MEDICAL TREATMENT MODALITIES IN HAMSTRING INJURIES

BEWARE TO DO NO HARM

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INTRODUCTION

To get the athlete with a hamstring injury back to play as soon as possible and minimize re-injury risk, there is a continuous search for medical treatments to improve and accelerate muscle healing. Skeletal muscle tissue initiates a rapid healing response following injury, which can be divided in three (overlapping) phases[1,2]:

1. degeneration & inflammation,
2. regeneration and
3. remodeling (Figure 1).

Medical interventions are aimed at modifying one or more of these phases by minimizing degeneration, optimizing or inhibiting inflammation, maximizing regeneration and/or inhibiting fibrosis. Although modifying these aspects of muscle healing may seem reasonable to facilitate healing after injury, the scientific evidence remains limited for the almost endless list of suggested interventions. In this article, the rationale and evidence for the most commonly practiced and/or promising medical treatment modalities for muscle injuries will be discussed.

ANTI-INFLAMMATORY THERAPY

After injury, the gap created by the rupture of muscle fibers is initially filled with hematoma. Activated platelets and endothelial cells release factors that activate and recruit inflammatory cells. Inflammatory cells migrate into the injured tissue to 'clean' the injured zone and contribute to the degeneration and inflammatory process. The inflammatory phase typically lasts for 72 hours. After this phase, the inflammatory cells switch to an anti-inflammatory profile to play an active role in promoting muscle regeneration[2].

Anti-inflammatory medication, such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, are aimed at reducing the inflammatory response after muscle injury. Historically, inflammation was believed to be detrimental for muscle injury healing, emphasized by the traditional widespread use of anti-inflammatory medication post-injury, especially NSAIDs. However, more recently multiple studies have shown that the various phases of inflammation play a critical role in orchestrating muscle regeneration following injury. There is accumulating evidence that pharmacologically inhibiting the inflammatory response is actual detrimental for acute muscle healing[2].

NSAIDs

Multiple studies in animal models found that the oral use of NSAIDs in muscle injury

