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Medical Treatment of Muscle Lesion

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1. Introduction

Though muscular lesions are the most common injuries in sport, there is limited evidence for the majority of management techniques. In particular, treatment aimed at minimizing the risk for recurrent muscle injuries has progressed little in the past few decades. None of the medical treatment currently used in clinical practice is supported by strong scientific evidence.

In the following chapter we will perform a short analysis of the main medical interventions for cases of muscle strain.

2. Immobilization/Mobilization

Immobilization has been shown to result in beneficial effects in the very early phase of muscle regeneration as it appears to provide the new granulation tissue with the necessary tensile strength to resist the forces created by muscle contractions [1,2]. This can be achieved simply by applying rigid adhesive taping. The use of crutches is also recommended in cases of major lesions. After the first few days, early mobilization should commence. This provokes more rapid and intensive capillary development in the injured area, better regeneration of muscle fibers, and more parallel orientation of the regenerating myofibers in comparison to immobilization, which was the previously preferred treatment for injured muscle [3,4].

3. RICE protocol

The first treatment of a muscle lesion, as with any other injured soft tissue, normally consists of the RICE protocol (Rice, Ice, Compression and Elevation). The rationale behind this

treatment is mainly to reduce hemorrhage. However, there are no randomized control trials (RCTs) which have proven the effectiveness of using RICE for soft tissue injury. However there is evidence on the effectiveness of the single components of the RICE regime [3,5].

3.1. Rest

Rest prevents an increase in the lesion gap which can occur as a consequence of the fibrotic tissue that forms with healing of the muscle lesion [4,6]. Rest also reduces the hemorrhage associated with the lesion.

3.2. Ice

There is evidence that ice utilization in the early stages of soft tissue injury is associated with a reduced haematoma and inflammatory process and therefore a quicker regenerative process [7,8].

3.3. Compression

Despite the fact that compression it has been demonstrated to reduce the blood flow in the injured area, its effectiveness is still controversial. In fact, there is no evidence,, that compression may accelerate the healing process in a muscle strain.

However, the clinical recommendations are usually to perform a combination of icing and compression for a period of 15-20 minutes, repeated in 30-60 minute intervals. This protocol has been demonstrated to reduce the intramuscular temperature to between 3° and 7° C, thus decreasing the blood flow by approximately 50% [9,10].

3.4. Elevation

It is advised to elevate the injured body part in order to decrease the hydrostatic pressure and therefore the interstitial fluid within the lesion itself.

4. NSAIDs

Experimental animal models of muscle injury have been used to examine the effect of NSAIDs on healing. These models have mostly demonstrated no effect on muscle healing, no reduction in muscle strength and no altered cytoarchitecture after injury (Jarvinen et al, 1992).

Studies conducted on humans subjects examining the effect of short courses of NSAIDs on acute muscle injury are contradictory [12,13,14,15,16].

While some investigations have not found any effect of NSAID administration on muscle recovery, there are several reports supporting a protective effect of NSAID medication, typically characterized by a lesser degree of muscle damage and functional deficit in the early period after injury.

One research study showed that Diclofenac taken prior to a strenuous exercise program produced lower levels of histological muscle damage in athletes compared with athletes who received placebo medication [17]. In addition, Naproxene has been demonstrated to decrease muscle pain post strenuous exercise [18], while ibuprofen proved to be less effective [19].

However, generally, in patients with acute hamstring muscle injury who were undergoing physiotherapy, the administration of NSAIDs had little effect on pain assessment or muscle performance.

It can be concluded that the short-term use of NSAIDs in muscle injury reduces pain and the time to return to full activity. Conversely, the few studies that have followed the repair process over a longer period of time suggest that any apparent benefit of NSAID treatment in the short term is not maintained in the long term and may result in a higher incidence of GI and CV adverse effects (ref).

An alternative to NSAIDs for analgesia is acetaminophen, which can be considered as effective as NSAIDs for pain reduction after musculoskeletal injury [20].

The prophylactic use of NSAIDs to prevent inflammation and pain that may accompany normal training and activity currently lacks scientific evidence and its use may create harmful collateral effects.

However, it is also worth considering that from a purely clinical viewpoint, the use of NSAIDs' for muscle lesions may possibly predispose to injury recurrence as a result of pain masking.

Finally on a biological level, a number of basic science studies showed that NSAIDs may inhibit muscle regeneration in the first stages of healing, which relies on the inflammatory process.

5. Injective therapy

Many injection protocols have been proposed for the treatment of muscle lesions. Corticosteroid injections, Muller-Wolfart protocol, prolotherapy, classic mesotherapy, mesotherapy with omeopathic products and others have been suggested. However, no protocol has strong scientific evidence, as there are no RCTs supporting their use. Although anecdotal clinical data and expert opinion can be found on each technique and their use in athletes [21], unfortunately, currently there is insufficient scientific evidence to support the use of such protocols..

