Our Experience on Actovegin, is it Cutting Edge?

Abstract

Muscle injuries are one of the most common sport related injuries, their incidence varying from 30–55% in all sports injuries. They account for the loss of 90 training days and 15 matches per club per season in elite football (soccer). In recent years, the use of Actovegin® in sports medicine has caused a lot of controversy in many sports disciplines. Although it is unlikely for this deproteinised substance to have oxygen-enhancing capacity, there is an anecdotal belief that Actovegin® can increase an athlete's performance. Actovegin® is produced by Nycomed Austria GmbH and has been used by doctors across Europe, China and Russia for over 60 years. Nevertheless, very little is known regarding the effects of Actovegin on muscle injuries. This article reviews the current evidence on Actovegin®, its legal status with sports governing bodies and its potential role in sport injuries. We will also report our experience with this drug in treating muscle injuries. In this pilot study, players in the Actovegin treatment group were able to return to play 8 days earlier (95% CI −1.249 to −14.7510) compared to physiotherapy alone (p=0.033). No adverse reactions were recorded in any of the participants.

Clinical Relevance

There are numerous anecdotal beliefs and there is much media attention regarding Actovegin injection therapy, but the published scientific evidence and clinical trials are largely ignored. This short review will “reintroduce” the scientific evidence around this contentious topic and will aid sports clinicians to examine evidence with an open mind. From our experience with this pilot study, Actovegin injection therapy seems safe and well tolerated. Further objective evidence is needed before any meaningful conclusions can be drawn for this new treatment of muscle injuries.

Introduction

Muscle injuries are one of the most common sports related injuries, their incidence varying from 30–55% [13,27]. An audit published by The Football Association (FA) in 2004 suggested that 12% of all injuries were hamstring injuries. They are 2.5 times more common than quadriceps injuries [3,29]. In the 2 seasons from 1997 to 1999, 749 hamstring injuries were reported across the 91 British football clubs [29]. They accounted for the loss of 90 training days and 15 matches per club per season [29]. A recent prospective cohort study published with the Union of European Football Associations (UEFA) confirmed that hamstring injuries were the single most common injuries in professional football players, representing 17% of overall injuries [11]. Similar observations regarding hamstring injuries were reported by Bennell et al. [5] in Australian Rules footballers, with hamstring injuries accounting for 86.4 injuries per 10000 playing hours.

Hamstring injuries are often diagnosed and managed by the team clinician. Ultrasonography and Magnetic Resonance Imaging (MRI) can be useful in confirming the diagnosis and aiding the clinician to make decisions with regards to treatment. Rest, immobilization [13], physical therapy and sometimes non-steroidal anti-inflammatory drugs (NSAIDs) [23] have been the mainstay of therapy for grade 1 and 2 muscle injuries [14]. Immobilization can lead to improved granulation of the injured muscle and promote healing, but it will cause significant atrophy of healthy myofibers and joint stiffness [13]. Although some studies have shown that the administration of NSAIDs promotes muscle healing by reducing degenera-
tion and inflammation [1], other research has demonstrated that NSAIDs are detrimental to the entire healing process [19, 25]. Recently, new treatment options such as growth factor injection therapy have shown good therapeutic results. However, due to their performance enhancing and anabolic properties, growth factors are prohibited by the World Anti-Doping Agency (WADA) under section M1 and S2 of the WADA prohibited list [28].

In 2008, a best practice statement summarised that currently almost all our knowledge in treating muscle injuries has a basis of level 4 or level 5 [20]. This panel of experts also concluded that Actovegin injection therapy could be important in the treatment of muscle injuries [20]. Although its intramuscular use is not prohibited by the regulatory authority, World Anti-Doping Agency (WADA) [28], athletes and coaches have reservations about its use. In this paper, we have reviewed the evidence for Actovegin and report our experience with this drug in treating muscle injuries in our pilot study.

