THE BENEFITS AND RISKS OF A TRICOMPONENT GEL CONTAINING PIROXICAM, LIDOCAINE AND CYCLOBENZAPRINE, IN MUSCULOSKELETAL INJURIES IN ATHLETES

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Abstract

Sport-related injuries produces local inflammation, pain, oedema and local sensitivity. The pain is accompanied by impaired mobility and functionality and, in severe traumas, by disability. The present non-interventional study assessed the efficacy and safety of a topical combination of a NSAID (piroxicam 5 mg/g) with two sodium channel blockers anaesthetics (lidocaine 20 mg/g, cyclobenzaprine hydrochloride 5 mg/g) as a topical tricomponent gel (PLC) *versus* a topical gel only with a NSAID (piroxicam 10 mg/g) but in higher concentration, in the management of pain in sport related musculoskeletal injuries. The study was conducted on 90 rugby players from Romanian National Rugby Lot. The significant effectiveness of PLC gel was obvious from the first results in day 2: in the PLC gel group, pain on movement decreased by 17.91% and pain on pressure by 19.6% *versus* 9.28% and 10.12% respectively in the Piroxicam 1% gel group. Patients in the PLC gel group reported pain alleviation 15 minutes subsequent to topical application, and the effect lasted for an average of 11 hours. The effect of Piroxicam 1% gel was reported after an average of 52 minutes, but longer intervals of 80 minutes were also reported. The effect of Piroxicam 1% gel lasted up to 6 hours. The results from day 7 and then day 14 confirmed the superior efficacy of PLC gel *versus* Piroxicam 1% gel previously noticed in the results of the first visit. In day 14 in the PLC group pain alleviation increased by 70% considering both parameters, while in the Piroxicam 1% gel group it did not go beyond 45%. The analysis of the pain-free patients at the end of the treatment revealed an efficacy of 32% in pain on movement and 57% in pain on pressure in the PLC group and 2.32% in pain on movement and 6.97% in pain on pressure in the Piroxicam 1% gel group.

Rezumat

Traumatismele sportive produc inflamație locală, durere, edem și sensibilitate locală. Durerea este însoțită de afectarea mobilității și funcționalității și, când traumatismul este suficient de sever, de dizabilitate. Studiul non-intervențional de față a evaluat eficacitatea și siguranța unei gel topic cu 3 componente (PLC) care conține un AINS (piroxicam 5 mg/g) și două anestezice blocante ale canalelor de sodiu (lidocaina 20 mg/g și ciclobenzaprina clorhidrat 5 mg/g), *versus* un gel pentru aplicare topică ce conține doar AINS-ul, dar în concentrație mai mare (piroxicam 10 mg/g), în managementul durerii din traumatismele musculoscheletice la sportivi. Studiul a inclus 90 de jucători de rugby din Lotul Național de Rugby al României. Eficacitatea semnificativ superioară a PLC gel a fost observată încă de la primele rezultate obținute la 2 zile de la începerea tratamentului: în grupul PLC gel durerea la mișcare a scăzut cu 17,91%, iar durerea la presiune cu 19,6% *versus* 9,28% respectiv 10,12% în grupul Piroxicam 1% gel. Pacienții din grupul PLC gel au raportat o ameliorare a durerii după 15 minute de la aplicare, iar efectul a durat în medie 11 ore. Instalarea efectului Piroxicam 1% gel a fost raportată în medie după 52 de minute, dar au fost raportate și intervale mai lungi, de 80 de minute. Efectul Piroxicam 1% gel s-a menținut până la 6 ore. Rezultatele din ziua 7 și apoi din ziua 14 de tratament au confirmat superioritatea eficacității PLC gel *versus* Piroxicam 1% gel observată la primul control. În ziua 14 în grupul PLC gel ameliorarea durerii a crescut până la 70% la ambii parametri studiați, în timp ce în grupul Piroxicam 1% gel ameliorarea nu a fost mai mare de 45%. Analiza pacienților la care la sfârșitul tratamentului durerea a fost remisă complet a arătat o eficiență de 32% în cazul durerii la mișcare și de 57% în cazul durerii la presiune în grupul PLC gel și de 2,32% pentru durerea la mișcare și 6,97% pentru durerea la presiune în grupul Piroxicam 1% gel.

