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Celecoxib *versus* indomethacin as prevention of arthrofibrosis. A perspective case-control study

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Summary

Nonsteroidal anti-inflammatory drugs (NSAIDs) remain the most commonly utilised prophylaxis to reduce arthrofibrosis (AF) related to the inflammatory response which leads to a pathological condition called arthrofibrosis. Several NSAIDs have shown to be effective, although postoperative indomethacin has been the historical gold standard. More recently, credit has been given to the use of COX-2 selective inhibitors, due to concerns over gastrointestinal effects, as peptic ulcers, with non-selective COX.

However, to date, few studies have compared the therapeutic effects of the two drugs. The aim of this study is to compare the postoperative administration of indomethacin and celecoxib in patients with diagnosis of AF treated with arthroscopic lysis and evaluate joint recovery.

In this prospective study, 42 patients were diagnosed with hip, knee and elbow residual AF. The inclusion criteria were age > 18 years and a diagnosis of residual AF, following exposure to a previous traumatic event or surgical treatment; exclusion criteria were patients with < 18 years, BMI > 35 or < 18 kg/m^2, affected by peripherical neuropathies and presence of heavy functional limitations, active infection, complex regional pain syndrome diagnoses. All patients underwent to arthroscopy, operated by a single surgeon with the same team in the same clinic and postoperatively were randomly divided into two groups, one treated with indomethacin, and the other with celecoxib. Of the patients examined, the following parameter was considered: joint range of motion (ROM) preintervention and post-intervention at 3 months and after 12 months. ROM was analysed with Student t test. The comparison of the ROM between both the 3 months postoperative groups has been shown to be not statistically significant. On the other hand, after 1 year, t-Student test referred to preoperative condition was significantly in favour of the group treated with celecoxib (p = 0.02). Lastly, neither celecoxib nor indomethacin showed any gastrointestinal side effects.

Key words: arthrofibrosis, celecoxib, indomethacin, gastrointestinal effects, NSAIDs

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Conflict of interest
The Authors declare no conflict of interest

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Introduction

Arthrofibrosis (AF) is a fibrotic joint disorder characterised by the presence of excessive collagen production and adhesions that lead to restricted joint motion and

pain. It can occur in most joints and is referred to by a number of names including frozen shoulder, adhesive capsulitis, joint contracture, stiff knee and stiff elbow [1]. The main causes are chronic or repetitive injuries or previous surgery that provoked a dysregulated immune reaction and residual fibrosis in and/or around a joint [2] to varying degrees. The fibrotic scar tissue that forms in the joint is known as extracellular matrix (ECM), and is primarily composed of collagen. This causes the loss of joint flexion and/or extension and scarred bursa may create impingement into the joint, which maintains inflammation. Together with reduced range of motion (ROM), pain and varying amounts of swelling are commonly reported by patients. Arthrofibrosis affects people of all ages, although it is rare in children [3-4].

On a cellular level, AF is characterised by upregulated myofibroblast proliferation with reduced apoptosis, adhesions and aggressive synthesis of ECM that can fill-in and contract joint pouches and tissues [1-13,14]. Although ECM is necessary for healing and wound repair, dysregulation of the balance between production and degradation leads to pathologic fibrosis [1-15].

Faced with the objective finding of rigid articulation, in fact, it is first necessary to evaluate which articulations and how much they are affected, then to investigate about the previous history of trauma or surgical interventions at the joint level.

During clinical examination, pay attention to the condition of soft tissues, presence of cicatrices, and evaluate muscle and tendon function; only at this point, perform radiographic instrumental examinations that will give information about the conditions of the bone facing surfaces and bone trophism [16-17].

Prevention is obviously the best treatment, but once the disease is manifested early diagnosis and physical therapy programs are the best treatment option. If conservative treatment fails, surgery is the only solution [18]. Arthrofibrosis research has often focused on treatments that address the structural pathology of the condition. These treatments include surgical interventions, such as arthroscopic lysis and debridement of ECM, open surgery to remove ECM and release of tendons and ligaments, and manipulation under anaesthesia (MUA). Arthroscopic lysis of ECM is the most commonly performed treatment compared to MUA for AF, because of the obvious benefit of removing the physical restriction to ROM [18-19].