**Background**

Actovegin® is a deproteinised haemodialysate produced by Nycomed Austria GmbH. Clinically, it is used as an intravenous infusion to treat acute stroke [7, 10], postpartum haemorrhage [2] and as a topical form to treat skin ulcers [6]. Recently, it has also been reported to be used as an intra-arterial infusion to treat long bone fractures [15] and radiation damage [4]. Clinicians across Europe, China and Russia have used Actovegin for over 60 years [4, 18, 22, 30]. It contains physiological components, electrolytes and essential trace elements, 30% of organic components are amino acids, nucleosides, intermediary products of carbohydrates and fat metabolites [18]. It does not contain growth factors or hormone like substances, as it is ultra filtered to 6000 Daltons. It can be administered as tablets, topical formulations, injections or infusions via intramuscular, intravenous or intra-arterial routes [18].

Many studies have tried to identify the active ingredients in this mixture, but have been unsuccessful. Schoenwald et al. [24] suggested that the active fractions in Actovegin were strongly negatively charged and were thought to be phosphorylated and/or sulfated oligosaccharides of approximately 3000 Daltons in molecular weight and different to the IPO fraction reported by other studies. This fraction is also resistant to proteinase K digestion, which suggests that it is unlikely to contain peptides [24]. Actovegin also showed a synergistic effect on cell proliferation with growth factors such as Epidermal Growth Factor (EGF), Basic Fibroblast Growth Factor (bFGF), and Endothelial Cell Growth Factor (ECGF), causing an increase in cell numbers, increase activity of acid phosphatase and an improved level of thymidine incorporation compared to Actovegin alone [24].

Therefore, the active compounds in Actovegin are unlikely to be these growth factors or their derived fragments [24]. The trivial nutritive effects of Actovegin were excluded as a mixture of the same level of amino acids and substrates did not stimulate proliferation or have insulin like activity in vivo [24].

**Clinical Evidence**

Although the active ingredients within Actovegin are yet to be identified, there are many clinical studies to confirm its safety and effectiveness. There has been one case report of a possible anaphylactic reaction related to the use of intravenous Actovegin injection by an amateur sportsman. In this report, the so-called “anaphylactic reaction” was not confirmed with any biochemistry and the patient improved with antibiotics. The author later stated in the communication letter that this patient had taken Actovegin once before with no adverse reaction. Therefore, the most likely cause for this acute shock was due to bacterial contamination during injection not anaphylactic reaction to the drug [16]. A double-blind placebo controlled single centre study with recreational athletes demonstrated that ultrasound guided para-tendon injection of Actovegin was effective in the treatment of Achilles tendinitis [22]. The tendon cross section measurement was reduced significantly (p<0.0001), patients’ physical activity and perception to pain was also improved (p<0.002) in the treatment group [22]. Although it is a relatively small-scale study with limited power, it is a well-conducted study that was featured in a Cochrane review. Ziegler et al. [31] reported a double-blind multicentre randomized control study with 567 patients treated with daily high dose intravenous Actovegin infusion for symptomatic diabetic polyneuropathy. No anaphylactic reactions were reported in this study after 5620 infusions of the maximum dose of Actovegin. The adverse effect profile was no different compared to placebo [31].

**Legal Status**

Besides its clinical properties, there are anecdotal beliefs amongst athletes that Actovegin possesses an oxygen carrying capacity and has the potential to enhance oxygen uptake, which leads to better performance. Although these claims are not based on any objective scientific evidence, the IOC announced in December 2000 that Actovegin was banned under the classification of blood-doping agents. 2 months later, however, the IOC lifted the ban as there was no evidence that Actovegin actually enhances performance [26]. In a recent study with 567 diabetic patients, no improvement of muscle strength or condition was found after treatment with the maximum recommended dose of Actovegin for 160 days [31]. Currently, intramuscular use of Actovegin is not prohibited in or out of competition according to the latest search of the Global Drug Reference Online (Global DRO), 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 [9].