Keywords: piroxicam, lidocaine, cyclobenzaprine, pain, athletes, musculoskeletal, synergistically

Introduction

Sport-related injuries can affect almost any part of the musculoskeletal system including muscles, bones, joints, tendons and ligaments. Dislocations, sprains, strains and contusions are frequent diagnoses. Each

of these traumas produces local inflammation, pain, oedema and local sensitivity. Acute pain (spontaneous, on palpation, on movement) is the most accused symptom. The pain is accompanied by impaired mobility and functionality and, in severe enough traumas, by disability [12]. The initial treatment

depends on the severity of the injury but is generally geared toward reducing the swelling and pain using methods such as cold compression and anti-inflammatory agents [6] in order to limit the extension and exacerbation of the inflammation and pain and to promote the recovery of mobility and functionality. The use of NSAIDs is due to their anti-inflammatory, analgesic and anti-pyretic properties. The basis of the pharmacological action of NSAIDs is their ability to inhibit cyclooxygenase (COX) enzymes thereby blocking the formation of certain prostaglandins [13]. Besides reducing the inflammation, this inhibition of prostaglandin synthesis may potentially result in serious side effects as gastrointestinal disturbances [13]. Because of the negative side effects from a systemic non-steroidal anti-inflammatory drug, an alternative delivery method such as topical application can be used [15]. Topical route has the benefit of a superior local drug delivery and at the same time the systemic side effects are reduced [15].

A new pharmacological concept states that topical combination of a NSAID from the class of non-selective or partially selective cyclooxygenase inhibitors with sodium channel blockers from the class of local anaesthetics produces a more long-lasting analgesia than is attainable with either of the substances alone. The dual mechanism of action of these substances on the cellular level interferes with pain components of both inflammatory and neuronal genesis and is functionally synergistic. The therapeutic indication is the symptomatic reduction of neuro-muscular pain of traumatic or metabolic origin. The already more favourable safety profile for topical application can be improved further by a possible dose reduction of the two substances [10]. This concept was confirmed in various pain models in non-clinical studies [4, 21] and also by clinical use in some case series [18].

The present non-interventional study assessed the efficacy and safety of a topical combination of a NSAID (piroxicam 5 mg/g) with two sodium channel blockers anaesthetics (lidocaine 20 mg/g, cyclobenzaprine hydro-chloride 5 mg/g) as PLC gel *versus* a topical gel only with a NSAID (piroxicam 10 mg/g) but in higher concentration in the management of pain in sport related musculoskeletal injuries. To our knowledge, this is the first organized study that investigates comparatively the efficacy of a topical combination with NSAID and sodium channel blockers acting substances *versus* a topical gel containing only the NSAID substance,

in humans, in order to verify the pharmacological concept presented above. There is a single other study performed with PLC gel that investigated its efficacy in the pain management during extra-corporeal shock wave lithotripsy, but comparatively with no treatment [16].

Materials and Methods

Materials

Study population

The study was conducted between June 2015 and January 2016 in the Medical Centre of the Romanian Rugby Federation on rugby players from the Romanian National Rugby Lot (men and women). As a preliminary selection, the patients had to fulfil two criteria simultaneously: to have a musculoskeletal injury following a sport activity, and to have a physician's advice on the necessity of a topical product in the therapeutic decision. A non-interventional study includes patients treated only within the approved terms of Marketing Authorization (indications, administration route and regimen etc.), without any intervention outside these information, thus a bioethical commission approval was not necessary. The non-interventional study protocol was notified to the Romanian National Agency for Medicines and Medical Devices in January 2015, without any additional requests.

