No Effect of Intravenous Actovegin® on Peak Aerobic Capacity

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- ergogenic aid
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- arm crank ergometry
- haemodialysate

Abstract

There is much speculation that Actovegin® is ergogenic, but no scientific work has been published in this field. 8 participants [mean(±SD) age, height and mass of 24 (7) years, 1.76 (0.07) m and 80.1 (9.1) kg, respectively] completed 3 exhaustive arm crank ergometry tests. Following Baseline testing 2 further tests were performed 2 h following the injection of either 40 ml of Actovegin® or a saline Placebo. Peak power (W_{peak}), peak physiological responses, concentrations of blood glucose and lactate, exercise efficiency (%), VO_2 gain ($ml \cdot W^{-1}$), and the respiratory compensation point (RCP) were determined. Repeated measures ANOVA tests were used to analyse data with significance accepted at $p \leq 0.05$. Values of mean (±90% CI) bias were calculated to further explore quantitative differences between trials. Strong trends for variations in W_{peak} ($p = 0.054$) and RCP ($p = 0.054$) were evident; likely meaningful effects existed between the Baseline and both injection trials, but only a trivial effect was noted between Placebo and Actovegin® (bias: W_{peak} 0.8 ± 3.2 and RCP; 2.5 ± 4.7 W). Concentrations of blood lactate and glucose changed across time, but did not differ between the 3 trials. Our data suggests the Actovegin® is not ergogenic and did not influence functional capacity in the context of the exhaustive, upper-body test employed.

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Introduction

Actovegin® is a deproteinised haemodialysate of ultra filtered calf serum of animals under 8 months of age, produced by Nycomed Austria GmbH and, according to the manufacturers, can be used to treat a wide variety of ailments [14]. For example, clinically, it is used as an intravenous infusion to treat acute stroke [4,7] and postpartum haemorrhage [1] and, in a topical form to treat skin ulcers [3]. It is also believed to improve the utilization of oxygen at cellular level, and promotes the uptake of nutrient media into cells [10,12,19].

Several studies have reported upon the clinical efficiency and safety associated with the use of Actovegin®. Ziegler et al. [26] reported that Actovegin® was effective in the treatment of 562 diabetic patients with peripheral neuropathies. However, no improvements in muscle strength or reflex were found after 160 days of intravenous infusion of Actovegin® [26], suggesting that Actovegin® did not display any anabolic activity in terms of muscle development. Lee et al. [13] recently reported upon their experience using intramuscular Actovegin® injection therapy in treating grade 1 muscle injuries. The Actovegin® treatment group were, on average, able to return to play 8 days earlier [13], and further demonstrated the safety of using the drug as well as its potential role in sports medicine.

Besides its apparent clinical properties, athletes have provided subjective and unfounded anecdotal evidence that Actovegin® is ergogenic and can improve exercise capacity. Historically, the International Olympic Committee (IOC) announced in December 2000 that Actovegin® was banned under the classification of blood-doping agents. However, only 2 months later the IOC lifted the ban stating there was insufficient evidence that Actovegin® could enhance performance [24]. According to the latest World Anti-Doping Association (WADA) guidelines, the use of Actovegin® is acceptable, and is not included on the comprehensive List of Prohibited Substances and Methods [25]. In this regard, an intravenous injection of the drug using a simple syringe is permitted providing the volume of any single injection

administered is equal to or less than 50 ml; any volume greater than 50 ml is deemed to represent "a chemical or physical manipulation" and is not permitted according to section M2 of WADA's list of Prohibited Substances and procedures. Further, serial injections have to be separated by at least 6 h [25]. Actovegin® is prohibited if administered by intravenous infusion or single intravenous injection with a volume exceeding 50 ml.

To the authors' knowledge no previous scientific reports have explored the ergogenic benefits associated with the intravenous injection of Actovegin®. However, based upon subjective, anecdotal reports, coupled with the encouraging clinical evidence mentioned above [8, 13, 15] it is clear that this area warrants scientific enquiry.