Further research is required to assess the efficacy of these injection therapies preferably with the integration of various techniques in order to obtain a holistic approach.

5.1. Corticosteroids

The use of corticosteroids in the treatment of muscle injuries is controversial. There are concerns due to the risk of incomplete healing or rupture of the healing tissue. Moreover,

any injection carries the risk of introducing infection. Experiments on animal models have been promising. An accelerated recovery of contractile tension after a single dose injection of corticosteroids provided soon after a muscle strain, was proven effective in rats, without any major adverse effects recorded [22].

Unfortunately, evidence is lacking on human subjects. To our knowledge, only two studies have been performed on athletes, both of which show promising results. However, neither has been confirmed by other researchers. The first research study [23] retrospectively reviewed American football players treated with corticosteroid intralesional injections for acute hamstring strain. The results demonstrated that the return to play time was reduced and that there were no adverse effects. In the second study [24], baseball pitchers were treated with corticosteroid injection for abdominal strains. This treatment resulted in a quicker recovery and return to play, without any reinjuries. Unfortunately, these studies contained many limitations which warrant further research studies before considering an implementation of such treatment.

5.2. Traumheel®

A frequently used preparation for the symptoms associated with acute musculoskeletal injuries, is Traumheel® (Biologische Heilmittel Heel GmbH, Baden-Baden, Germany). This is an antiinflammatory and analgesic homeopathic remedy combination that contains small amounts of belladonna, arnica montana radix, Aconitum napellus, chamomilla, Symphytum officinale, Calendula officinalis, Hamamelis virginiana, millefolium, hepar sulphuris calcareum, and mercurius solubilis, plus a fixed combination of biological and mineral extracts. Its use in sport medicine is based on its effect on pain (Atropa belladonna), inflammation (Echinacea), bruising (Arnica montana), wound healing (Matricaria recutita, Calendula officinalis), bleeding (Achillea millefolium), edema (Mercurius solubilis), and infection (Hepar sulfuris). All these effects may have a positive effect on muscle strain healing, however, its ability to accelerate healing has not yet been demonstrated [25]. Traumheel is described to be well tolerated and without adverse effects, which are important characteristics for a product to be utilized on athletes.

5.3. Actovegin

Actovegin® is a deproteinised haemodialysate produced by Nycomed Austria GmbH. It enhances aerobic oxidation in mammals, which improves absorption of glucose and oxygen uptake in tissue. It does not contain growth factors or hormone-like substances, however, since it has been thought to be a performance enhancing agent, Actovegin has been banned for a period by WADA. This is despite the fact that there is evidence in the literature, that oral Actovegin does not have any anabolic or ergogenic activity in terms of muscle development [26]. There is also some scientific evidence that Actovegin may facilitate healing and reduce time of return to play following soft tissue injury [27]. However, its use is mainly based on expert opinion, which are reporting good results on the use of Actovegin in athletes.

6. Mesotherapy

Mesotherapy is a term that derives from Greek *mesos* (middle) and *therapeia* (therapy). It employs multiple injections of pharmaceutical and homeopathic medications, plant extracts, vitamins, and other ingredients into subcutaneous fat. This technique has been purposed and implemented by Michel Pistor (1924–2003), a French physician which performed the first clinical research on this treatment. Mesotherapy is quite a diffusely used treatment method, especially in the sport medicine field. However there are concerns over its efficacy due to the lack of strong scientific evidence supporting its use.

In particular, there is no scientific research on the use of mesotherapy for muscle strains. However, international guidelines purpose weekly sessions to be started as soon as possible after the lesion. Common substances proposed are an anesthetic, a vasodilator and an anti-inflammatory with deep injection techniques and a miorelaxant with superficial injection techniques in the region of the lesions.

7. Prolotherapy

Prolotherapy derives its name from "proliferation therapy," or "proliferative injection therapy". It has also been called "regenerative injection therapy" ("RIT"), and some contemporary authors name the therapy according to the injected solution. The precise mechanism of action is not known. It involves injecting a non-pharmacological and non-active irritant solution into the body. This is hypothesized to reinitiate the inflammatory process which deposits additional new fibers, thereby repairing lax tendons or ligaments and also possibly promote the release of local growth factors. However, the precise mechanism of action still remains unknown. It has been used for approximately 100 years, however, its modern application can be traced to the 1950s. This was when the prolotherapy injection protocols were formalized by George Hackett, a general surgeon in the U.S., and were based on his clinical experience of over 30 years. The concept of creating irritation or injury to stimulate healing has been recorded as early as Roman times when hot needles were poked into the shoulders of injured gladiators [28].

