A sensible approach to the use of NSAIDs in sports medicine

Tscholl Ph M, Gard S, Schindler M
Unité de Orthopédie et Traumatologie du Sport (UOTS), Service de Chirurgie Orthopédique et Traumatologie de l'Appareil Moteur, Hôpitaux Universitaires de Genève, Genève, Suisse

Abstract

Non-steroidal anti-inflammatory drugs (NSAIDs) have the highest intake of all medication in elite and non-elite athletes. The high consumption by athletes (30–50%) participating in team and single-sports leads to the assumption that not only injuries are being treated, but that masking symptoms of minor complaints or post-exercise fatigue might be the primary indication for their intake, without considering their potential harmful side-effects on general health but also on training adaptive processes. Vast information campaign to team physicians since 2011 could not decrease the prescription practice in the past few years highlighted by the persisting high numbers reported during the FIFA World Cups 2002–2014.

There is moderate evidence in literature, of earlier return to sport after ankle sprains using NSAIDs systematically, however which is directly related to a decreased range of motion and increased joint instability. Evenmore, recent studies have reported impaired muscular and tendinous adaption to exercise if NSAIDs are ingested. In the early inflammation phase of injured tissue, its use might decrease additional tissue damage especially in muscle injuries, however prolonged intake has been associated for example with delayed fracture healing by intervening with the proliferative phase.

NSAIDs are potent analgesic medications, but due to their anti-inflammatory property their intake should be wisely indicated; inhibiting early excessive inflammation without decreasing tissue-healing potential. Their use should be more controlled by the health care specialist especially by sports physicians. Neither over-the-counter use nor administration by non-medical staff should be supported; alternative treatment options however need to be educated.

Keywords: sport, NSAIDs, fracture, muscle injury, ligament, tissue healing

Zusammenfassung

Nicht-steroidale Antirheumatika (NSAR) sind die meist-verwendeten Medikamente im Spitzen- und Breitensport. Aufgrund der hohen Inzidenz an Athleten in Einzel- wie auch Mannschaftsportarten, welche NSAR regelmässig einnehmen (30–50%), wird angenommen, dass mit deren Einnahme nicht nur Verletzungen therapiert, sondern vor allem Symptome minder-schwerer Verletzungen maskiert werden und somit die Verletzungsgefahr erhöht wird; hierbei wird den potenziellen Nebenwirkungen und Begleiterscheinung keine Rechnung getragen. Obgleich eine grosse Informationskampagne anlässlich der FIFA-Weltmeisterschaften 2010 durchgeführt wurde, konnte seitdem keine Reduktion vom NSAR-Gebrauch beobachtet werden.

Nach ligamentären, oberen Sprunggelenksverletzungen kann die systemische NSAR-Einnahme eine frühere Rückkehr in den Sport unterstützen, wobei scheinbar ein direkter Zusammenhang mit vermehrter Gelenksbeweglichkeit wie auch erhöhter Rest-Instabilität nachgewiesen werden konnte. Weitere Studien konnten ebenfalls eine Verschlechterung der adaptiven Reparaturprozesse nach einer Belastungseinheit aufzeigen, sowohl für die Proteinsynthese im Muskelgewebe wie auch die peritendinöse Durchblutung. Nach strukturellen Muskelverletzungen kann jedoch die Einnahme von NSAR während 2–3 Tagen die frühe Entzündungsphase vermindern und somit den Gewebeschaden signifikant vermindern. Eine längere Einnahme jedoch ist nicht nur im Muskelgewebe, sondern auch bei Frakturheilungsprozessen in der proliferativen Phase deletär.

NSAR sind potente Schmerzmedikamente mit anti-entzündlicher Eigenschaft und sollten daher nur eingesetzt werden, wenn die Entzündungshemmung auch teil der Therapie ist. Andernfalls sollten Alternativen gesucht werden. Den Gebrauch von NSAR zu vermindern gelingt nur dann, wenn Athleten wie auch alle medizinischen Betreuer aufgeklärt werden und die Eigenmedikation der Athleten eingeschränkt oder besser kontrolliert wird.