Actovegin® does not contain any peptide, growth factors or hormone-like substances, and it has been proposed that the drug works at cellular level [8, 10, 12, 13, 19]. We speculated that Actovegin® was unlikely to influence factors associated with central fatigue, including the oxygen carrying capacity of the blood, but might play a role in the attenuation of mechanisms and symptoms associated with peripheral (muscular) fatigue. We, therefore, used arm crank ergometry to test this hypothesis, as the principal limiting factors associated with this mode of exercise are related to acute muscular fatigue [5, 11], and maximal physiological responses are seldom observed [20].

The principal objectives of this study were to examine whether or not an intravenous injection of 40 ml of Actovegin® influenced functional capacity, and to explore submaximal and peak physiological responses during exhaustive exercise. Owing to the lack of information currently available in this research area we developed a null hypothesis stating that Actovegin® would not demonstrate any benefit compared either to a Baseline test or the intravenous injection of a saline Placebo.

Methods

Participants

8 physically active men with a mean (±SD) age of 24 (7) years, stature of 1.76 (0.07) m, and body mass of 80.1 (9.1) kg volunteered to participate. Additionally, all participants provided written informed consent once they had been informed of the principal objectives and potential risks associated with their involvement. Prior to any testing all processes and procedures obtained institutional ethical approval. However, owing to the invasive nature of the study, and potential health and safety concerns expressed by members of the ethics committee, the research study was only permitted to be conducted as a single-blind study where participants remained unaware of the trial order, but the researchers were aware in case any unforeseen complications arose. Our study was performed in accordance with the ethical standards of the IJSM [9].

Graded exercise test

The participants refrained from heavy exercise and the consumption of alcohol and caffeine for at least 24 h before each exercise test, and arrived at the laboratory following a 12-h overnight fast. Participants arrived at our human physiology laboratory at 08:00, which was approximately 2 h before the start of each exercise test. During the initial (Baseline) visit participants consumed a standardised breakfast at 08:10 and were asked to return to the laboratory at 10:00. During the baseline trial no injection was administered. In the 2nd and 3rd visits participants were intravenously injected with either 40 ml of normal saline (Placebo) or Actovegin® using a tinted 18 G Venflon® syringe 10 min before they ate breakfast; the order of the substance injected was counterbalanced. In line with this procedure a metabolic wash-out period of at least 48 h was permitted between trials, though in some instances a period of 7 days elapsed between successive tests. As the study adopted a placebo-controlled, counter-balanced, single blind design, none of the participants were aware of the order in which the 2nd and 3rd tests were undertaken.

Participants completed 3 graded exercise tests using an electrically-braked arm crank ergometer (Angio, Lode, Groningen, Netherlands). Following 5 min of quiet rest, the exercise protocol started at an external work rate of 50 W for 2 min with subsequent 20 W increments every 2 min until volitional exhaustion. During the tests participants maintained a crank rate of 75 rev · min^{-1}, and were instructed to continue exercising for as long as possible. Owing to the study being run as a single-blind trial, the researchers provided the participants with limited encouragement during the respective exercise trials, though participants were informed of the amount of time elapsed and/or remaining during each exercise stage. Each test was terminated when the participants were unable to maintain a crank rate at or above 70 rev · min^{-1} [18]. Peak aerobic power (W_{peak}; W) was calculated as the average work rate achieved during the final minute of each test.

Experimental data collection and processing

During all tests heart rate was recorded (RS400, Polar, Kempele, Finland). Earlobe samples of arterialised-venous blood were collected at rest, immediately post-exercise and then after 5 min and 20 min of passive recovery for the purpose of determining concentrations of whole (lysed) blood lactate (B[La]; mmol·l^{-1}) and glucose (B[G]; mmol·l^{-1}) using a fully automated analyser (Biosen C-line, EKF Diagnostics, Barleben, Germany).

