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Review Article

Should We Treat Soft Tissue Injuries with Actovegin?

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Abstract

Actovegin is a biological drug produced from deproteinised hemodialysate of calf serum with over 50 years of history for its clinical use. There have been many *in vitro* studies to speculate its potential role and mechanism of action in cells; due to the nature of this drug and serum based culture techniques for most *in vitro* experiments, presumptuous conclusions and claims from these studies on performance enhancement should be cautiously interpreted. There have been well-designed human *in vivo* studies suggesting it does not enhance human performance, and has potentially good clinical applications to treat injuries, strokes and diabetes. Recently, evidence has emerged suggesting Actovegin has anti-inflammatory and anti-apoptotic effects on injured tissues; further clinical research is needed to define these effects. This article also provides a narrative review of Actovegin summarizing outcomes from recent publications.

Keywords: *Actovegin; Doping; Soft Tissue Injury; Treatment; Sports; Orthopaedics*

Muscle injuries are common in sport and are best treated using a regime of rest, immobilization, compression and physical therapy [1]. However, this so-called "knowledge" is based upon long-standing convention and expert opinion, which at best could be classified as level 4 evidence [2]. It has been suggested that injection therapy might have a role to play in the treatment of muscle injuries [1,3]. Different treatment options such as growth factors have been explored and have demonstrated encouraging therapeutic results [1]. However, due to anabolic properties, treatment approaches incorporating growth factors, autologous blood and autologous conditioned serum are prohibited by the World Anti-Doping Agency (WADA) [4].

Recent developments in Sports Medicine have led to many substances being used in the context of injection therapy [5]. Platelet rich plasma (PRP) and autologous conditioning serum (ACS) have become popular substances of choice for injection therapies – it is alleged that such treatments facilitate muscle healing by optimizing provision of growth factors involved in the regeneration of muscle, as demonstrated by several animal studies [6-8]. A recent double-blind, randomized controlled trial by Reurink., et al. [8] found that there were no statistical or clinical differences between their PRP and placebo groups in the treatment of muscle injuries [8]. Further, there are currently no universally accepted PRP preparation protocols to ensure consistent concentration and quality control between individual injections. The principle of using blood products as a drug to treat muscle is not new, as biological drugs form a major part of pharmaceutical drug development. As medicine has evolved and scientific knowledge continues to develop, a number of "older drugs" could be used in the effective treatment of acute muscle injuries.

Actovegin (Takeda Pharmaceutical Company Ltd, Osaka, Japan) is a biological drug produced from deproteinised hemodialysate of calf serum with a high standard of quality control (Figure 1). There are over 50 years of history for its clinical use with much *in-vitro* as well as clinical evidence to support its efficacy [9]. Indeed, the role of calf blood derivatives in the maintenance of *in vitro* cellular viability and survival is well established, for example, it is commonly used in the form of fetal bovine serum (FBS) supplement in tissue culture media, and the success of many *in-vitro* experiments is dependent on the batch of FBS employed. Therefore, Actovegin can be viewed as a highly controlled and approved form of FBS with an excellent clinical track record for use in human participants.

As noted above, the active component(s) and mechanisms of action of Actovegin have yet to be identified. There is limited supporting evidence concerning the role it might play in the treatment of muscle injuries, and there is no objective evidence pertaining to its properties as an ergogenic aid. Several published clinical studies have investigated its role in muscle injuries with promising results [10,11]. Anecdotally, an unpublished case series with Dr. Hans-Wilhelm Müller-Wohlfahrt's Actovegin, that used a mixture injection regimen, seems to have produced encouraging results, and many high-profile athletes have endorsed the use of Actovegin for the treatment of muscle injuries. Recently, Lee., *et al.* reported on the effects of standalone Actovegin injection therapy, which reduced return to play time in injured, professional footballers [10].

