our patients differed numerically, they were not statistically significant. This result may be due to the administration of dexketoprofen before spray applications.

Limitations

The main limitation of the study is that it is single-centered. On the other hand, administration of dexketoprofen to all patients before spray drugs makes it difficult to compare the effects of these drugs with placebo. However, in the absence of dexketoprofen administration, it reveals the situation of not using analgesics in the placebo group. This situation is incompatible with ethical rules.

CONCLUSION

The analgesic efficacy of lidocaine 10% spray, etofenamate spray, and placebo spray used together with dexketoprofen 50 mg intravenous treatment, which is applied as standard in the pain management of rib fractures, were similar to each other and although there was a difference at the 120th min, this difference was not statistically significant. In addition, although there was a numerical difference between all three groups, there was no statistically significant difference between them in terms of the need for salvage treatment. The difference in the rate of rescue medication need and the 0–120th min NRS difference may become important in future studies with a larger sample size. We think that the difference in the rate of need for rescue medication, especially in the lidocaine spray group, is clinically significant, although not statistically significant. New placebo-controlled studies can be planned, especially with lidocaine spray.

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ORİJİNAL ÇALIŞMA - *ÖZ*

Kot kırıklarının ağrı kontrolünde lidokain sprey ve etofenamat spreyin analjezik etkinliğinin plasebo kontrollü randomize çift kör karşılaştırması

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AMAÇ: Tespit edebildiğimiz kadarı ile literatürde lidokain ve etofenamatın sprey formlarının kot kırığındaki analjezik etkinliğine dair bir araştırmaya rastlamadık. Bu çalışmada amacımız, ampirik olarak travmaya sekonder izole kot kırığına bağlı ağrı yönetiminde etofenamat sprey, lidokain %10 sprey ve plasebo spreyin analjezik etkinliklerini karşılaştırmaktır.

GEREÇ VE YÖNTEM: Araştırma tek merkezli, prospektif, randomize, plasebo kontrollü çift kör araştırma modeline göre tasarlandı. Her 3 grup için 30'ar kapalı zarf hazırlanmış ve her gruba 30 hasta alındı. Çalışmaya alındıktan sonra çalışmadan çıkarılan vakalar sonrasında toplam 84 olgu çalışmaya alındı [üç grup: 27, 28, 29].

BULGULAR: Üç grup arasında başvurudaki ve 15-30-60-120. dakikalardaki NRS dereceleri benzer bulundu [p>0.05]. Başlangıçtaki NRS düzeyi ile 15-30-60-120. dakikalardaki NRS düzeyleri farkları analiz edildiğinde 0-120. dakika NRS farkı lidokain sprey grubunda daha fazla olmakla beraber bu dört parametrenin hiçbiri için 3 grup arasında istatistiksel olarak anlamlı bir farklılık saptanmadı.

SONUÇ: Kot kırığının ağrı yönetiminde standart uygulanan deksketoprofen 50 mg intravenöz tedavi ile birlikte kullanılan lidokain %10 sprey, etofenamat sprey ve plasebo spreyin analjezik etkinlikleri birbirlerine benzer çıktı ve 120. dakikada bir fark oluşsa da bu fark istatistiksel olarak anlamlı bulunmadı.

Anahtar sözcükler: Kot Fraktürleri; acil servis, lidokain sprey; etofenamat sprey; ağrı.

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