Nonetheless, the benefits of surgical lysis and MUA should be tempered by an understanding of the problems associated with these procedures. Both treatments damage tissues, and tissue injury stimulates an inflammatory response [20] that may enhance further fibrogenesis. Therefore, it becomes essential to set up a post-intervention therapy to avoid these problems.

Oral non-steroidal anti-inflammatory drugs (NSAIDs) are universally recommended in several studies for the management of AF [21-22].

Although effective, a systematic literature review and meta-analysis up to 2011 found an increased risk of serious gastrointestinal (GI), cardiovascular (CV), and renal harm with NSAIDs compared with placebo, particularly in the elderly [23].

Selective COX-2 inhibitors are an option to consider as well, given the risk of gastrointestinal distress associated with non-selective NSAIDs [18,24].

Materials and methods

The preliminary study was approved by the Local Scientific Department. Verbal and written informed consents were obtained before the study started. The present study was carried out in accordance with the approved guidelines.

From January 2018, 42 patients, aged 21-58 (average 42.3 ± 6.5) years, 18 females and 24 males, diagnosed with residual AF, secondary to trauma or surgery, were included in this prospective study.

The inclusion criteria were age > 18 years and a diagnosis of residual AF, following exposure to a previous traumatic event or surgical treatment; exclusion criteria were patients with < 18 years, BMI > 35 or < 18 kg/m^2, affected by peripherical neuropathies and presence of heavy functional limitations, active infection, complex regional pain syndrome diagnoses.

The inclusion and exclusion criteria adopted in the patient selection for this study are shown in Table I.

Each patient underwent clinical examination with analysis of the range of motion (ROM) of the joint affected by AF, assessed using a goniometer [18]. Of the patients examined, we considered ROM before surgical procedure and post-intervention at 3 months and after 12 months and changes in ROM pre- and postoperatively.

All patients underwent arthroscopic lysis. All surgeries were done by the same experienced orthopaedic surgeon. The hospital stay lasted 1 day postoperatively. Mobilisation started from the day of surgery; a single physiotherapist implemented the same rehabilitation scheme on every patient.

All patients were randomly extracted and divided into two groups, one treated with indomethacin, and the other with celecoxib.

Table I. Inclusion and exclusion criteria of the study.

Inclusion criteria	Exclusion criteria
Age > 18	Age < 18
Residual arthrofibrosis diagnosis, secondary to trauma or surgical procedure	BMI > 35 or < 18 kg/m^2
	Peripherical neuropathies
	Presence of heavy functional limitations
	Active infection
	Complex regional pain syndrome

The first group, consisting of 19 patients, 12 women and 7 men, was treated with indomethacin 75 mg BID for 21 days (associated to PPI): 13 suffered from knee AF (5 left and 7 right), 5 from ankle AF (all right) and 1 patient was affected at the left elbow.
The second group was treated with celecoxib 200 mg/day for 21 days; 6 women and 17 men; 12 patients suffered from knee AF (including 7 right and 5 left), 4 from elbow AF (of which 2 left and 1 right) and 7 ankle AF (including 5 left and 2 right).
The normality of distribution for continuous numeric variables was assessed by Kolmogorov-Smirnov test. According to normally distributed or not, the variables are presented as means with SD, and otherwise as medians with inter-quartile ranges (95% confidence intervals, CI). Student's t-test for normally distributed continuous variables, while others using a χ^2 test.

