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REVIEW ARTICLE

Mechanisms and Treatment of Delayed Onset Muscle Soreness in Athletes - A Review

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ABSTRACT

Objective: The purpose of this study is to review mechanisms for Delayed Onset Muscle Soreness (DOMS) and the pharmacological treatment options with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Method: Our review of published research literature was based on an appropriate number of subjects included in the study with a statistical power of .80 or higher and an effect size of .30 or higher. In the case of review articles, two cited references from each article where significant data were used to establish the conclusion were examined for type II error using the criteria mentioned above. Our review also includes inflammation, tissue damage, and the treatment of DOMS with both selective and non-selective NSAIDs.

Results: Frequently cited mechanisms of DOMS are "mechanical strain" and "metabolic overload" within the muscle structure. The inflammation associated with DOMS is caused by eccentric exercise-induced muscle damage. NSAIDs inhibit prostaglandin synthesis and/or block cyclooxygenase and there by reduce the pain and swelling associated with inflammation. There are both selective and non-selective NSAIDs, the former being the COX-2 inhibitors (e.g., celecoxib) and the later (e.g., ibuprofen, naproxen, and aspirin).

Conclusion: For the treatment of DOMS, naproxen taken at antiinflammation levels for at least 3 days shows the most consistent results for improving the recovery rate of affected muscle.

Introduction

Muscle injuries, acute and delayed onset, are common in athletes and non-athletes. It is well known that Non-Steroidal Anti-Inflammatory Drugs (NSAID) are among the most frequently prescribed drugs by physicians specialized in sports medicine and/or family medicine to reduce symptoms of muscle injury associated inflammation, swelling, fever and pain [1-3]. The associated symptomatology usually peak 24-48 hours post-injury and subsided 72-96 hours after the injury [3,4]. NSAIDs are highly effective in the alleviation of pain, fever and inflammation.

The primary concern for competitive athletes, coaches, athletic trainers, and team physicians is the reduction of muscular function following muscle injury. Post-exercise muscle soreness, pain, and reduction in muscle function are among

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the problems that affect the athlete's performance. It is known that unfamiliar physical activities such as endurance exercise when there is a greater component of eccentric actions, such as downhill running [5-7], shuttle running [8], marathon running [4], cycling [9], and stepping exercise [10] are known to induce severe Delay Onset Muscle Soreness (DOMS). DOMS is characterized by intensity of symptoms beginning 24-48 hours after exercise and lasting for several days [11], and has been described as muscle stiffness and swelling, loss of force-generating capacity, reduced joint range of motion, and loss of proprioceptive function [5,12]. The underlying physiological mechanism causing DOMS is unknown and highly disputed. At least six hypothesized theories for the mechanism of DOMS have been proposed [13]. They are 1) metabolic overload and "mechanical strains" [14-16], 2) lactic acid [17], 3) muscle spasm, 4) connective tissue damage, 5) muscle damage [15,16,18], 6) inflammation, and 7) enzyme efflux theories. We believe that effective preventive therapies for DOMS could be developed if the underlying physiological mechanism can be identified.

Thus, the purpose of this study is to review mechanisms for DOMS with an emphasis placed on pharmacological treatment options with selective and Non-Selective Anti-Inflammatory Drugs (NSAIDs).

Methods

We searched MEDLINE, google scholar, PubMed, the Internet (www.RxList.com; www.voxx.com. www"celebrex.com), and the library collection from the University of Toledo, Midwestern University (Illinois), and California State Polytechnic University at Pomona (California) from 1983 to 2017. Terms used for the search were "DOMS", "muscle soreness", "NSAID", "athlete", "exercise-induced", "eccentric exercise", "therapy", "inflammation", "pain", and "cyclooxygnase inhibitors".

Our review of published research literature was based on an appropriate number of subjects included in the study with a statistical power of .80 or higher and an effect size of .30 or higher. In the case of review articles, two cited references from each article where significant data were used to establish the conclusion were examined for type II error using the criteria of downhill running [5-7] shuttle running [8], marathon running [4] and stepping exercise [10]. None of the reviewed literature has committed a type II error. A total of 47 articles which meet the above criteria were identified and reviewed.

Overview of inflammation and DOMS

Signs and symptoms of DOMS include dull aching pain and stiffness [4,19,20], decreased range of motion, tenderness, pain with movement or tension [4,18], strength reduction [19,21-23), and swelling [21,23]. DOMS associated with a reduction of muscle strength production is a result of tissue damage, which is caused by high eccentric force production during eccentric actions [22]. Growing evidence from human studies shows that appropriate pre-training using eccentric exercise prevents muscle damage and soreness, also known as an acclimatization or adaptation effect [21,23,24].