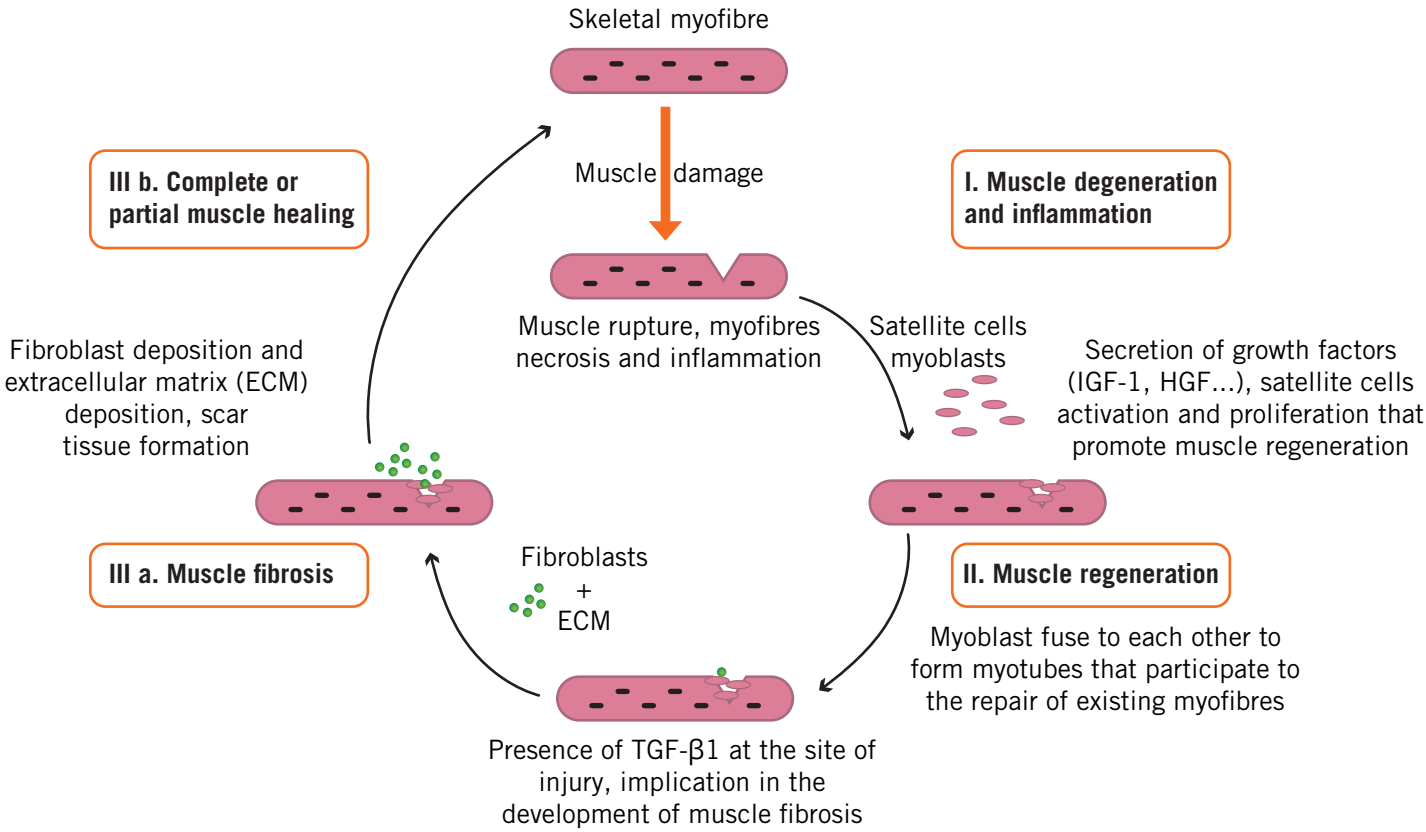

Figure 1: Sequential cycle of muscle healing phases. Adapted with permission from 'Acute muscle injury'of Kerhoffs and Servien, page 19.

resulted in impaired myofiber regeneration and was associated with increased fibrosis[2]. Although NSAIDs are usually administered orally, intramuscular injection of NSAIDs have been shown to be locally myotoxic, resulting in muscle degeneration, edema, hemorrhage, and increased plasma creatine kinase levels[3].

Only one clinical randomised control trial (RCT) has assessed the efficacy of NSAIDs administered orally in athletes with muscle injuries. This RCT showed that NSAIDs did not have an effect on pain and muscle strength compared to a placebo intervention[4]. Considering the lack of clinical efficacy and the possible detrimental effect found in animal models, it is hard to justify the use of NSAIDs in the management of hamstring muscle injury.

Corticosteroids

Similar to NSAIDs, the purpose of corticosteroids is to reduce the inflammatory response. Animal model studies have shown that corticosteroids after muscle injury delay the inflammatory response. However, its use leads to increased necrotic tissue, less regeneration, and atrophy after several weeks. Nevertheless, there are case reports and a low-level case series suggesting a role for corticosteroids injections in athletic muscle injury. Considering the known detrimental effects on muscle healing and the lack of high-level clinical studies we do not support the use of corticosteroids in muscle injury.

Traumeel®

Traumeel® is a homeopathic combination of diluted plant and mineral extracts and is administered either orally, topically, or by injection. It is believed to have an anti-inflammatory effect[5]. The injection therapy is used alone or in combination with Actovegin® (discussed later in this article) in muscle injuries[6], but any evidence regarding the effect of intramuscular injection of Traumeel® in muscle injuries is absent.

Given the increasing evidence that pharmacological inhibition of the inflammatory response is detrimental for muscle healing after acute injury, and the lack of evidence regarding clinical efficacy, it is hard to justify the use of any 'anti-inflammatory' medical treatment modality in the management of acute hamstring injury.

MUSCLE REGENERATING THERAPY

The regeneration phase consists of two processes: regeneration of muscle fibers and the formation of connective (scar) tissue. Myogenic reserve cells called satellite cells become activated, migrate to the site of injury and fuse with myoblasts to form myotubes, which fuse with existing damaged muscle fibers. Scar tissue formation occurs simultaneously and forms a matrix to bridge the gap between the stumps of the ruptured muscle fibers. Regenerating myofibers start to form new musculotendinous junctions and penetrate the connective scar tissue. Ultimately, in the remodeling phase, there is maturation of the regenerating myofibers that further replace the connective scar tissue by mature contractile tissue. A thin layer of scar tissue remains that separate the ends of the ruptured fibers.