Actovegin has recently received a great deal of media attention in the field of Sports Medicine. In addition to its use in the treatment of injury, many anecdotal testimonies have suggested that Actovegin is ergogenic, and has the potential to improve athletic performance. In December 2000, the International Olympic Committee (IOC) banned Actovegin under the classification of blood-doping agents. However, two months later the IOC lifted the ban as no indisputable evidence demonstrated that Actovegin had ergogenic properties [12]. In a study with 567 diabetic patients, no improvement of muscle strength or condition was found after treatment with Actovegin infusion for 160 days [13]. A more recent study by Lee., *et al*. [14] provided definitive evidence that Actovegin does not have the potential to enhance athletic performance. These investigators performed a blinded, crossover peak aerobic capacity study in healthy human participants with intravenous Actovegin compared to placebo saline solution as well as a baseline control. No significant differences were observed in peak values for aerobic power, blood lactate concentration and blood glucose concentration. Additionally, values of gross and net efficiency, and calorific energy equivalents associated with VO_2 were similar [14].Their results, therefore, confirmed that a maximum, permitted intravenous dose of Actovegin did not improve human peak aerobic capacity [14]. Currently, intravenous and intramuscular injections of Actovegin are permitted during training and competition according to the latest search in the Global Drug Reference Online, which is approved by UK Anti-Doping (UKAD), the Canadian Centre for Ethics in Sport (CCES), the United States Anti-Doping Agency (USADA) and WADA [4,15].

As a deproteinised hemodialysate, Actovegin does not contain peptide, growth factors or hormone-like substances [16]. Many studies have attempted to identify the active ingredients in Actovegin, but have been unsuccessful. Studies *in vitro* have suggested that Actovegin promotes oxidative metabolism and shifts the redox-balance of cells in the direction of oxidized substrates, which might protect against hypoxic cell injury [16]. The most important goal of any post-ischaemic therapeutic strategy is the early interruption of the process of cell-damaging events and, ultimately, the avoidance of cell death. Because Actovegin promotes oxidation and energy production, its efficacy was assumed to benefit post-ischaemic metabolic events. However, current experimental results from a series of studies with human macrophages by the authors using RT-PCR and flow cytometry have tentatively demonstrated a possible role of Actovegin as an anti-inflammatory agent: this is consistent with the finding that Actovegin can reduce recovery time in mild muscle injuries. Furthermore, incubation of human muscle biopsies with Actovegin resulted in the up-regulation of a number of genes including the anti-apoptotic gene TNFRSF1b. Of course, more research would be required to ascertain the biological roles of Actovegin in inflammation and cell survival, but these authors' work has indicated additional roles of Actovegin not directly related to cellular metabolism.

Søndergård., *et al*. [17] suggested in their *in vitro* study with human skeletal tissue, that Actovegin can affect mitochondrial oxidative function which is similar to many other *in vitro* studies with different cell types. However, they also made unsubstantiated, speculative claims that this finding could be translated to performance enhancement in humans. The muscle cells in their experiment were treated with a cocktail of chemicals as well as a cytotoxic detergent, saponin, which damages the cells' membrane [18]. Saponin is extremely poisonous to marine creatures, and it can be used as a cytotoxic chemotherapy drug in the treatment of cancers with major side effects [19]. It stimulates both the Th1 immune response and the production of cytotoxic T-lymphocytes, with the serious side-effects of haemolysis of the cells [19]. Clinically, saponin has been used in clinical trials but toxicity associated with sterol complexation remains a major problem [18,19]. Therefore, the experiment performed by Søndergård., *et al.* [17] should be viewed as an *in vitro* cell membrane injury study, similar to the scenario of grade I or II muscle injuries, but most certainly should not be interpreted as a performance-based study. As mentioned earlier, work *in vivo* by Lee., *et al.* [14] has shown Actovegin did not improve human peak aerobic capacity. Therefore, the *in vitro* finding from Søndergård., *et al*. [18] will not necessarily translate to an improve performance in terms of aerobic capacity in humans. Nevertheless, results from this study were interesting as they suggested Actovegin had an effect on injured human muscle tissue, which further supports the clinical use of intramuscular Actovegin injections therapy for injuries as used by Lee., *et al*. in their clinical study using a group of professional footballers [10].