**Evidence on Actovegin in Muscle Injuries**

The treatment of muscle tears with intramuscular Actovegin was first published by Pfister and Koller in 1990 [21]. Their partially blinded case control study with 103 patients, showed a reduction in recovery time with the treatment group of 5.5 weeks compared with 8.3 weeks for the control group [21]. However, in this study, the diagnosis of specific muscle injuries was only based on clinical finding and was not graded according to MRI. Patients were recruited from various sports and levels and the treatment regimen and rehabilitation protocol were not standardised. Actovegin was mixed with local anaesthetics before injection, therefore its pharmacodynamics and pharma-
cokinetics were altered. The final outcomes were based on patients and various clinicians' subjective observations and there was no pre-injury data to compare outcomes. Despite these limitations, it is the first published study regarding the use of Actovegin as an intra-muscular injection and no adverse events were reported in this paper. Wright-Carpenter et al. [30] compared Autologous Conditioned Serum (ACS) to Actovegin in a small non-randomised study. The Actovegin group was created by the retrospective analysis of the Pfister and Koller study, therefore should not be seen as new evidence. Ziegler et al. [31] reported a double-blind multicentre randomized control study with 567 patients treated with 20 daily infusions followed by 140 days of oral Actovegin. Although muscle assessment was not the primary objective in this study, it suggests that Actovegin does not have anabolic or ergogenic activity in terms of muscle development. It does not improve muscle strength (p=0.731) or muscle reflex (p=0.571) [31]. Furthermore, there was no significant difference in the adverse event rate compared to placebo [31].

In 2006, an article from the Times newspaper reported a comment from Dr. Hans-Wilhelm Müller-Wohlfahrt, team doctor for the German national football team and Bayern Munich Football Club regarding the use of Actovegin®. In this report Dr. Müller-Wohlfahrt discussed his experience with Actovegin® and the success of its treatment with high profile sports people such as Maurice Green, Asafa Powell, Diego Maradona, Darren Gough and Paula Radcliffe [8] “I am an empirical doctor and, over 30 years, I have treated so many that nobody can tell me it doesn't work. Nobody I have seen has had an adverse effect, or an allergic or other reaction.” [8]. Although it is not a published clinical study, his 30 years specialist experience with muscle injuries in elite athletes should not be overlooked [20]. There is no study that reports the use of intramuscular injection of Actovegin as a single therapy to treat muscle injuries. Therefore, we will report our experience with this drug in this pilot study.

Method

Prospective data was collected during the 2008–2009 season from a professional football team competing in the UK Championship League for players who sustained grade 1 or 2 hamstring injuries according to the grading system described by Jarvinen et al. [13].

After initial assessment and diagnosis by the team physician or physiotherapist, all injured players underwent MRI to confirm the diagnosis. Actovegin injection therapy was initiated immediately once muscle fiber tears were defined as moderate strains, characterized by a stretch injury with detection of bleeding on MRI scanning (grade I or II tears) [13]. Players with normal MRI findings or grade III tears were excluded in this report. Players who refused Actovegin treatment were allocated to the control group. All players in the Actovegin treatment group followed the same injection protocol (Fig. 1) of 3 intramuscular injection therapies and the same hamstring specific rehabilitation protocol. There was no bleeding or randomization in this study. 2 ml of Actovegin were injected into the injury site under direct palpation. The injection process was repeated after 24h (Fig. 1). Players who opted-out of the injection therapy followed the same rehabilitation protocol. All players were discouraged from taking any anti-inflammatory (NSAIDs) or oral supplements during the rehab period. Players were able to return to training with the first team once they had completed the rehabilitation program and passed the assessment by the team physiotherapist as per stage D in the rehabilitation program (Fig. 1).

Statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago). Actovegin treatment group was compared to Control group using Student’s 2 two-tail unpaired t-test, p-value <0.05 was considered to be significant. Our study has been performed in accordance with the ethical standards of the IJSM [12]. It has been ethically reviewed and approved by the Cardiff University.