Tissue inflammation: Inflammation is a physiologic response to injury which mobilizes the body's immune systems. When inflammation exceeds the proper duration and intensity, it then becomes a greater concern for both athletes and their healthcare providers. Inflammation is described as having 3 phases: a) acute b) sub-acute, and c) chronic [16]. Because the acute phase is known to last 3-4 days, it is with this phase of inflammation that DOMS is thought to be associated [16,25]. Inflammation associated with DOMS carries the following signs and symptoms: 1) heat, 2) redness, 3) swelling, 4) pain, and 5) loss of function. Nosaka and Clarkson [16] found that with DOMS 24-hours after eccentric exercise, muscle function (i.e., maximal isometric force) decreased to 55% of pre exercise levels, and that the circumference of the arm 8 cm below and 4 cm above the elbow increased significantly over five days. The increase in arm circumference was the result of swelling.

Progression of acute inflammation: Upon injury to muscle tissues, the damaged blood vessels show a leakage of substances into the tissue to initiate the healing process. Bradykinin increases vascular permeability and stimulates the release of prostaglandins from the macrophages [26,27]. Prostaglandin G/H synthase, a bifunctional enzyme, contains both the cyclooxygenase activity that converts arachidonic acid into Prostaglandin G2 (PGG2) and the peroxidase activity that reduces PGG2 to Prostaglandin H2 (PGH2) [28]. The enzyme is known as Cyclooxygenase (COX).

Prostaglandins as well as histamine, kinins and others, sensitize nociceptors [24,27]. Macrophages are thought to begin synthesizing and releasing prostaglandins within 30 minutes of injury and to continue for a minimum of 24 hours [16]. Smith [29] hypothesized that the macrophages that are found responsible for biosynthesis of prostaglandins after eccentric exercise during acute inflammation are found in laboratory animal studies. It is known that macrophages are the predominant cell type at 24 and 48 hours following eccentric activity in rodents [16,25]. This is also the time of peak levels of DOMS in humans (4). The progression of acute inflammation involves 1) initial injury, 2) inflow of macrophages, 3) release of prostaglandins, and 4) increased sensitivity of nociceptors (group III and IV afferent pain receptors) [16]. These events occur between 30 minutes and 24 hours following the initial injury induced by eccentric exercise or endurance exercise. It is around the 24-hour point that DOMS appears [4,23,30].

The acute phase of inflammation is initiated by cytokines that are produced by several different cell types [16,23]. Cytokines play a vital role in immuno response. These acute phase reactants, such as increased blood oxidative-stress

marker, and protein carbonyl from oxidation of amino acids, are elevated 24 to 48 hours after exercise [29]. The release of these proteins may aid in reducing tissue degradation and in the deleterious effects of inflammatory response [16,20]. Inflammation causes the release of creatine kinase [23]. Elevation of the plasma level of Creatine Kinase (CK) and its subfraction CK (MM) is believed to be associated with tissue damage [23,29]. Independently, CK study cannot detect the quantity of muscle damage [4,19]. Sonkodi, et al. [12] found that DOMS is masked by sympathetic nervous system activity initially, and when the associated signs and symptoms of DOMS subside, a safety mode comes into play to prevent further tissue injury. Sonkodi, et al. [12] further suggested that the increasing sympathetic nervous system activity during unaccustomed or strenuous exercise is an essential underlying factor in DOMS.

Similarities of inflammation and DOMS: As mentioned before inflammation and DOMS both carry common signs and symptoms, and they occur at the same time after a bout of eccentric exercise (i.e., 24-hours post-exercise) [26]. Decreased range of motion and reduction in muscle strength are due to mechanical interference of swelling and the reflex inhibition of painful muscles [16,22,26]. Using an animal model, Warren, et al. [22] demonstrated that during the first 72 hours of tissue injury, approximately 75% of the strength reduction is due to a failure of Excitation-Contraction (E-C) coupling, and the remainder of strength reduction is due to structural disruption and/or alteration of force-bearing elements within the muscle. After the 72 hours of muscle damage, strength reduction is attributed to a decreased contractile protein content, most likely from the removal of disrupted myofibrillar structures [22]. What we learn from research derived from the animal model is that strength reduction after muscle damage appears to result from an overly complex interaction of mechanisms. In humans, strength reduction has been shown to return to baseline between two and 14 days [4,26]. In athletic competitions, decreased training time and reduction of strength would affect the athletes' subsequent performance.