Results

Forty-two patients were assessed for eligibility and randomly divided into two groups (indomethacin, group A and celecoxib, group B). Pre- and perioperative baseline physical conditions were similar in both groups. All had diagnoses of residual AF and all underwent arthroscopic lysis surgery by the same operator. No patient presented intra- and postoperative complications and the postoperative path was similar in all patients.
Analysing the 3-month postoperative by Student's t test, the preoperative ROM in the celecoxib and indomethacin groups were both 0.62 with a significance level of 0.53%. Consequently, the comparison between the two groups for ROM was not significant.
However, Student's t test of ROM after 1 year compared to the preoperative condition showed a significance difference ($p = 0.02$) in favour of the group treated with celecoxib.
Moreover, the duration of pharmacological post-intervention treatment was similar (21 days each), and no patient treated with wither celecoxib or indomethacin complained of gastrointestinal disorders, but those who received indomethacin completed therapy in association with a proton pump inhibitor (PPI) to reduce the risk of heartburn and gastrointestinal injury.

Discussion

NSAIDs are the most commonly prescribed drugs to manage articular inflammation and pain in outpatients, for a wide spectrum of diseases [25].
They are are frequently prescribed to treat arthrofibrosis [21].Their primary mechanism of action is the blockade of prostaglandin synthesis by cyclooxygenases (COX): constitutively expressed COX-1 is involved in fundamental mechanisms of homeostasis, whereas the inducible COX-2 mediates inflammation. The therapeutic effects of NSAIDs are primarily related to their ability to inhibit COX-2, whereas some of their most frequent adverse effects may be caused by COX-1 inhibition [26,27].
Indomethacin is a nonselective cyclooxygenase COX-1 and COX-2 inhibitor, commonly administered at an oral dose of 75 mg twice per day or 25 mg three times per day for three to six weeks postoperatively [28,29]. Indomethacin is a non-selective inhibitor of COX, which are fundamental for production of prostaglandins that play a role in fracture healing and bone metabolism [30].
In contrast to most "classic" NSAIDs which block both isoforms, the so-called Coxibs preferentially inhibit COX-2. This may result in better tolerability, namely reduction of gastrointestinal side effects.
Selective COX-2 inhibitors are an option to consider, given the risk of gastrointestinal distress associated with nonselective NSAIDs [22,31,32].
NSAIDs are nonetheless the only currently prescribed medications to treat post-surgical or traumatic arthrofibrosis. Therefore, COX-2 selective inhibitors may inhibit the inflammatory cascade while potentially reducing pathologic myofibroblast activation, thereby reducing scar tissue formation and increasing the ROM in arthrofibroses joints [22,33,36,37].
COX-2 selective inhibitors have been found to be associated with an increased risk of heart disease during prolonged use, but at moderate doses, celecoxib was found to be noninferior to other NSAIDs drugs with regards to cardiovascular safety [40].
More recently, consideration has been given to the use of COX-2 selective inhibitors, due to concerns over gastrointestinal distress associated with nonselective NSAIDs [18,24].
In this study, we considered the anti-inflammatory effects of celecoxib, comparing its efficacy with indomethacin.
The results did not show a significant difference in improving ROM between the two drugs.
After one year, however, the average of ROM improvement, compared with preoperative data, in the celecoxib group was significantly higher than that of the indomethacin group.
Our study had several strengths: this was a prospective case-control study. All patients were screened and followed at a single center and received a standardised pre-, peri-, and postoperative regime. The detailed assessment of outcomes was collected by a single data collector, resulting in few missing data.
However, there were also limitations including a relatively very small sample size and short follow-up. Nevertheless, this small number of patients illustrated the importance of celecoxib on inflammatory response, namely postoperative functional outcome in ROM, following arthroscopic treatment.
Our best result is the evidence about the short-term efficacy of this class of drugs, avoiding the well-known side effects of indomethacin. Therefore, the use of a PPI most likely reduced the gastrointestinal side effects of indomethacin.

Conclusions

Celecoxib can therefore be considered as a valid drug for patients at risk of gastrointestinal adverse effects if treated with traditional NSAIDs. It has been shown to have the same and, in

some cases better, efficacy as indomethacin in recovering the range of joint movements after arthroscopy to prevent formation of further joint fibrosis.
Given the widespread use of NSAIDs in short-term treatment of trivial signs and symptoms, the availability of coxibs for these indications would be advantageous since their use for short periods is unlikely to increase cardiac risk.

Human and animal rights

This article does have not relation with any studies performed on human beings and animals by the authors.

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