Respiratory data were collected continuously using an on-line gas analysis system (Jaeger Oxycon Pro, Viasis Healthcare, Hong Kong) that was calibrated according to the manufacturer's instruction before each test. All respiratory data were initially collected at 5-s intervals however, for the purpose of determining peak responses, rolling 30-s averages were calculated and the highest values subsequently identified. Respiratory data was also averaged at consecutive 30-s intervals for several purposes; firstly, to explore the VO_2-work rate relationship over the entire duration of the respective tests (the VO_2 gain); secondly, to generate submaximal VO_2 and RER data for the purpose of estimating submaximal values of gross and net efficiency; and thirdly, to identify the respiratory compensation point (RCP). The RCP was determined using corresponding values of VCO_2 and VE measured at consecutive 30-s intervals, and was specifically related to the point at which the VCO_2-VE curve started to rise abruptly and systematically (**Fig. 1**). The RCP was identified using visual inspection by 2 experienced reviewers, and a graphical example is provided in **Fig. 1**. The VO_2-work rate relationship was established using the final 30-s data from each distinct exercise stage. Separate XY scatter plots were generated and fitted with a linear regression equation; the gradient (ml·W^{-1}) component of the regression equation was noted and compared between trials (see **Fig. 2**).

Submaximal measures of gross and net (mechanical) efficiency were estimated at work rates either at or just below the gas exchange threshold to ensure we could be confident that there was little or no

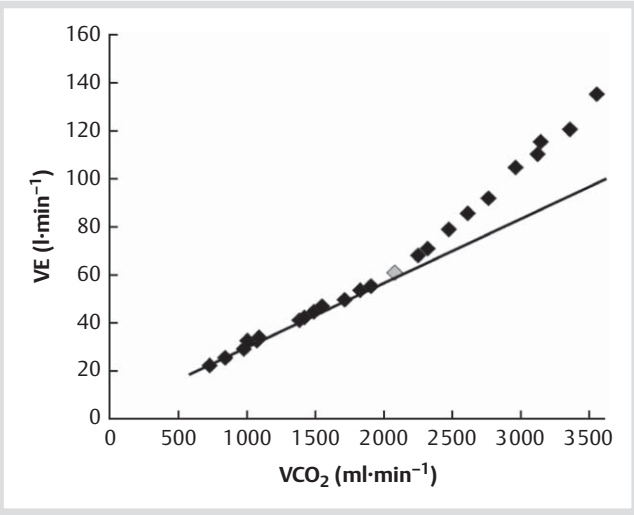

Fig. 1 An example of the determination of the respiratory compensation point for a typical participant.

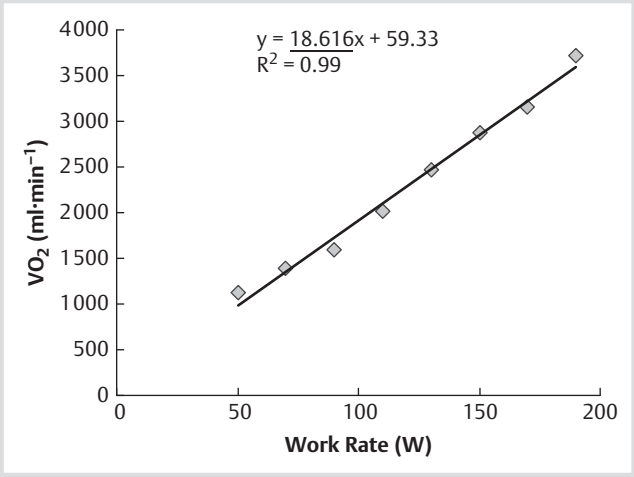

Fig. 2 An example of the determination of the rate of VO_2 gain associated with work rate increments for a typical participant.

contribution from anaerobic energy production; in this way our estimates of (aerobic) energy expenditure were precise. In making the calculations of gross (GE) and net (NE) efficiency calorific energy equivalents associated with VO_2 were determined using a table of non-protein respiratory exchange ratios [16], and the respective equations used to derive these parameters were [16]:

GE = (External Work Done / Total Energy Expended) * 100 (%)

NE = (External Work Done / Energy Expended above rest) * 100 (%)