In this review, we focused our discussion on the inflammation theory. The inflammation theory has some validity because of the striking similarities between the acute inflammation response, including muscle damage and DOMS. These include dull aching pain, stiffness, swelling and loss of function at the area of interest as well as the timelines seem to match up with DOMS response (i.e., increase in severity for about 24-48 hours and showing signs of healing at 72-96 hours) [4,11,19,20]. However, after Smith [29] reported the relationship between DOMS onset and inflammatory biomarkers (i.e., white blood cells and neutrophils) have failed to find cause-effect relationship between the two, this leads us to believe that inflammation does not associate with or cause DOMS. This conclusion was reinforced from an earlier study by Kuipers, et al. [30] who found the ineffectiveness of anti-inflammatory drugs (i.e., prostaglandin-inhibiting drug) on preventing muscle pain and soreness after eccentric exercise induced DOMS.

The inflammation theory was brought to light by Murase's study [31] in a rat experiment who found that bradykinin and nerve growth factor play critical roles in muscular mechanical hyperalgesia after exercise induced DOMS. In their study, Murase, et al. [31] demonstrated that an inflammatory mediator bradykinin B_2, injected 30 minutes before eccentric exercise completely prevented DOMS. Thus, the inflammation theory may deem satisfactory and acceptable as the cause of DOMS. However, more research on human subjects is warranted to elucidate the physiological pathway that leads to DOMS. Recent human studies by Morelli, et al. [32] found that NSAID use for treating DOMS was effective for reducing strength loss, soreness, and blood creatine kinase level after an acute muscle injury. However, there are still questions regarding the use of NSAIDs for treating DOMS. More research is needed to resolve why NSAID use appears to be more effective when lower-body muscles in humans are injured, and why NSAID use appears detrimental at later times after injury in animals but not humans [32].

Muscle fiber structure and Z-Line disruption: During eccentric actions, the muscle fibers elongate as they generate mechanical force. Eccentric muscle damage occurs when the load imposed on the muscle is greater than the contractile force produced by that muscle [23,25]. Although the generation of muscular force is doubled, the total number of tightly bound crossbridges is only 10% more than that of an isometric contraction [23]. Thus, there is a greater amount of strain exerted per individual crossbridge [21,23]. Muscle damage is believed to be from the muscle fiber strain that occurred during the lengthening action of activated muscle fibers [22]. The strain exerted on the muscle fibers during eccentric actions may account for muscle damage [22,23]. The myosin filament stores potential energy that is released upon E-C coupling, and binds to actin and is then transformed into the mechanical events of the crossbridges [22].

With muscle damage due to eccentric action there is thought to be two parts to the injury of DOMS, the initial and the secondary injury [21]. The initial injury is a mechanical injury to the sarcomeres when they were stretched beyond overlap [21]. The secondary injury lies at the biochemical level and is the response to the initial injury [21,22,25]. The magnitude of the secondary injury can help to predict the length of recovery time.

Various treatment options for DOMS

While the mechanism of DOMS is still unclear, research has been conducted to determine effective treatment options. A variety of treatment modalities have been applied which include, but are not limited to cryotherapy, ultrasound, phonophoresis, osteopathic manipulative

techniques, acupuncture, acupressure techniques, electromagnetic shield (Farabloc), several types of electrical nerve stimulation, exercise, massage, and hyperbaric oxygen therapy [27,28]. Also, a great deal of research has been conducted using various anti-inflammatory medications (Table 1) [33,34]. This review focused primarily on the non-selective and selective NSAIDs or COX-2 inhibitors.

Table 1: NSAIDs listed by pharmacologic class (source: Epocrates).

Pharmacologic Class	NSAID Subclasses
Acetic Acids	Diclofenac, Etodolac, Indomethacin, Ketorolac, Sulindac, Tolmetin
COX-2 Inhibitors	Celecoxib
Fenamates	Meclofenamate, Mefenamic Acid
Naphthylalkanones	Nabumetone
Oxicams	Meloxicam, Piroxicam
Propionic Acids	Fenoprofen, Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen, Oxaprozin
Salicylates, Non-acetylated	Choline Salicylate, Choline Magnesium, Trisalicylate, Diflunisal
	Magnesium Salicylate, Salsalate, Sodium Salicylate, Trolamine Salicylate

Basic pharmacology of NSAIDs

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are frequently prescribed for sports or activity related injuries as an anti-inflammatory agent and as a pain reliever [27]. However, their use is limited by serious adverse effects. This is because NSAIDs share aspirin's trait of gastrointestinal toxicity, mediated by the inhibition of COX-1 effects on the gastric mucosa. There are selective and non-selective NSAIDs. The non-selective NSAIDs include the carboxylic acids and acetic acid class with the former being the largest. Within the carboxylic acids class is the subclass of propionic acids. In this subclass are ibuprofen, naproxen, oxaprozin, flurbiprofen, fenoprofen, and ketoprofen.