Results

There were 11 MRI confirmed hamstring injuries in the club during the 2008 and 2009 seasons. The mean age of injured players was 23 and all injuries occurred at the musculotendinous junction of biceps femoris. There were 3 grade II injuries and 8 grade I injuries. 4 players had previous hamstring injuries but had been symptom free for at least 6 months. All players were able to progress through the rehabilitation program.
Table 1 Results for Actovegin and control group.

<table>
<thead>
<tr>
<th>Season</th>
<th>Age</th>
<th>Treatment</th>
<th>MRI findings</th>
<th>Day loss</th>
<th>Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>26</td>
<td>Actovegin</td>
<td>grade II tear</td>
<td>22</td>
<td>18.7</td>
</tr>
<tr>
<td>2009</td>
<td>24</td>
<td>Actovegin</td>
<td>grade II tear</td>
<td>21</td>
<td>S.D. 4.93</td>
</tr>
<tr>
<td>2009</td>
<td>18</td>
<td>Actovegin</td>
<td>grade II tear</td>
<td>13</td>
<td>S.E.M. 2.85</td>
</tr>
<tr>
<td>2008</td>
<td>22</td>
<td>Actovegin</td>
<td>grade I tear</td>
<td>10</td>
<td>12*</td>
</tr>
<tr>
<td>2009</td>
<td>25</td>
<td>Actovegin</td>
<td>grade I tear</td>
<td>9</td>
<td>S.D. 2.94</td>
</tr>
<tr>
<td>2009</td>
<td>19</td>
<td>Actovegin</td>
<td>grade I tear</td>
<td>14</td>
<td>S.E.M. 1.47</td>
</tr>
<tr>
<td>2009</td>
<td>26</td>
<td>Actovegin</td>
<td>grade I tear</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>19</td>
<td>control</td>
<td>grade I tear</td>
<td>26</td>
<td>20*</td>
</tr>
<tr>
<td>2008</td>
<td>28</td>
<td>control</td>
<td>grade I tear</td>
<td>16</td>
<td>S.D. 4.54</td>
</tr>
<tr>
<td>2008</td>
<td>22</td>
<td>control</td>
<td>grade I tear</td>
<td>21</td>
<td>S.E.M 2.27</td>
</tr>
<tr>
<td>2008</td>
<td>24</td>
<td>control</td>
<td>grade I tear</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

*p<0.05 between groups, S.D. = Standard Deviation, S.E.M. = Standard Error Mean

Pain free. No recurrent muscle strains or injuries were recorded during rehabilitation. No adverse reactions were reported with Actovegin injections and all players in the Actovegin group received 3 doses of Actovegin as stated in the treatment protocol.

7 players had Actovegin treatment and 4 players opted-out of the injection therapy. In the Actovegin group 3 players had grade II injuries and 4 players had grade I injuries. All 4 players in the control group had grade I injuries. The mean number of days lost in the control group was 20 with a range from 16 to 26 days; in the Actovegin group the mean number of days lost with grade I injuries was 12 with a range from 9 to 15 days (Table 1). There was a significant statistical difference when the Actovegin group was compared to the control group (p=0.033). In grade I hamstring injuries, players in the Actovegin treatment group were able to return to play 8 days earlier (95% CI = 1.249 to −14.7510) compared to physiotherapy alone. For Grade II injuries, the mean number of days lost in the Actovegin group was 18.67 with a range from 13 to 26 days. Statistical analysis cannot be performed as there were no subjects with grade II injuries in the control group.

Discussion

It is evident that hamstring injuries are very common in sports with high demands on speed and power such as football (soccer). The incidence during our study was comparable to recent literature [11,29]. The Actovegin injection therapy regimen described in this paper for grade I hamstring injuries appears to significantly reduce the number of days for return to play, with a mean of 8 days reduction compared with rehabilitation therapy alone (p<0.05). It is difficult to perform full economic costing for elite football players, as it is impossible to attach a value for a player to be able to play the next game.