There are no trials on the use of prolotherapy in a population with acute muscle tears. There is some evidence for its use in chronic pathologies such as LBP [29], groin pain [30], and knee OA [31]. However, existing evidence is inconclusive. Its actual use is based on "expert opinion" and some practitioners advocate a positive impact of the use of prolotherapy in athletes in term of return to play timeframes.

8. Antifibrotic agents

Many reports indicate that the overproduction of transforming growth factor (TGF)- β in response to injury and disease is a major cause of tissue fibrosis both in animals and humans.

It has been shown that anti-fibrotic agents (suramin which acts as a TGF- β 1 inhibitor by competitively binding to the growth factor's receptor) inhibits fibroblast proliferation and neutralizes the stimulating effect of TGF- β 1 on the proliferation of fibroblasts in vitro (ref). An in-vivo injection of suramin (5.0 mg) two weeks after strain injury reduced muscle fibrosis and enhanced muscle regeneration, thereby leading to improved muscle strength recovery (ref). The clinical use of suramin has already been approved by the Food and Drug Administration. Although suramin can lead to side effects when administered intravenously, local intramuscular injection may not elicit the same deleterious effects and could be very useful in improving muscle healing. However, further studies are necessary in order to assess the safety and the effectiveness of this treatment [32].

9. Hyperbaric oxygen therapy

Theoretically, the restitution of blood supply to the injured area is fundamental for the regeneration process, in particular for the myotubes which depend solely on aerobic metabolism as the source of energy required for their regeneration. This is the basis for the application of Hyperbaric Oxygen Therapy in muscle lesions. Clinical trials are lacking, however a recent experimental study showed positive effects of this treatment on muscle injury. Further research should assess the clinical outcome of Hyperbaric Oxygen Therapy before it may be suggested for this kind of pathology [33].

10. Platelet Rich Plasma (PRP)

Platelet-rich plasma (PRP) is derived from centrifuging whole blood and has a platelet concentration higher than that of whole blood. It is the cellular component of plasma that settles after centrifugation, which contains various growth factors (GFs). Unfortunately, despite its increasing popularity as a treatment for soft tissue injuries, there remains neither a uniform terminology nor an understanding as to what constitutes PRP. Terminology in common usage includes platelet enriched plasma (PEP) and plasma (preparation) rich in GFs (PRGFs); however, many of these terms are associated with commercial products [34].

Based on a limited number of animal model studies that have shown a positive impact of isolated recombinant GF on muscle regeneration, the application of PRP to an injured muscle is thought to accelerate regeneration, enhance healing and decrease the risk of re-injury. Studies using animal models show a reduction in the recovery time, in particular on the early stages of reparation. Early clinical trials, though mainly consisting of level 3 and level 4 evidence, show an improvement of healing for muscle injury in terms of earlier return to play [35,36].

The use of PRP as a source of GF seems attractive because it is easily obtainable with a simple apparatus and is relatively affordable. Moreover, its use has rapidly gained the support of the

popular media as a result of its purported “natural” properties, high level of efficacy, and lack of side effects.

Limited risk of infection is linked to any injective technique but risk may be limited by the use of a correct sterile procedure. Moreover, the utilization of autologous blood guarantees the elimination of the risk of allergic reactions and the possibility to become in contact with infected blood. Previously, bovine derived drugs sometimes led to potentially lethal pathologies of coagulation and they have since been withdrawn from the market.

It seems that PRP does not have a systemic effect, but there is minimal research demonstrating this fact.. Nowadays, there is no evidence that PRP has a carcinogenetic effect. This is also supported by the mechanism of action as growth factors do not penetrate the cellular membrane; therefore they cannot generate DNA mutations. Actually, no other carcinogenetic mechanisms are known, so in general, PRP technique seems to be safe in this respect.

The risk of local complications linked to the use of the PRP technique seems to be more disputed. However, local tissue degeneration, muscular architecture alteration, increasing recurrence rate are all complications which have been taken into consideration in both basic and clinical research. Currently, no studies support such complications.

Different considerations regarding the risk of fibrosis are also of concern. TGF- β 1 is the main regulating factor of fibrosis. Thus, it can be speculated that an incorrect use of growth factors may lead to an increase of fibrosis and a potential negative outcome in term of return to play.

From an anti-doping perspective, the topical use of growth factors has been approved. This was probably due to the demonstrable absence of any systemic effect of growth factors.

However, despite its elevated public profile and theoretical benefits, there remains many unanswered questions surrounding the use of these techniques in the management of muscle injuries, and the burden of proof remains with scientists and practitioners to confirm or refute the clinical utility of this technology.

