



Muscle injuries and PRP: what does the science say?

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Muscle strains and contusions are extremely common in sport and account for significant time loss.^{1,2} The healing process can be slow, and reinjury is common.³ Recently there has been significant interest in the use of platelet-rich plasma (PRP) to enhance healing. In this issue, Mei-Dan *et al* (see page 618) discuss the biological background and clinical rationale for the use of PRP.⁴ This paper will address the use of PRP to enhance the speed and quality of repair in muscle injury.

FIRST PHASE OF HEALING

When muscle is injured, capillary rupture and bleeding leads to a sequence of highly coordinated events. The first phase is the degeneration/inflammation phase and is characterised by the rupture of myofibrils and their ensuing necrosis. A haematoma forms between the stumps of the ruptured myofibrils, and inflammatory cells invade.³ Platelets arrive, adhere to the exposed collagen, become activated and immediately begin to release growth factors and cytokines further amplifying the inflammatory process. Neutrophils begin to migrate to the area and arrive as early as 1–2 h after injury.⁵

The neutrophils are phagocytic and contain over 40 hydrolytic enzymes. Their activation leads to phagocytosis of debris, and also to the release of oxygen free radicals and proteases. This release of toxic molecules from the neutrophils can lead to secondary damage to the muscle.^{2,5,6} In fact, the time of peak muscle injury correlates to the time of maximal neutrophil invasion and not to the initial injury.⁵ In models where neutrophils were depleted prior to injury or their respiratory burst blocked, the amount of damage was significantly reduced.^{7,8} There is debate as to whether or not neutrophils play any type of beneficial role in muscle injury, but it is clear they may be detrimental.^{1,2,5}

Macrophages follow the neutrophils and have many roles, but do not appear

to have a role in secondary muscle injury. Macrophages are phagocytic and switch from a proinflammatory type to an anti-inflammatory phenotype as the muscle begins to regenerate.² In addition, macrophages prevent muscle cells from undergoing apoptosis and also secrete cytokines and growth factors.

REGENERATIVE PHASE: MAKING NEW MUSCLE

After a few days, the regenerative phase begins. Satellite cells are activated and produce myoblasts, which eventually fuse with other myoblasts resulting in mature, multinucleated myofibres.¹ This is the key phase in muscle regeneration. Depending on the growth factor milieu, the satellite cells can be influenced to become either myoblast, which produce muscle cells, or myofibroblasts, which produce fibrotic scar tissue. In particular, insulin-like growth factor 1 (IGF-1) appears to play a critical role in enhancing muscle regeneration by stimulating myoblast proliferation, differentiation and myofibre protein synthesis and hypertrophy.⁹ IGF-1 is found in trivial amounts in platelets, and most IGF-1 in PRP will be present in the original plasma.¹⁰ Conversely, transforming growth factor β 1 (TGF β 1) appears to encourage the formation of fibrosis by stimulating the production of extracellular matrix proteins and inhibiting their degradation.¹¹

REMODELLING AND FIBROSIS

In the second week, remodelling begins and involves the maturation of the regenerated myofibres, retraction and reorganisation of the scar tissue and recovery of functional capacity.³ Fibrosis is the key inhibitor of complete muscle healing.¹⁰ The fibrotic tissue provides an early framework for ruptured myofibres. As the fibrous tissue becomes increasingly dense, it restricts the regeneration of the muscle by preventing the stumps of the myofibres from rejoining and may prevent axons from creating new neuromuscular junctions.^{1,11} Fibres that are not innervated will ultimately undergo atrophy.

CAN TREATMENT ACCELERATE MUSCLE HEALING?

There have been many attempts to speed muscle healing. Traditionally, ice, rest, anti-inflammatory medications and rehabilitation have been the mainstays of treatment. The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been questioned. NSAIDs increase the expression of TGF β 1 and decrease prostaglandin E2, which has a key role in the proliferation and differentiation of satellite cells.¹ Recent studies have shown that NSAIDs likely tip the delicate balance of regeneration versus fibrosis toward fibrosis (scar).

In Europe, there is great enthusiasm for a combination of Traumeel S, Actovegin and local anaesthetic which is injected into injured muscle and in the corresponding area of the lumbar spine, despite the fact that there is no good clinical evidence of efficacy and little theoretical scientific basis. This dichotomy of practice and science has been debated by Orchard *et al*¹² and McCrory *et al*¹³ in recent issues of *BJSM*.

With PRP, the growth factors are provided in physiological proportions with the hope this will accelerate healing and lead to a balance of proliferative and inhibitory effects. Although this has theoretical and basic science underpinnings (if perhaps a little simplified) there has been little published quality research on the use of PRP in muscle.

ANIMAL/LABORATORY STUDIES

PRP has been shown to stimulate cell migration and myofibroblastic differentiation in vitro.¹⁴ Hammond *et al* noted increased healing of repetitive muscle injury in rats, but not in those with injury due to a single lengthening contraction.¹⁵ Wright-Carpenter *et al* found improved healing of muscle injuries in mice with autologous conditioned serum.¹⁶ Autologous conditioned serum is serum containing released growth factors, essentially activated PRP, which produces a lower yield of growth factors than most PRP.

HUMAN STUDIES

Studies in human muscle injury are few and of low methodical quality. Wright-Carpenter *et al* treated 18 professional sportsmen with a variety of muscle strains with ACS and reported improved healing by almost a week compared with a similar group of 11 professional athletes.¹⁷ The numbers in this study are small, the muscle strains are heterogenous, and there was no true 'control' group, as the 'control

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group' had been treated with Traumeel S and Actovegin, and was reviewed, retrospectively. Sanchez reported in a poster presentation a case series of 20 professional athletes with hamstring muscle injuries who received PRP therapy that functional recovery was regained in half the expected time, but we have found no peer-reviewed publication from this poster (Sanchez 2005).

CLINICAL ADVICE: 2010

Serious questions remain as when and how to use PRP in muscle injury. A muscle is an actively healing, acutely inflammatory entity, and there remains potential to affect both the timing and the quality of repair adversely. PRP is heterogenous, and it may be that certain types of PRP are more effective than others. The timing, quantity and frequency of injections required are also in question. Given the pathophysiology of muscle healing, if PRP is used, the following can be considered:

- ▶ PRP should not be administered in the first 24 h after injury. Attempts should be made to limit the 'secondary injury' using traditional means of controlling inflammation, namely compression, elevation and ice;
- ▶ a leucocyte-poor product may mitigate the potentially adverse affects of neutrophils;
- ▶ a product which includes a higher proportion of plasma may have increased

levels of IGF-1 and potentially enhance healing and decrease fibrosis.¹⁰

Although acute muscle injuries are typically self-limited and heal if given enough time for recovery, they result in significant morbidity and time lost from competition. There is theory and preliminary evidence regarding the effectiveness of PRP, but its use is still investigational. It is incumbent upon physicians using this treatment to disclose its experimental status and to follow outcomes in a structured way. Further studies are needed to establish the effectiveness, indications and protocols for using PRP in the treatment of acute muscle injuries.

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