One hundred and three patients fulfilled these conditions. Participant inclusion criteria were as follows: patients over 15 years old regardless of sex, musculoskeletal injury following a sport activity without any treatment already begun, a therapeutic decision including a topical product with or without systemic analgesic products. Exclusion criteria were as follows: patients under 15 years old, musculoskeletal injury following a sport activity with a therapy already begun in the last 7 days, treatment with corticosteroids or other products that were not recommended, fractures, injuries requiring surgery. After applying the inclusion and exclusion criteria, the study group consisted of 90 patients. The 13 patients were excluded 7 days after the injury due to immobilization in gypsum splint - one patient - and for simultaneously using 2 topical products - twelve patients.

Patients were randomly distributed into two groups based on their topical treatment: the PLC groups and Piroxicam 1% groups (Table I). Because in both groups there were patients who needed ice packs and patients who did not, or systemic analgesics in the first days, a secondary distribution was made based on the type of the treatment.

Table I
Treatment groups

	PLC gel (n = 47)	Piroxicam 1% gel (n = 43)
Without systemic analgesics	n = 26 (55.3%)	n = 15 (34.8%)
With systemic analgesics	n = 21 (45.6%)	n = 28 (65.1%)
Paracetamol	n = 17	n = 16

	PLC gel (n = 47)	Piroxicam 1% gel (n = 43)
Diclofenac	n = 1	n = 2
Ketoprofen	n = 2	n = 7
Naproxen	n = 1	n = 3
Without ice applications	n = 17 (36.1%)	n = 16 (37.2%)
With ice applications	n = 30 (63.9%)	n = 27 (62.8%)

Safety assessment

Side effects that could occur following administration of both topical products have been monitored.

Evaluation criteria and outcomes

At the first visit the patients were diagnosed and were asked to evaluate their pain on movement and on pressure on a Visual Analogue Scale (VAS) from 0 to 10 [9].

At the follow-up visits (day 2, day 7 and 14) the patients were asked to evaluate their pain on movement and on pressure (VAS) and to assess the onset time of each topical used and the effect duration.

Statistical analysis

Descriptive statistics were used for demographic data. ANOVA, z-test two samples for means were used to compare values between baseline and subsequent visits (intragroup analysis) and between

treatment groups at subsequent visits (intergroup analysis) for a confidence interval of 95%, statistical significance was considered for $p < 0.05$.

Results and Discussion

The baseline characteristics of the patients are presented in Table II and Table III.

Table II

Diagnosis of the patients included in the study

Diagnosis	Patients no. (%)
Sprain	40 (44.44%)
Contusion	18 (20.00%)
Contracture	8 (8.88%)
Strain	7 (7.77%)
Dislocation	4 (4.44%)
Tendon inflammation	13 (14.44%)

Table III

Initial pain values in the two groups

Clinical parameters	PLC gel (n = 47)	Piroxicam 1% (n = 43)	p
Pain on movement VAS (average score)	5.7 ± 0.68 (extremes 5 - 8)	5.51 ± 0.59 (extremes 4 - 7)	0.16
Pain on pressure VAS (average score)	5.42 ± 0.87 (extremes 4 - 7)	5.27 ± 0.66 (extremes 4 - 6)	0.37

From the second visit (day 2) and also in the following ones (day 7 and 14) the patients from the PLC gel group reported significantly improved clinical responses for

pain on movement and on pressure from baseline. (Table IV, Figure 1).

Table IV

Global assessment for clinical parameters

	PLC gel (n = 47)			Piroxicam gel 1% (n = 43)		
	Day 2	Day 7		Day 2	Day 7	
Pain on movement (mean VAS score $\pm$ SD)	4.68 ± 0.69	3.57 ± 0.94	1.6 ± 0.98 ($p < 0.01$, baseline vs. day 14)	5.00 ± 0.53	4.27 ± 0.54	3.16 ± 0.84 ($p < 0.01$, baseline vs. day 14)
Pain on pressure (mean VAS score $\pm$ SD)	4.36 ± 0.67	3.04 ± 0.93	1.3 ± 0.79 ($p < 0.01$, baseline vs. day 14)	4.74 ± 0.58	4.04 ± 0.53	3.02 ± 0.83 ($p < 0.01$, baseline vs. day 14)

Figure 1.