The acetic acid class includes diclofenac, etodolac, indomethacin, ketorolac, sulindac, and tolmetin. The only selective COX-2 inhibitor currently available in the U.S. is celecoxib. For treatment of DOMS, naproxen taken at anti-inflammatory levels (1000 mg daily for at least 3 days) shows the most consistent results for improving the recovery rate of DOMS [2,34-38]. For other non-selective NSAIDs used for treating DOMS the results were equivocal [19,23-25,30].

In the United States, most physicians specializing in sports medicine and/or family medicine were likely to prescribe one or a combination of these medications for treating DOMS: ibuprofen, flurbiprofen, ketoprofen, naproxen, oxaprozin, diclofenac or aspirin [25,35,38,39]. After 1999, three selective Cyclooxygenase-2 (COX-2) inhibitors: celecoxib, rofecoxib, and valdecoxib were temporarily available as options for treating DOMS [40] until rofecoxib was withdrawn in 2004 and valdecoxib in 2005.

The use of coxibs: celecoxib (trade name celebrex) has many clinical advantages over traditional non-selective NSAIDs due to the distinct properties of COX-2 [34,36,40]. Expression of COX-2 upregulated by bacterial lipopolysaccharide, cytokines, growth factors and tumor promoters make it a distinguishable form from the expression of COX-1 isoform [40,41]. The discovery of the multiple COX isoforms is one of the greatest contributions toward the development of selective NSAIDs as drugs for the treatment of DOMS.

For athletes, the advantage is that a selective COX-2 inhibitor is less likely to causes serious gastrointestinal (GI) adverse effects than non-selective NSAIDs [34], and that it produces sufficient analgesic and anti-inflammatory efficacy for the treatment of DOMS [34,40]. The question all physicians ask is how safe are selective NSAIDs for a long-term use. In general, 10-20% of patients taking selective NSAIDs daily experience dyspepsia [36] but experience less frequent serious GI problems [34,36]. Singh and Triadafilopoulos [42] reported approximately 0.22% annual mortality rate associated with GI effects of non-selective NSAIDs.

The mechanism of action of selective NSAIDs: NSAIDs work by inhibiting prostaglandin synthesis to block cyclooxygenase [27,33,34,43]. Cyclooxygenase and lipoxygenase then convert the arachidonic acid to prostaglandins and leukotrines, respectively. Prostaglandins act to increase the intensity of the other inflammatory mediators and to prolong their effect [34,35,40,43]. Another advantage of prescribing a COX-2 inhibitor is that by blocking the synthesis of prostaglandins, NSAIDs may be able to reduce the discomfort of inflammation [40,42].

Drug-induced side effect of NSAIDs: Do selective NSAIDs have any interaction with other drugs? As with any drug celecoxib has the potential for interaction with the Angiotensin Converting Enzyme (ACE) inhibitors, and therefore athletes with asthma, urticaria, or an allergic-type reaction after taking aspirin or other NSAIDs should not be prescribed celecoxib [34,36]. Non-selective NSAIDs also have some drug-induced side effects. For example, NSAIDs inhibit the production of prostaglandins by blocking COX enzyme, causing analgesic, antipyretic, and anti-inflammatory benefits, but at a risk for increased gastro-intestinal bleeding and ulcerations [2,34,36,39,43]. These side effects seem to occur mostly in those being chronically treated with anti-inflammatory drugs. There are studies reported on preventive measures for the development of NSAID related gastro duodenal toxicity. These are either directed at preserving the integrity of the stomach wall and mucous lining (i.e., the use of COX-2 selective NSAIDs) and/or concomitant use of prostaglandin analogues, or alternatively at inhibiting the secretion of gastric acid (i.e., concomitant use of histamine H_2-receptor or proton-pump inhibitors [2].

NSAIDs are widely used to treat symptoms for DOMS.