Schlüsselwörter: Sport, NSAR, Fraktur, Muskelverletzung, Ligament, Gewebeheilung

Practical Implications

Up to 30–50% of all elite and even non-elite athletes are frequent users of NSAIDs during competition and training sessions.

NSAIDs are not only potent analgesics but also interfere with adaptive processes in response to exercise and with tissue healing due to their anti-inflammatory characteristic.

A decrease in protein synthesis and proliferation of satellite cells in muscular tissue, and a decreased hyperemia in the peritendinous tissue have been reported after intake of NSAIDs.

Whereas NSAIDs may be beneficial for the first 2–3 days after structural muscle injuries or in paratenonitis, deleterious effects might be found in early and late administration for fracture healing or chronic tendinopathy treatment.

General use of medication in elite athletes

Most information about the use of medication in youth and adult elite sports are published by F-MARC (FIFA Medical Assessment and Research Centre), highlighting a high intake of medication from 2002 throughout 2014. [78,79,81] The most frequently used medication were painkilling agents, whereas one third of the adult players and one fifth of the youth players reported their use prior to every match, regardless whether they were actually playing. Although a worldwide campaign has been performed to inform team physicians participating at the 2014 FIFA World Cup, the incidence remained at the identical high level. [84] Studies from other sports are showing a similarly high intake of medication and nutritional supplements. [1,14,27,52,77,82]

An un-published, pubmed-based meta-analysis [80] including published data up to 2009 of the use of medication 24 to 72 hours prior to the doping control reported either by the team physician or the athlete [1,27,73,77–79,82,85] found several critical risk factors: the reporting sports physician, geographic origin (which was associated with the type of sport), the age of the athlete, the type of sport and gender. No association was found to the reported injuries, team success, or whether the player was in the starting formation or on the bench during the entire game. [77,79]

In every study, the potential bias of underreporting was mentioned, which even raises more attention to the prescription practice and the use of medication in elite sports.

The use of NSAIDs in elite and non-elite athletes

One of the first studies published about the use of NSAIDs in sports was performed at the alpine "Jungfrau-Marathon", which identified NSAIDs in the urine in 34.6% of the participating athletes. [47] A similar incidence was found at the ultramarathon El Andalus (47% of the athletes were taking painkilling agents, wherefrom 60% NSAIDs) [65], in triathletes (59.9% of the athletes taking NSAIDs within the last 3 months) [24] and during the city marathon of Bonn 2009 (61%). [8] In the city marathon of Berlin in 2010, 49% of the participants took NSAIDs prior to the race, but "only" 11% started with pain into the race and 15% took more than one type of NSAIDs. [39]

Systemic side effects of NSAIDs in athletes are well known. Gastro-intestinal events, with minor symptoms of dyspepsia in 20% has been reported by Alaranta et al. [1] Malabsorption due to increased intestinal membrane permeability has been highlighted [41], and in some cases even with local ischemia and gastro-intestinal bleeding in the context of sport. [40,83] During the 2010 Berlin Marathon, four events of major gastro-intestinal bleeding occurred, all of them after ingestion of 500–1000mg acetyl salicylic acid. [39] Hyponatremia has also been described, especially in long-lasting endurance activities, however is controversially discussed in literature. [25,56] Again, at the 2010 Berlin Marathon, three athletes were treated for oliguria or anuria, all with an intake of 1x600mg or 2x400mg ibuprofen prior to the race. [39] A relation to sudden cardiac arrest is discussed, however not proven; although the recurrent risk of myocardial infarction is increased also in young patients when using NSAIDs especially with diclofenac, and to a lesser extend with ketorolac. [67] Studies about athletes without prior cardiovascular events or risk factors are so far missing.