Statistical analyses

All statistical analyses were performed using the Statistical Package for Social Scientists (SPSS, version 17, Chicago, USA). Values of W_{peak} mechanical efficiency, VO_2 gain, the work rate associated with the RCP and peak physiological responses were analysed using separate one-way ANOVA tests with repeated measures. Concentrations of blood lactate and glucose were analysed using separate two-way ANOVA tests with repeated measures. Prior to running all ANOVA tests, data were checked for sphericity using Mauchly's test. Where sphericity violations were noted Huyn-Feldt corrections were used to modify the degrees of freedom employed in the subsequent statistical analyses. Statistical significance was accepted at $p \leq 0.05$ and, where statistical significance was noted, post-hoc (Bonferroni) pairwise comparisons were made to determine specifically where differences existed. Owing to our small sample size and limited statistical power, we also explored elements of our data set using an alternative quantitative approach. In line with recommendations proposed by Batterham and Hopkins [2], the likelihood of observing a meaningful difference was examined by way of calculating the 90% Confidence Interval for the average bias observed between respective pairs of exercise trials (i.e., Baseline vs. Placebo; Baseline vs. Actovegin®; Placebo vs. Actovegin®). Thereafter, by accepting the least conservative, worthwhile effect size of 0.2 [6], we determined the meaningfulness of differences observed between trials. All subsequent data are presented as mean (±SD) unless otherwise stated.

Results

All participants completed 3 separate exhaustive tests and did not experience any adverse events associated with the respective injections of Actovegin® or the saline Placebo. Peak [mean (±SD)] values for aerobic power (W_{peak}) and selected physiological parameters are presented in **Table 1**; while no significant differences were observed between any of the 3 trials, strong trends existed for W_{peak} ($p = 0.054$) and RCP ($P = 0.054$), respectively. Group mean (±SD) values of submaximal parameters are presented in **Table 2**; similarly no significant differences existed between trials. However, when selected dependent variables were examined by calculating the mean bias (±90% CI; **Table 3**), a somewhat different picture emerged. It became evident that small, but meaningful differences existed for W_{peak} and the RCP between the Baseline test and both injection trials. In contrast, only a trivial effect was observed for the selected parameters between the Placebo and Actovegin® trials resulting in an effect size of 0.03 for W_{peak} and 0.10 for the work rate associated with RCP.

Table 4 summarises the mean (±SD) values of B[G] measured during each of the 3 trials. The only significant difference observed was for the main effect of "Time" ($p = 0.034$), indicating that the average B[G] measured across the 3 trials following 20-min of recovery was lower ($p = 0.004$) compared to that measured after 5-min of recovery. **Fig. 3** summarises the B[La] profile during each of the 3 trials. As expected, there was a significant rise ($p = 0.0002$) in B[La] from rest to the end of each test, and a further rise ($p = 0.0004$) was observed following 5-min of recovery. Following 20 min of recovery B[La] was significantly lower ($p = 0.0003$) in all tests compared to the values measured at the end of exercise and after 5 min of recovery. However, the B[La] observed following 20 min of recovery was lower ($p = 0.015$) in the Baseline test compared to Placebo.

Discussion

The principal finding of this study was that the injection of 40 ml of Actovegin® did not influence the magnitude of W_{peak} or the attainment of related peak physiological and metabolic response during exhaustive arm crank ergometry compared to Baseline or the injection of a saline Placebo. Importantly, the intravenous

	Baseline	Placebo	Actovegin®	*p*-value
W_{peak} (W)	171 (28)	178 (26)	178 (29)	0.054
VO_{2peak} (l·min^{-1})*	3.41 (0.54)	3.42 (0.59)	3.42 (0.66)	0.917
VO_{2peak} (ml·kg^{-1}·min^{-1})*	42.8 (5.6)	43.1 (6.2)	42.9 (7.0)	0.910
VCO_{2peak} (l·min^{-1})	4.05 (0.55)	4.12 (0.57)	4.06 (0.64)	0.646
RER_{peak}	1.21 (0.05)	1.23 (0.07)	1.22 (0.08)	0.562
VE_{peak} (l·min^{-1})	155.3 (26.1)	157.1 (23.5)	149.8 (24.7)	0.397
fb_{peak} (cycles·min^{-1})*	62 (14)	63 (13)	62 (13)	0.815
HR_{peak} (b·min^{-1})	181 (13)	182 (10)	180 (11)	0.920

*violated assumptions of sphericity

Table 1 Mean (±SD) values of peak responses achieved during the Baseline, Placebo and Actovegin® trials.