Differences in clinical parameters values in day 14 from baseline

The two-treatment groups reported significantly different results for onset time and effect duration (Table V).

The results with subtype of treatments are also presented below (Tables VI and VII).

Table V

Values for onset time and effect duration for each treatment group

	PLC gel (n = 47)	Piroxicam gel 1% (n = 43)	p ($\alpha = 0.05$)
Onset time (min) (mean $\pm$ SD)	15.02 $\pm$ 2.75 (extremes 10 - 20)	52.20 $\pm$ 13.77 (extremes 30 - 80)	p < 0.01
Effect duration (hours)	11.14 $\pm$ 0.83 (extremes 10 - 12)	6.41 $\pm$ 0.81 (extremes 4 - 8)	p < 0.01

Table VI

Values for clinical parameters in day 2 in the two main groups considering the systemic analgesics

	PLC with analgesic (n = 21)	PLC without analgesic (n = 26)	p	Piroxicam with analgesic (n = 28)	Piroxicam without analgesic (n = 15)	p	p with analgesic	p without analgesic
Pain on movement (mean VAS score $\pm$ SD)	4.66 $\pm$ 0.65	4.69 $\pm$ 0.73	0.9	5.1 $\pm$ 0.49	4.8 $\pm$ 0.56	0.07	0.01	0.6
Pain on pressure (mean VAS score $\pm$ SD)	4.23 $\pm$ 0.62	4.46 $\pm$ 0.70	0.26	4.82 $\pm$ 0.61	4.6 $\pm$ 0.5	0.23	0.002	0.5
Onset time (min) (mean $\pm$ SD)	14.95 $\pm$ 2.53	15.07 $\pm$ 2.96	0.87	51.92 $\pm$ 14.39	52.73 $\pm$ 13.00	0.85	< 0.01	< 0.01
Effect duration (hours)	11.09 $\pm$ 0.88	11.19 $\pm$ 0.80	0.69	6.32 $\pm$ 0.76	6.6 $\pm$ 0.91	0.29	< 0.01	< 0.01

Table VII

Values for clinical parameters in day 2 in the two main groups considering the ice packs

	PLC with ice (n = 21)	PLC without ice (n = 26)	p	Piroxicam with ice (n = 28)	Piroxicam without ice (n = 15)	p	p with ice	p without ice
Pain on movement (mean VAS score $\pm$ SD)	4.8 $\pm$ 0.71	4.47 $\pm$ 0.62	0.11	5.0 $\pm$ 0.55	5.0 $\pm$ 0.52	1	0.28	0.01
Pain on pressure (mean VAS score $\pm$ SD)	4.53 $\pm$ 0.73	4.05 $\pm$ 0.42	0.11	4.85 $\pm$ 0.60	4.56 $\pm$ 0.51	0.11	0.07	0.004
Onset time (min) (mean $\pm$ SD)	14.93 $\pm$ 2.91	15.76 $\pm$ 3.48	0.38	50.00 $\pm$ 12.93	55.93 $\pm$ 14.74	0.17	< 0.01	< 0.01
Effect duration (hours)	11.06 $\pm$ 0.86	11.29 $\pm$ 0.77	0.37	6.44 $\pm$ 0.69	6.37 $\pm$ 1.00	0.79	< 0.01	< 0.01

For the last evaluation (day 14) a comparative analysis was made for the patients considered pain

free (pain scores 0 and 1) in the two main groups (Table VIII).

Table VIII

Pain free patient's analysis

	PLC gel (n = 47)		Piroxicam gel (n = 43)	
	Pain on movement (no., %)	Pain on pressure (no., %)	Pain on movement (no., %)	Pain on pressure (no., %)
Score 0	8 (17.02%)	6 (12.76%)	-	-
Score 1	7 (14.89%)	21 (44.68%)	1 (2.32%)	3 (6.97%)
Total	15 (31.91%)	27 (57.44%)	1 (2.32%)	3 (6.97%)

No side effects attributable to the treatment were reported in any of the analysed groups.