Most interpellant in this context, that the majority of the athletes taking NSAIDs are not aware of the potential side-effects [65], and sports physician are rarely the source of information in this context. [8,24,26,39,65] As found during the FIFA under age World Cups [78], the use of NSAIDs in youth athletes is almost as high as in the adult group. These findings are confirmed with more than 50% of the 14–15 years old collegiate athletes taking NSAIDs regularly. [26]

Most NSAIDs are taken orally. [78] Studies comparing the efficacy of topically versus oral application of NSAIDs mostly show no difference in the analgesic effect, whether in chronic or acute musculoskeletal injuries. [38,48] Most interesting, synovial concentration is 10 to 20 fold increased compared to plasma if applied topically and equal or increased concentration in muscle, tendon and periosteal tissue is observed compared to oral ingestion; hence topical application potentially decreases systemic side-effects with identical effect at the site of action. [17,32]

The most frequently prescribed substances are non-specific COX-I inhibitors as ibuprofen or diclofenac [78], although more selective COX-2 inhibitors as etoricoxib or celecoxib might be pharmaceutically more relevant, due to more influence on pain perception and thermoregulation and to a lesser extent on thrombocyte aggregation, renal vascularization, intestinal mucosa and mineral excretion.

NSAIDs and their influence on the musculoskeletal tissue

Mechanism of action of NSAIDs

NSAIDs have analgesic, antipyretic and anti-inflammatory properties. In sports medicine, the primary aim and indication of NSAIDs is reduction of pain at the primary site of injury, by reducing inflammation. Cyclooxygenase (COX) enzymes are inhibited, which are responsible to convert arachidonic acid of the cell membrane into prostaglandines, prostacyclines and leukotrienes. The COX-I enzymes and its products are found in all organs, regulating gastric mucus production, renal blood flow, neovascularization, platelet aggregation, development of fever, modulating pain receptors amongst others. Its isoform COX-II is produced only in case of tissue damage, induced by inflammatory mediators, and propagates inflammation through prostaglandines and thromboxane A2.

The effect of NSAIDs on musculoskeletal tissue healing

Tissue healing occurs in three stages – inflammation, proliferation and maturation. During the first 3–7 days after injury (or surgery), pro-inflammatory and phagocytic cells (neutrophils and macrophages) are predominant. The length in time and extend of inflammation is highly dependent on the type of injury, the local metabolism influenced by vascularization and swelling. This early phase is triggered and regulated by several pathways, either directly by growth hormones, as PDGF due to tissue injury, or by inflammation and prostaglandines. During proliferation phase, granulating tissue is formed, producing extracellular matrix and collagen, which lasts for 4 weeks and longer. At this stage, the pro-inflammatory cascade is essential for healthy granulation tissue, which depends on fibroblast receiving sufficient nutrients. During maturation phase, collagen fibres are cross-linked and aligned. Each of these steps are mediated by cytokines and different types of prostaglandines, in which NSAIDs might interfere. [10,11]

Effect on muscle healing

The initial stage of inflammation in muscle injuries might vary significantly in time in function of the size, the type and location of the injury. Cell migration of neutrophils and macrophage is triggered by prostaglandines and cytokines (such as PDGF), which might lead to additional muscle tissue injury. Therefore, NSAIDs might show some benefit in this early phase (2–3 days) of injury decreasing further damage to the muscular tissue. [35,60] Nevertheless, macrophages are indispensable in the latter early stage of the healing process to produce cytokines, growth factors and oxygen radicals to initiate the proliferation phase [35,60] in which satellite cells are recruited, which then proliferate and fuse with myocytes. [45] As a consequence, a long-term repair deficit might occur at the myocyte itself, but also in the interfibre connective tissue if NSAIDs are used for a longer period of time. [46]

Hence, NSAIDs are able to interfere in every phase of the muscle healing process. [45] Whether they have the potential to influence the reparative microarchitecture of muscle tissue and its function remains a conflicting debate in literature. [31,49,62,68,69]