Table 2 Mean (±SD) values of gross efficiency (GE), net efficiency (NE), the work rate associated with the respiratory compensation point (RCP) and the rate of VO_2 gain observed during the Baseline, Placebo and Actovegin® trials.

	Baseline	Placebo	Actovegin®	*p*-value
GE (%)*	13.7 (1.4)	13.9 (1.1)	13.4 (0.9)	0.495
NE (%)	17.7 (1.9)	18.2 (1.9)	17.0 (1.3)	0.105
RCP (W)*	114 (24)	125 (20)	128 (19)	0.054
VO_2gain (ml·W^{-1})*	18.6 (1.6)	17.4 (1.5)	17.5 (1.9)	0.285

* violated assumptions of sphericity

Table 3 A summary of the mean (± 90% CI) of the differences for a selection of dependent variables between respective pairs of exercise trials.

	Baseline vs. Placebo	Baseline vs. Actovegin®	Placebo vs. Actovegin®
W_{peak} (W)	7.0; ±6.8*	7.8; ±5.7*	0.8; ±3.2**
VO_{2peak} (l·min^{-1})	0.02; ±0.12**	0.01; ±0.20**	0.00; ±0.10**
HR_{peak} (b·min^{-1})	1; ±4**	0; ±4**	1; ±4**
B[La]end (mM)	0.4; ±1.0**	0.3; ±1.2**	0.6; ±1.2**
RCP (W)	11.3; ±9.8*	13.8; ±11.8*	2.5; ±4.7**
VO_2 gain (ml·W^{-1})	1.2; ±1.5**	1.0; ±1.9**	0.2; ±0.8**

* denotes a likely meaningful difference

** denotes almost certainly a trivial effect

Table 4 Mean (±SD) values of blood glucose concentration (mmol·l^{-1}) measured before exercise (Pre), at volitional exhaustion (End) and after 5 min and 20 min of recovery during the Baseline, Placebo and Actovegin® trials.

	Baseline	Placebo	Actovegin®
pre	5.21 (0.35)	4.96 (0.42)	4.70 (0.50)
end	5.39 (0.93)	5.58 (1.04)	5.71 (1.16)
5-min*	5.53 (0.56)	5.58 (0.82)	5.60 (0.84)
20 min	4.58 (0.29)	4.84 (0.57)	4.77 (0.46)

* denotes a significant (p = 0.034) time effect; 5 min vs. 20 min

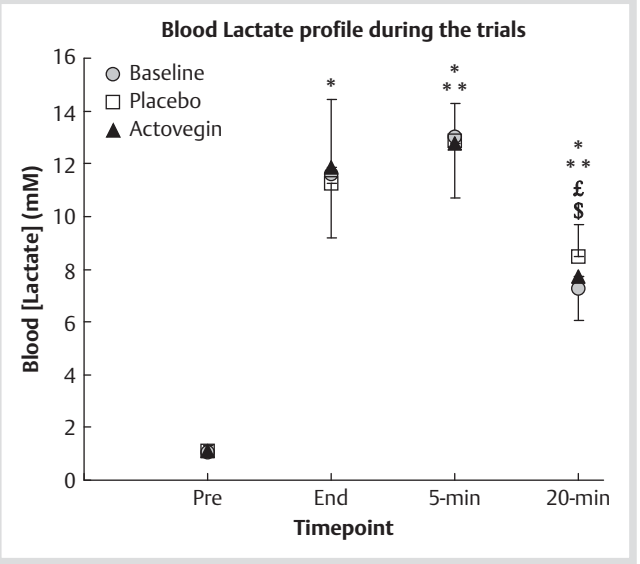

Fig. 3 * denotes different (p = 0.0001) compared to Pre in all trials
* * denotes different (p = 0.044) compared to End in all trials
£ denotes different (p = 0.003) compared to 5-min all trials
$ denotes different (p = 0.015) at 20-min; Baseline Vs. Placebo

injection of Actovegin® displayed no adverse effects in any of our participants, and no differences existed between trials when submaximal variables were examined. Finally, the profiles of B[La] profile B[G] were similar during the 3 trials.