Traumatic injuries including dislocations, sprains and strains represent the majority of sport-related injuries. These injuries produce local tissue inflammation and consecutively pain, oedema, sensitivity, limited mobility and even disability, when the injury is severe enough. In tissue damages, along with serotonin and histamine, cell membranes also release phospholipids that are converted to arachidonic acid by phospholipase A2. Arachidonic acid is a substrate for cyclooxygenase (COX) and produces prostaglandins. This pathway and the substances produced in this

cascade are responsible for pain and inflammation in sport-related injuries [7]. Generally, the initial treatment consists of rest, ice packs, compression and elevation of the affected limb in vertical plane (RICE) and administration of analgesics and anti-inflammatories substances in order to limit the extent of inflammation and to alleviate the pain [2, 3, 14]. The treatment is followed by physical therapy for the rehabilitation of muscle force and mobility. As pharmacological treatment, analgesics are the first line. These include paracetamol, codeine or tramadol, single or in combinations. Oral or topical NSAIDs are often added. Simultaneous administration of two

NSAIDs is usually avoided, even if they are administrated on different routes (e.g. oral or topical) in order to avoid the risk of increasing the adverse effects. Systemic administration of an analgesic (p.o. or i.m.) and topical administration of an NSAID is preferred [7].

The present study investigated the benefits of a combination with an NSAID (piroxicam 5 mg/g), an analgesic (cyclobenzaprine hydrochloride 5 mg/g) and a local anaesthetic (lidocaine 20 mg/g) in a single product for topical administration, PLC gel, to treat pain in musculoskeletal injuries in athletes, as monotherapy or associated with systemic analgesics *versus* a topical with a single NSAID used in the same conditions. Piroxicam is an NSAID non-selective COX inhibitor with both analgesic and antipyretic properties [5]. Lidocaine is a local anaesthetic and works by blocking sodium channels [8]. It was demonstrated that the analgesic effects of sodium channel blocker local anaesthetics may occur at doses below those necessary for a complete local anaesthesia by inactivating neurotransmission [10]. Cyclobenzaprine has similar structure and mechanism with tricyclic antidepressants [20] but it was used in systemic administration for more than 40 years for its muscle relaxant, analgesic and sedative predominant effects. Recent researches demonstrated that tricyclic antidepressants locally administrated produce analgesia by mechanisms independent from antidepressant effect, the analgesic effect being faster [17]. The mechanism of action in local administration of this group of substances has proved to be a complex one and involves interference with adenosine system and a common mechanism with local anaesthetics (blocking sodium channels involved in nervous impulse transmission). Moreover, it has been found that analgesic effect of topically administrated tricyclic antidepressants is located in the peripheral site of administration rather than systemic [19].

Ankle injuries are the most frequent injuries reported during sport activities, up to 20%. 85% of them are sprains [11]. The investigated lot confirmed this statistic, with 44.44% of patients diagnosed with sprains, most of them with I-II degree ankle sprains. Both topical products were efficient considering the significant decrease of symptomatology in 2 weeks from baseline. But PLC as monotherapy or as a part of a larger therapeutic scheme has had better results *versus* those reported with Piroxicam 1% gel, even if PLC gel has half of the piroxicam concentration (piroxicam 0.5%). The combination of analgesic mechanisms in PLC gel has acted synergistically and has developed a more intense analgesic effect than Piroxicam 1% gel. These results confirmed for the first time in humans the previous cited theory that "The dual mechanism of action of NSAID and sodium blocker channels anaesthetics on the cellular level interferes with pain components of both

inflammatory and neuronal genesis and is functionally synergistic" [10].