From the Canadian consensus guidelines on long-term NSAID therapy and the need for gastroprotection [44], we support the following recommendations from the Canadian consensus guidelines on long-term NSAID therapy use and the need for gastroprotection. For managing patients who require long-term NSAID therapy, it is recommended to prescribe low-dose acetylsalicylic acid in patients with Cardiovascular (CV) risk. For patients with low Gastro-Intestinal (GI) and CV risk, a traditional NSAID alone may be acceptable. For patients with low GI and high CV risk, full-dose naproxen may have a lower potential for CV risk than other NSAIDs. For patients with high GI and low CV risk, a COX-2 inhibitor plus a Proton Pump Inhibitor (PPI) may offer the best GI outcomes. For patients with both GI and CV risk are high where NSAID therapy is necessary, risk should be prioritized. For example, if the primary concern is GI risk, a COX-2 inhibitor plus a PPI is recommended, and if the concern is CV risk, naproxen 500 mg twice a day plus a PPI would be preferred. Note that coxibs therapy may be appropriate for a selected patients with high risks of GI complications and lower CV risk [45].

NSAIDs can interact with other drugs and cause either an increase or decrease in that drug's effectiveness and can react with blood pressure medications by reducing the effects of the antihypertensive drug [34,36,39,43]. Conversely, NSAIDs can increase the effects of oral anticoagulant drugs, which will impair blood coagulation [34,36,43]. Athletes who travel a lot and frequently eat on the road would prefer the selective NSAIDs such as celecoxib because the drug has fewer side effects and is easier to take (e.g., single dose) [34,36].

Summary

One cannot discriminate between analgesic effects and anti-inflammatory effects because they are so closely related [19]. At presence, the inflammation theory may be satisfactory and acceptable as the cause of DOMS. However, by examining the dosage prescribed versus the dosage needed for anti-inflammatory effects, it is unlikely that the benefits of the treatment were due sorely to a decrease in the inflammation process [30]. A selective COX-2 inhibitor has a lower potential to cause serious gastrointestinal (GI) adverse effects than non-selective NSAIDs [34], and it produces sufficient analgesic and anti-inflammatory efficacy for the treatment of DOMS. Thus, Coxibs therapy may be appropriate for selected patients with a high risk of GI complications and a lower CV risk. The use of NSAID to treat DOMS should be kept as short as possible and should consider the specific type of injury, the level of muscle dysfunction, and pain [46]. Lecomte, et al. [35] showed that naproxen taken at a dose of 1000 mg daily increased the rate of muscle recovery of the quadriceps. It is the rate of muscle recovery that is most important in the healing of DOMS. NSAIDs may be able to reduce the discomfort of inflammation but there are some side effects. The side effects of NSAIDs occur mostly in patients being chronically treated with anti-inflammatory drug, i.e., increased gastro-intestinal bleeding and ulcerations [2,34,36,39,43]. Coxibs therapy may be appropriate for selected patients with high risks of GI complications and lower CV risk (46). We summarize Mehallo and co-workers' suggestions that NSAIDs may be used in the management of acute ligament sprains, muscle strains, tendinitis, and eccentric muscle injury, and that NSAID are not recommended for the treatment of complete fractures, stress fractures at high risk of nonunion, or chronic muscle injury [47]. More research on human subjects is warranted to elucidate the physiological pathway that leads to DOMS.

Conclusion

Healthcare providers for athletic injury should not just consider decreased soreness after DOMS, but a complete or near complete return of muscle function, such as muscular force production. In some cases, DOMS was still present because the markers of inflammation did not change between pre- and post-treatment assessments. These would indicate that DOMS is independent of inflammation. It is widely agreed that NSAIDs are effective analgesic, antipyretic, and anti-inflammatory drugs. However, their use is limited by serious adverse effects such as gastro-intestinal toxicity, mediated by inhibition of COX-1 effects on the gastric mucosa. For treatment of DOMS, naproxen taken at anti-inflammatory levels (i.e., 1000 mg daily) for at least 3 days shows the most consistent results for improving the recovery rate of affected muscle. If the athlete is not significantly limited by reduction in muscle strength, but instead by muscle soreness, the current medications available on the market seem to have consistent analgesic benefits (Table 1). More is yet to be learned about the treatment of DOMS, acute pain, and inflammation.

Conflict of Interest Statement

Mark E. McKeigue, Michael T.C. Liang, Kristen Ulety and Thomas W. Allen declare that they have no competing commercial interests and have no professional relationships with the manufacturer of drugs presented in this review.

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