Meaningful, quantitative differences in the mean (±SD) values of W_{peak}, and the absolute work rate associated with the RCP were observed between the Baseline test and both injection trials. Due to the relatively unfamiliar exercise mode employed, these observations were, in part, anticipated and they confirm the importance of including such a Baseline (familiarisation) trial where the impact of specific interventions are examined [18,22]. However, it was reassuring to note that no such quantitative differences existed between the crossover Placebo and Actovegin® trials.

In the context of submaximal parameters, the rates of VO_2 gain observed during the 3 trials were similar, translating to equivalent values of delta efficiency. Additionally, the respective values of GE and NE were similar during the 3 trials, and to values that have been previously reported for this exercise mode [21]. Finally, the absolute work rate associated with the RCP was the same during the Placebo and the Actovegin® trials. We acknowledge that this preliminary study employed a relatively small sample size and we were required to adopt and implement a single-blind, placebo-controlled research design. However, in considering all of the objective evidence collected it is reasonable to speculate that Actovegin® is not ergogenic, and would not significantly impact upon performance capacity during arm crank ergometry. However, our findings cannot be generalised to all exercise modes, and it is imperative that future studies consider how this drug influences performance capacity using well-designed, self-paced time trials that are undertaken by experienced competitors.

Numerous anecdotal athlete testimonies and media reports have suggested that Actovegin® is ergogenic and has the potential to improve athletic performance. These reports suggest that it has similar properties to erythropoietin to boosts the O_2-carrying capacity of blood and can, therefore, attenuate central (cardio-respiratory) limitations of fatigue. However, as Actovegin® is a deproteinised haemodialysate that does not contain any peptide, growth factors or hormone-like substances [10,12,13,19], such reports associating the drug with blood doping are unlikely to be founded.

Alternatively, it has been proposed that Actovegin® works at the cellular level and is beneficial to ischaemic cells [10,12,13,19]. While it is unlikely to influence central limitations to performance, it might play a role in the attenuation of mechanisms associated with peripheral (muscular) fatigue. The principal limiting factor during arm crank ergometry is acute muscular fatigue [5,11], and maximal physiological responses are seldom observed [20]. The principal (subjective) limiting factor reported by all participants in the present study was pain and general fatigue of the *m. biceps brachii* and *m. triceps brachii*, and this concurs with previous reports [17,23].

An interesting fact was that during debriefing 4 of the 8 participants reported that the exhaustive test was easier with Actovegin® compared to Placebo, while the other participants could not distinguish between the trials. In this regard it might permit individuals who are less accustomed to exercise, or have experienced acute trauma [in the form of a sporting injury or clinical surgery], and are more susceptible to developing sensations of pain and fatigue to achieve a greater volume of work in an attempt to evoke improved training adaptations. Therefore, Actovegin® could potentially have a role in a clinical rehabilitation setting. However, it must be reiterated that the favourable (subjective) perceptions being considered here did not translate into an improvement in peak aerobic capacity and, as such, should be treated with caution. Further research should consider this potential clinical application of Actovegin®.

The career lifespan for the professional elite athlete is often short lived; they are often under pressure to seek new ways to improve their performance. Professional athletes are often not interested in being part of a clinical trial, and would willingly believe "word of mouth", anecdotal evidence [6]. To our knowledge this is the first study to explore the physiological and metabolic responses to the intravenous injection of Actovegin® during exercise. The power of this study is limited due to the small number of participants; nevertheless, it is a well-designed, counter-balanced study where individuals acted as their own control. While we acknowledge that this preliminary study has a number of limitations, we have reported fresh evidence that questions unscientific, anecdotal beliefs. Overall, our findings suggest the injection of Actovegin® was not ergogenic and is unlikely to aid performance.

Conclusion

To our knowledge this represents the first research study that has investigated the potential ergogenic properties associated with the intravenous injection of Actovegin®. Although our study included some limitations, it has provided important evidence that the administration of Actovegin® did not influence functional capacity or a selection of submaximal and peak physiological responses during exhaustive exercise. Further investigations are required in this field using a variety of exercise modes, with participants who are highly trained and experienced competitors. There may also be a potential clinical application of this drug to facilitate physical rehabilitation following acute trauma.

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