One of the main issues seems to be determining the appropriate PRP concentration to use. Different products are present on the Orthopedics and Sport Medicine market.. However, each product presents different protocols and methods to concentrate the platelets resulting in products with different biological properties. Even if most of the products yield 10% (that means 2ml of PRP for every 20ml of blood withdrawn), their concentration of growth factors is different. It has been estimated that the growth factor concentration may vary from 3 to 27 times blood concentration. Considering that a low concentration of PRP may not give satisfactory clinical results and an excessively elevated concentration may start inhibitory processes, it appears fundamental that the concentration should be carefully monitored and controlled. Some authors indicate that the ideal concentration of PRP is four to six times the normal platelet blood concentration.

Another source of discussion is related to the presence (or absence) of White Blood Cells (WBC) in PRP. It is unclear whether the presence of white cells in PRP is an advantage or an obstacle to healing. In fact, if the anti-infective potentialities of WBC may be of benefit, their proinflammatory nature may actually be counterproductive to healing. This premise is consistent

with the current understanding of the potential negative effects of inflammatory mediators on muscle healing.

Currently, it remains unclear what the impact PRP, with or without the presence of WBC, may have on the inflammatory cascade following muscle injury [37]. In addition, each muscle has distinct anatomical and physiological characteristics, and as demonstrated in rabbit studies, also has distinct GF response profiles to injury. Thus, each location of injury may theoretically require different PRP preparations.

Another dilemma is the method of PRP subministration. The physiological impact on an acute muscle injury of a bolus infiltration of an unknown concentration of platelets, and thus of GF, and other factors that are found in any PRP preparation is still a mystery. Animal studies suggest that a bolus dose of recombinant GF is not as effective as sustained release. However, with the current utilized technique, all GFs are released within 1 hour from their application and this may potentially reduce their effectiveness.

The timing of application is also a source of discussion. Apparently, the first ten days (inflammatory and regenerative phases) after the lesion may constitute the ideal moment for PRP injection. An application two to three weeks after an injury, with an environment preferentially upregulated by platelet TGF- β 1, may actually favor fibrosis over regeneration.

Finally, although the physiological milieu should be sufficient to activate platelets, it is unknown if a preinfiltration activation is necessary [38].

In conclusion, the use of PRP is actually based on anecdotal reports and expert opinion (Level IV evidence). Further research is necessary in order to confirm or deny the effectiveness of PRP in muscle strain. However, the apparent safety and facility of application suggests that sport medicine practitioners should consider PRP when treating elite athletes, for whom such innovative approaches may be fundamental in terms of success.

11. Stem cells

Stem cells are biological cells found in all multi-cellular organisms that can divide (through mitosis) and differentiate into diverse, specialized cell types and can self-renew to produce more stem cells. There are three accessible sources of autologous adult stem cells in humans: bone marrow, adipose tissue (lipid cells) and blood. Scientists believe that stem cell therapy has the potential to significantly revolutionize medicine. A number of adult stem cell therapies already exist, particularly bone marrow transplants that are used to treat leukemia. There is also the potential for a wider variety of diseases to be treated with stem cells (cancer, Parkinson's disease, spinal cord injuries, Amyotrophic Lateral Sclerosis, Multiple sclerosis, and some forms of myopathies). Successful trials on the implantation of stem cells directly on detrusor muscle to treat urinary incontinence have opened the way to their use in muscle pathology. Clinical trials have commenced, but the clinical use of stem cells for the treatment of muscle strains is still for the future. One concern of stem cell treatment is the risk that transplanted stem cells could potentially form tumors [39].

12. Conclusion

Medical treatments of muscle injuries have limited scientific evidence. Their use is often based on level four studies and on personal clinical experience. While /immobilization/mobilization and RICE seem to be established protocols and “classic” treatment (NSAIDs, painkillers) appears to have a limited impact, the effectiveness of any new options for treatment has yet to be demonstrated in sport medicine. While further research is warranted, the sharing of clinical experience amongst sport medicine practitioners seems fundamental in order to perform the best “clinically-based” choices. Our personal experience is that patient reactions to medical treatments are often unpredictable. The same treatment applied to the same kind of lesion in different subjects may have a completely different outcome. However, in our personal clinical experience, oftenthe same patient reacts well to the same treatment when proven successful with a previous injury. The placebo effect component of treatment is undeniable, however there could also be benefits which are highlighted more in some patients and less in others. Our conclusion is that different techniques must be considered when approaching management of a muscle lesion, due to the fact that no one technique has a strong scientific evidence base to its effectiveness. The physician should try to tailor the therapeutic choice on the bases of the lesion’s characteristics, the patient needs and expectations, and the subjective reaction to different treatments in the past. Of course, the basic Hippocratic principle of the treatment safety (“Primum, non nocere”), should be always respected, in particular when approaching these kind of lesions which have been proven to heal very well without any therapeutic intervention.

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