Platelet rich plasma (PRP)

Among all medical treatment modalities for muscle injuries, platelet-rich plasma (PRP) is probably the most popular at present. Since the World Anti-Doping Agency permitted the intramuscular injection of PRP in 2011, this it has been increasingly used to

treat acute muscle injuries in athletes[7]. PRP is obtained from autologous whole blood using a variety of commercially available centrifuge separation systems to separate the plasma that is rich in platelets from other blood components.

When injected in the injured muscle, platelets release various growth factors like platelet derived growth factor (PDGF), insulin-like growth factor (IGF-1), basic fibroblast growth factor (bFGF-2) and nerve growth factor (NGF). Basic science studies have shown that growth factors can stimulate myoblast proliferation and increase muscle regeneration in deliberately injured animal muscles[8]. There are a multitude of autologous platelet-rich blood products commercially available that differ in their preparation procedure and cellular components. Superiority is often claimed of one PRP product over the others, but it remains unproven whether the composition of the PRP is relevant for the efficacy of PRP treatments and this is subject of an ongoing debate in the literature.

Despite these promising results in animal studies and apparent widespread clinical use, the positive effects of PRP cannot be confirmed in high-level scientific studies on human subjects. A meta-analysis with pooled data of six RCTs showed no superiority of PRP in treating muscle injuries on the time to return to play and the re-injury rate, nor were any substantial differences found in pain, muscle strength, flexibility, muscle function, or imaging[9].

There is even evidence that a PRP injection in addition to exercise may be detrimental for muscle healing. In the 'traditional' animal studies, any effect of active rehabilitation is neglected. In a recent ingenious laboratory study, researchers accounted for a rehabilitation effect by assigning rats with muscle injuries to 5 groups[10]:

1. control group receiving no intervention,
2. placebo group receiving a single saline injection,
3. PRP group receiving a single PRP injection,
4. exercise group performing daily treadmill running and,
5. PRP + daily exercise group receiving both a single PRP injection and performing daily treadmill running.

The results revealed that the exercise alone group had the best improvement in histology and force recovery outcomes. The outcome of this active rehabilitation was adversely affected by the PRP injection[10].

In conclusion, considering the lack of evidence for efficacy, in addition to evidence for potential adverse effect on outcome of rehabilitation, we discourage PRP treatment in hamstring muscle injuries.

Actovegin®

Actovegin® is a deproteinised hemodyalisate of calf serum that is believed to enhance muscle regeneration[11]. To date there is only one non-randomized clinical pilot study that examined Actovegin® in muscle injury[12]. In this study athletes with grade I injuries that were treated with Actovegin® injections returned to play significantly earlier (12 days on average, n=4) than those that only received physiotherapy (20 days on average, n=4). This pilot study is at high risk of bias due to the lack of blinding and randomization. Future larger randomized studies, including a placebo-group and assessment of potential side effects, are necessary to determine whether Actovegin® injections are safe and improve muscle healing. We do currently not recommend it as a treatment for hamstring injuries.

Stem cells

There is increasing interest for the use of stem cell therapy in muscle injuries. Stem cells are undifferentiated cells that can renew themselves or differentiate into cells that are programmed for a certain tissue lineage. Stem cells may have the ability to contribute to muscle regeneration after injury. Therefore, the concept of transplanting stem cells has been explored for some time, however the available literature focuses mostly on degenerative

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muscle disorders, such as muscular dystrophies.

Evidence for the efficacy of stem cells in acute injury is currently limited to two murine contusion model studies[13,14]. These studies found that intramuscular transplantation of muscle derived stem cells promoted angiogenesis and increased the number and diameter of regenerative muscle fibers. Although these findings are promising, it should be explored whether the same results can be found in human muscle tissue. Furthermore, concerns have been raised regarding the potential tumorigenic risk of stem cells. The Australasian College of Sports and Exercise medicine has released a formal Position Statement in 2017 regarding the use of stem cells in sports and exercise medicine[15]. In this statement, they currently do not support the use of stem cell treatment due to insufficient evidence. As both safety and efficacy data are lacking, they state that it is unethical and unprofessional to market stem cell interventions directly to patients. Stem cell research that contributes to level 1-3 evidence is endorsed.

Despite promising results, we currently do not advocate the use of stem cells in hamstring injuries, as its safety and efficacy in human use is yet to be determined.