There is nov evidence of true benefit using NSAIDs in MINOR muscle injuries. [61,63] Myalgia in muscle soreness (muscle injuries without structural damage) are typically reduced, without improving the reactive muscle weakness. [43,57,74] Therefore, early return to sports due to masked pain puts the athlete at increased risk for recurrent or overuse injuries, since proprioception especially in complex senso-motory tasks might still be disabled or altered. The use of NSAIDs in structural muscle injuries shows no advantage over other analgesics in terms of early return to sports or to function. [49,57,62]

Prophylactic use of NSAIDs in middle-aged subjects (above 60 years of age) performing resistance training seems to be beneficial in terms of muscle strength gain. [3,75] This effect was not found in younger subjects (25 years of age). [13,37] This might be a short term benefit only, since NSAIDs reduce intramuscular protein synthesis significantly. [76]

Effect on tendon healing

Chronic tendinopathy of the proximal patellar tendon or the Achilles tendon are characterized by a lack of inflammatory cells, and resembles rather a bradythrophic tissue. [71] Whereas physical activity, especially eccentric training has been proven to be most valuable and effective, the post-exercise inflammatory response with hyperemia in the paratendinous tissue does not occur if NSAIDs are taken. [34] Therefore, its use is limited or even regarded as obsolete, as it has been demonstrated in a randomized study in Achilles tendinopathy, where no difference in strength, pain, or swelling was observed. [2] In acute tendinopathy and parathenonitis, NSAIDs decrease the associated pain and fibrinous exsudate, and therefore might be indicated for some time. [71]

Postoperatively, there are two situations where tendinous tissue needs to heal: either direct tendon healing or tendon to bone healing after anterior cruciate ligament surgery, for example. Weaker tendon healing especially when COX-2 are administered has been observed in animal studies, [21] which however is not completely consistent in literature. [11] Tendon thickness however seems to be decreased [11], which might be an advantage in some circumstances, especially in hand surgery. There is no study in humans analyzing tendon to bone healing. Two studies in rats found lower load to failure and lower pull-out strength of the tendon when administered 7 to 14 days [12,16] suggesting that NSAIDs should be avoided after anterior cruciate ligament reconstruction.

In the absence of tendinous injury, but as a response to exercise, hyperemia is found peritendinous tissue. This mechanism is mandated by PGE2, and therefore can be inhibited by NSAIDs, leading to a lesser growth in tendon thickness. Mechanical properties and microarchitecture seem not to be altered by NSAIDs. [55]

Effect on ligamento-capsulary healing

Early analgesic and especially anti-inflammatory treatment after grade I to II injuries to the lateral capsuloligamentory complex of the ankle has shown to be beneficial with earlier functional recovery and less pain. [18,72] Early pain-treatment by decreasing the early inflammatory phase, enables early functional rehabilitation, however might predispose to premature return to sport, which was associated in a randomized controlled trial published by Slatyer et al. [72] with decreased range of motion, more swelling and increased instability. Weakened ligamentous tissue healing in terms of collagen orientation and strength is discussed [19,51], and remains unclear whether it is a consequence of the anti-inflammatory effect of NSAIDs or too early return to activity due to its painkilling effect.

To our knowledge, there is no study analyzing the effect on NSAIDs on exercise depending adaptive process of the capsulo-ligamentary process in neither human nor animal subjects. However, paracetamol seems to be as effecting threatening pain in ankle sprains as NSAIDs. [30]

Effect on bone healing

During the bone healing process, prostaglandine E2 (PGE2) – which is activated by the cyclo-oxygenase (COX)-II enzyme – plays a major role in the activation cascade of osteo-

blasts and osteoclasts, and potentially in the differentiation process of mesenchymal cells into osteoblasts. [11,33] A negative effect of NSAIDs inhibiting COX-II enzyme was observed in several animal studies by delayed, and structurally immature and weaker bone healing under the treatment of ketorolac and others. [4,70] It seems that the very early use of NSAIDs might be the cause of this negative effect in fracture healing [70], especially if administered for more than 1–2 weeks. [4,20,54] Application of paracetamol did not have a negative influence on bone healing in neither low nor in high-concentrations, supporting a direct effect of NSAIDs on early fracture healing [4] rather than a purely analgesic effect enabling too early weight-bearing.