The significant effectiveness of PLC gel was obvious from the first results in day 2: in the PLC gel group, pain on movement decreased by 17.91% and pain on pressure by 19.6% *versus* 9.28% and 10.12% respectively in the Piroxicam 1% gel group. The superior results in the PLC group are confirmed also by the values for onset time and effect duration. The global analysis from day 2 shows that patients in the PLC gel group reported pain alleviation 15 minutes subsequent to topical application, and the effect lasted for an average of 11 hours, but longer periods of 12 hours were also reported. The effect of Piroxicam 1% gel was reported after an average of 52 minutes, but longer intervals of 80 minutes were also reported. The effect of Piroxicam 1% gel lasted up to 6 hours.

In this first interval of 48 hours some patients also needed ice packs and therefore a secondary distribution was analysed, with or without ice in each main group. The results revealed that in patients that needed ice packs pain alleviation was similar in both groups because ice significantly influences pain perception. But in patients that didn't needed ice packs pain alleviation was significantly better in the PLC group *versus* the Piroxicam 1% gel. Onset time and effect duration were not influenced by the ice packs in either studied group; in the PLC group onset time was 14.93 minutes with ice and 15.76 minutes without ice.

A similar secondary analysis was performed considering the systemic analgesics used in the two groups because they can also influence pain perception and quantification. In both groups, considerably more patients needed paracetamol as compared to those who received other types of analgesics (81.95% in the PLC group and 57.14% in the Piroxicam 1% gel group). It should also be mentioned that the PLC group had fewer patients that needed a systemic analgesic as compared to the Piroxicam 1% gel group (45.65% *versus* 65.1%). This confirms the results obtained in the previous PLC gel study where it was concluded that topical application of PLC gel before lithotripsy provided a significant relief of the pain during this procedure and also reduced the need of rescue medication. PLC gel was confirmed as a valuable alternative for the management of pain during extracorporeal shock wave lithotripsy (ESWL) [16].

Sport-related injuries are commonly accompanied by intense pain that can persist till complete healing. In the first days the patient describes severe pain that often requires a combination of topical and systemic analgesics. The results demonstrated the superior effectiveness of PLC gel *versus* Piroxicam 1% gel, more significant in patients that received systemic analgesics. As in the analysis of the

secondary distribution of ice packs, it can be concluded that added systemic analgesics do not significantly influence the onset time and effect duration of the products applied topically: in the PLC group the onset time was 14.95 minutes with analgesic and 15.07 minutes without analgesic, and the effect duration 11.09 hours with analgesic and 11.19 hours without analgesic.

The results from day 7 and then day 14 confirmed the superior efficacy of PLC gel *versus* Piroxicam 1% gel previously noticed in the results of the first visit. The analysis of these results permitted a more homogenous conclusion considering that patients with systemic analgesic had finished this part of treatment by day 7 and ice was applied only in the first 2 days. Therefore, the influence of this part of the therapy was insignificant in day 7 and day 14 visit reports. In day 14 in the PLC group pain alleviation increased by 70% in both parameters, while in the Piroxicam 1% gel group it did not go beyond 45%. The analysis of the pain-free patients at the end of the treatment revealed an efficacy of 32% in pain on movement and 57% in pain on pressure in the PLC group and 2.32% in pain on movement and 6.97% in pain on pressure in the Piroxicam 1% gel group.

No adverse effect related to the treatment was reported in any studied group. It should be noted that the treatment was not significantly long, but athletes are commonly exposed to a higher consumption of analgesics and anti-inflammatories, often as self-medication, that predispose them, in time, especially to gastric and hepatic adverse effects [1]. Also, the number of patients included was not a very high one.

Conclusions

The topical administration of the PLC gel, a combination of piroxicam 5 mg/g, lidocaine 20 mg/g, and cyclobenzaprine hydrochloride 5 mg/g is more effective than piroxicam 10 mg/g gel for pain alleviation in a 14-day treatment. The topical administration of PLC gel is effective in 15 minutes and the effect lasts up to 12 hours. PLC gel is more effective than piroxicam 10 mg/g gel for pain in sport-related injuries as monotherapy and it is also included in the therapeutic scheme along with other analgesics.

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