ANTI-FIBROTIC THERAPY

From two to three days after muscle injury, connective tissue (fibrosis) starts to appear at the site of the injury. In the following weeks regenerating myofibers penetrate the injured area and the fibrous tissue diminishes in size over time. While formation of fibrous tissue is an essential component of muscle healing, excessive scar tissue formation is suggested to impair recovery of muscle function. This has led to the idea that pharmacological inhibition of fibrosis may be beneficial for recovery after muscle injury. Transforming Growth Factor-β1 (TGF-β1) has been identified as a key factor in scar tissue formation by activating fibrotic cascades. There are several agents known to reduce scar tissue formation through inhibition of TGF-β1, such as losartan, decorin, suramin, relaxin and interferon-γ. In animal studies these therapies are shown to decrease fibrosis and increase regeneration of muscle tissue after injury. Due to (severe) side effect profiles, lack of dosing formulations and lack of Food and Drug Administration (FDA) approval for use in humans, these therapies are currently not readily applicable in clinical practice, and remain experimental for treatment of muscle injury[16]. The one exception is Losartan.

Losartan

Losartan is an angiotensine-II (AT-2) receptor antagonist which is FDA approved for the use in hypertension management. This AT-2 receptor blockade modulates TGF- β1. Originally, it was discovered as a treatment for cardiac fibrosis in hypertensive disease, but it has also been found to reduce fibrosis after skeletal

TABLE 1

	Pro's	*Con's*	*Our recommendation for hamstring injury*
Anti-inflammatory therapy			
NSAIDs	*Analgesic effect*	*No effect on pain and muscle strength compared to a placebo* *Detrimental effect on muscle healing in animal models*	*Not recommended*
Corticosteroids	*Low-level case series suggesting a role in muscle injury*	*Lack of high-level clinical studies* *Detrimental effect on muscle healing in animal models*	*Not recommended*
Traumeel®		*Lack of studies: efficacy and safety unknown*	*Not recommended*
Muscle regenerating therapy			
PRP	*Promising results in animal studies*	*Level I evidence for no effect in athletes with hamstring injuries* *Adverse effect on outcome of rehabilitation*	*Not recommended*
Actovegin®	*Positive effect in pilot study (n=8)*	*Lack of high-level clinical studies: efficacy and safety unknown*	*Not recommended*
Stem cells	*Promising results in animal studies*	*Lack of clinical studies: efficacy and safety unknown*	*Not recommended*
Anti-fibrotic therapy			
Losartan	*Promising results in animal studies*	*Lack of clinical studies in muscle injury: efficacy unknown*	*Not recommended*

Abbreviations: NSAIDs, Non-steroidal anti-inflammatory drugs; PRP, Platelet rich plasma

Table 1: Summary of medical treatment modalities in hamstring injuries.

muscle injury. In animal models, the oral administration of Losartan was reported to reduce fibrosis and enhance the structural and functional regeneration of muscle after laceration and contusion[17].

As Losartan is already FDA approved for hypertension, and is widely available, it is an interesting accessible intervention for treatment of muscle injury. Despite the promising findings in animal models, there are currently no clinical trials in human muscle injury. Therefore, it is unknown whether Losartan has a clinically relevant effect in hamstring injuries.

DISCUSSION

There are currently no medical treatment modalities that have proven clinically relevant benefits in acute muscle injuries (summarized in Table 1). This is either attributable to a lack of evidence for efficacy or evidence for a lack of efficacy in high-level clinical trials (e.g. PRP). For some of these widely employed therapies, there is even (indirect) evidence that it may adversely affect outcome of muscle injury.

With a paucity of high-level evidence for safety and efficacy of medical treatment modalities in muscle injuries, clinicians should always remember the 'primum non nocere' ('first do no harm') dogma of Hippocrates. Frankly, it should also be acknowledged that the popularity of several of these therapies is the result of clever marketing strategies rather than a solid evidence base. In the continuous pursuit of accelerated and improved muscle recovery after injury, clinicians must withstand the pressure to perform interventions that have an insufficient evidence base.

Although modifying aspects of muscle healing may seem reasonable to optimize healing after injury in theory, there is

growing insight that muscle healing after injury is a complex process, resulting in the remarkable regenerative capacity of muscle tissue. Introduction of any treatment that interferes with this process should be done cautiously and only after a thorough assessment of its efficacy in high-quality intervention studies. At present, it is often the other way around.

The current available evidence does not support any of the available interventions in addition to active rehabilitation for acute muscle injury. Beware to do no harm.

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