In vivo and in vitro studies suggest that Actovegin contains some active components, although they are yet to be identified. It has been used by clinicians across Europe, China and Russia for over 60 years to treat stroke and diabetic neuropathies [6,15,18,22,30]. There is limited evidence on its role in the treatment of muscle injuries and no evidence regarding any performance enhancing properties. There has only been one published clinical study to investigate its role in muscle injuries when mixed with local anaesthetics [21]. Although an unpublished case series with Dr. Hans-Wilhelm Müller-Wohlfahrt’s injection regimen seems to have good results, it has also been mixed with Traumeel and local anaesthetics [8]. There have been no clinical studies investigating the effect of stand-alone Actovegin therapy in muscle injuries. From our review, Actovegin is a drug that has 60 years of track record in clinical use and it has a well-established safety profile. The only anaphylactic case report published could be discounted, as the cause is most likely to be bacterial contamination of injection site. There is no evidence of an ergogenic effect with Actovegin. Many official governing bodies including WADA, UKAD, CCES and USADA do not prohibit its use intramuscularly. On the other hand, it is not on the British National Formulary (BNF) and Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and Food and Drug Administration (FDA) in the USA have not approved its use.

In professional elite-level athletes, Orchard et al. [20] summarised that currently almost all our so-called knowledge in the treatment of muscle injuries was based on very poor scientific evidence. The career lifespan for the professional elite athlete is often short lived, shortened recovery time could mean continuing with training, increased game play and benefit to the team and club.

Due to the unique relationship between sports physicians and athletes, they are often under pressure to seek the latest “active” or “cutting edge” treatments [17]. Athletes are often not interested in being part of a Clinical Trial. Therefore, it is not always possible to get a large number of participants who are professional athletes. There is also much publicity about the use of this drug based on anecdotal assumptions on its questionable potential ergogenic properties [17]. Actovegin is not licensed to treat muscle or soft tissue injuries and its evidence is limited. Nevertheless, there is published evidence demonstrating its efficacy and safety [2,6,7,15,22,31].

Limitations

This is a non-blinded and non-randomised observational pilot study with subjective assessments for return to play. The potential psychological effect of injection therapy and placebo effect cannot be ruled out in this study; ideally a placebo injection should be used alongside Actovegin. Due to the competitions of the sport, it is not possible to standardise the rehabilitation regimen between clubs, therefore only a single football club was used, hence the patient numbers in each group were small. The power of this study is 84%.

In our study, all the injections were performed by one of the authors (LN). Injection sites were marked with permanent marker on the first injection, under direct palpation of the maximum tenderness point of the muscle. Ultrasound guidance was not used as our clinical marking corresponded to the location of injury on the MRI.

Conclusion

This article summarises the current evidence on Actovegin, there is no evidence that Actovegin can enhance athletes’ performance. Although our report is based on a non-randomised observational pilot study with subjective assessments for return to play, the impact of Actovegin injection therapy must not be overlooked. Compared with conventional conservative RICE and NSAID therapy, Actovegin proposes an exciting and legal alternative for high performance athletes. From our experience, Actovegin injection therapy seems safe and well tolerated. More
objective evidence is needed before any meaningful conclusions can be drawn for this new treatment of muscle injuries. Despite our positive experience with Actovegin, we do not advocate its use until further high quality evidence can be obtained. Medicine is a form of science as well as an art. Physicians should process the evidence (in whichever form that it may come) with an open mind. Premature conclusions should not be drawn based on limited evidence. Further research must be encouraged to investigate the effects of Actovegin on muscle injuries. Injection therapy could potentially revolutionise the treatment of muscle injuries, it should not be regarded as “Snake oil”.

Acknowledgements

None of the authors have received any support from any drug company. Material used in this study was purchased with full retail price.

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