Although the exact mechanism of action of this biological drug is yet to be fully understood, recent *in vitro* studies suggest that it has a positive effect on different injured cell types ranging from neuroblastoma cells [20], neutrophils [21] and renal cells [22]. It is clear that Actovegin is not a performance enhancing substance, but has an excellent profile to promote cell repair [9,23]. Further scientific effort of this drug should, therefore, be focused on its application in clinical medicine such as the ARTEMIDA study in patients with post-stroke cognitive impairment [24], wound healing and in the treatment of skeletal muscle injuries [9].

The use of intramuscular Actovegin injections in the treatment of muscle tears was first published by Pfister and Koller [11]. Their partially blinded, case control study included 103 patients, and demonstrated a reduction in recovery time from 8.3 weeks for the control group to 5.5 weeks in their treatment group [11]. However, patients in this study were recruited from a wide variety of sports and at different competitive levels. A criticism of this study relates to the fact that the treatment regimen and rehabilitation protocols employed were not fully standardised, and Actovegin was mixed with local anaesthetics before being injected; it is, therefore, possible that this would have altered the pharmacodynamics and pharmacokinetics of the drug. The final outcomes were based on subjective observations made by patients and clinicians, and there were no objective pre-injury data to compare outcome characteristics to. Lee., et al. [10] published a study associated with the intramuscular injection of Actovegin used to treat grade I hamstring injuries. Players in the Actovegin treatment group were able to return to play 8 days earlier compared to physiotherapy alone ($P = 0.033$)[10]. The patients in this study were professional football players from the same club, hence their physical fitness was comparable and the rehabilitation protocol used was standardised [10].

It is evident, that Actovegin has been clinically used for more than 60 years, and it is evident that the oral, topical, intravenous and intramuscular administration of the drug is safe [9]. Many official governing bodies including WADA, UKAD, CCES and USADA do not prohibit its use. However, it should be noted that Actovegin is not on the British National Formulary and Medicines and Healthcare products Regulatory Agency in the UK, and the Food and Drug Administration in the USA has not approved its use.

The career lifespan of a professional athlete is often short lived, and a shortened recovery time could translate to increased game play and benefit to the team and club. Due to the unique relationship between sports physicians and athletes, individuals are often under pressure to seek the latest "active" or "cutting edge" treatments [2], and athletes are often not interested in being part of a Clinical Trial. Therefore, it is not always possible to recruit a large sample of participants who are professional athletes. There is also much publicity about the use of Actovegin as an ergogenic aid, but such assumptions are founded on speculative and questionable anecdotal evidence. Actovegin is not licensed to treat muscle or soft tissue injuries, and the evidence relating to its effectiveness in this regard is limited. Critics have suggested that Actovegin is nothing more than "snake oil"[2]. Nevertheless, there is published evidence demonstrating its potential for clinical efficacy and safety [13,10,24].

Sport-related muscle injuries are very common, and result in significant morbidity and time lost from training and competitions. Recently, a number of novel treatment options have appeared in the market place. The use of platelet-rich plasma (PRP) and Actovegin has attracted significant interest in Sports Medicine. Although evidence is limited for both of these substances, PRP has received many so-called "expert opinions" and its use has been encouraged. In contrast, views associated with the use of Actovegin are somewhat more tainted, but with the exception of subjective, anecdotal opinion, there is no clear evidence that Actovegin has any ergogenic qualities. Evidence based medicine is an important aspect in modern medicine; we must not reject treatment base on limited evidence. However, we should be cautious in our consideration and interpretation of available evidence, strike a balance between potential risk and benefit associated with treatment, and tailor the use of any therapeutic intervention to the individual athlete's needs.

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