In humans, there are several comparative cohort studies showing negative effect of the use of NSAIDs. Patients (N=32) with non-union of femoral shaft fractures significantly used more NSAIDs and for longer periods of time than controls (N=67). [22] In another study of 105 humeral shaft non-unions, prolonged use of NSAIDs was associated with non-union [5], as well as after spinal fusion [23], and after acetabular fractures. [9]

A negative influence on bone metabolism, and especially of bone density has been discussed controversially. [36]

Alternative treatment options

Almost every sport injury is treated by cold therapy to alleviate pain perception and to reduce the swelling in the acute phase. The application goes from local icing, cold water immersion (CWI) and whole body cryotherapy (WBC). Although these methods are widely used (specially local icing) there no consensus on the best protocol. CWI and WBC both are used for faster recovery especially to reduce the perception of delayed onset of muscle soreness (DOMS). [15,44] Local icing is more generally used, in the acute and sub-acute setting. However, immediate return to sports after local cold application of muscular tissue of 20 minutes or more seems to impair performance [6] and short-term ice-spray application on the ankle joint might even decrease proprioceptive in basic landing tasks. [28]

Besides alternative painkillers with less or no anti-inflammatory potential, curcumin has been reported to have a positive effect on DOMS after eccentric exercises by decreased IL-6 concentration. [53] Bromelain, a food supplement obtained from the stem of the pineapple fruit is another adjunct alternative, that seems to reduce inflammation and pain through lower bradykinin plasma concentrations. [7,58] A more invasive medication frequently used in sports medicine are platelet-rich plasma preparations, containing growth factors and cytokines. They are injected for their potential healing capacity in muscle-, tendon and even chondral lesions. NSAIDs might interfere with the healing response and therefore should be discontinued two weeks prior to injection. [66]

Modulating pain-perception in musculoskeletal injuries can also be achieved by isometric and eccentric muscle contraction [64], manual therapy [59], several taping techniques [42,50,86] and electrotherapy such as transcutaneous nerve stimulation (TENS) relying on the "gate-control theory" [29], just to mention some of many other treatment modalities. They all have in common, that they are time consuming, and need to be evaluated and adapted on regular basis by a sports medicine trained health care specialist.

Conclusions

When shall we use NSAIDs in sports medicine? Should these medications even be banned? Since no correlation between declared injuries and the use of NSAIDs has been found, there is a high assumption that misuse and malpractice is occurring in low- and high-level sports. In some cases, NSAIDs are used without true medical indication, or even used in healthy and un-injured athletes, to mask symptoms that are a consequence of training adaptation, as myalgia after an intensive bout of eccentric exercise. Some may even use these medications "prophylactically", hence even before noticing any sports-activity related pain.

So far, it is not known whether regular use of NSAIDs might lead not only to gastro-intestinal side-effects, and more rarely cardiovascular and nephrotoxic events, but also to relevant alterations of the training adaptive processes in terms of sports performance and decreased tissue healing in terms of a lack of rehabilitation, hence increasing the risk of further or recurrent injury. Strongest evidence exists however, that early intake of NSAIDs might influence bone healing negatively, as well as prolonged intake (longer than 3 days) in the muscle and ligamentous healing response.

The medical staff and the athlete, using NSAIDs, should be aware that not only they are potent analgesics, but also modulating inflammatory and therefore healing response. Also, pain is a warning signal of incomplete healing, and should be respected and treated as such, and if necessary by analgesics only, to avoid further injury or chronification.

When prescribing NSAIDs and other inflammation-modulating medication, following axiom should be remembered: "there is inflammation without healing, but no healing without inflammation".

Corresponding author

Dr. med. Philippe M. Tscholl
Unité d'orthopédie et de traumatologie du sport (UOTS)
Swiss Olympic Medical Center
Cressy Santé Genève
Route de Loëx 99
1232 Confignon
Suisse
Tel. +41 22 727 15 50
Philippe.Tscholl@hcuge.ch

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