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Review Article

Blood Doping: Beneficial or Destructive

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Abstract

Blood boosting/ doping and especially Erythropoietin (EPO) doping has become a fundamental issue in many sports such as cycling, endurance running and cross-country skiing. These sports required strength and persistence power for their performance. Athletes use the drugs to retain their power for the better performance. Erythropoietin or EPO is a naturally occurring peptide hormone, which stimulates packed cell volume production in the body in response to cellular hypoxia and anaemia. However, clinically the drug rHu EPO is used to treat conditions like renal failure, malignant and inflammatory diseases by reducing anaemia with fatigue. Its therapeutic effects are erythropoiesis (increased RBCs formation), elevated Haematocrit (Hct) and haemoglobin. Present study aims to establish whether blood/ rHu EPO doping increase performance or health risk in the competitive endurance athletes?

Keywords: Blood dopping; Athletes; Sports medicine

Introduction

Doping is defined as 'the presence of prohibited harmful substances or its metabolites in the specimen of athlete's body which is used for the purpose of boosting sports performance' [1]. In other words, it is the artificial way of enhancing physical performance, contrary to the spirit of sports, which is meant to improve the health and wellbeing [2]. The use of ergogenic substances and performance-improving drugs is not new in sports and has been prevalent since ancient times, when alcohol, stimulants and other potions were believed to be the most effective performance enhancers [3-8]. However, its abuse seems to be predominant in the modern Olympics and other sporting events [9]. The aspirations to succeed at all cost and becoming a national hero is a strong motivation in athletes who want to acquire a competitive edge [9]. Moreover, if a minute gain through drug abuse can improve performance even a second faster can create a huge difference in winning a gold medal and losing a competition [10]. Even some countries have been doping their athletes without their knowledge and consent [11]. Additionally, performance is also maintained by the widespread use of non-prohibited dietary supplements [2,8,9]. Doping boost their confidence and feelings of being superior due to its psychological effect and hence their sporting performance [12]. Unfortunately use of such illegal substances has been one of the most common causes of sudden death other than congenital heart diseases and atherosclerosis in athletes [13-16], this led to the sports professional bodies to consider a sanction over such methods. In 1967, for the first time, the International Olympic Committee (IOC) made up a list of banned substances, which is regularly updated [13]. Its primary objective is to protect the wellbeing of athletes and restore the dignity and integrity of sports by providing fair and reasonable competition [9].

Table 1: According to WADA the banned substances.

WADA's List of banned substances [1]
1. Anabolic Agents (AAS) and its derivatives
2. Peptide hormones, growth factors and related substances
3. B2 agonists
4. Hormones and its metabolites, including oestrogen, insulin etc.
5. Diuretics and other masking agents
6. Narcotics, cannabinoids, stimulants

The world anti- doping agency, WADA was established in 1999 and validated by all sports and government organizations [1]. Some of the following varieties of substances banned are given in the Table 1 [1].

Aim of the Study

This study aims to establish whether blood/ rHu EPO doping increase performance or health risk in the competitive endurance athletes?

Blood Doping and its History in Sports

Blood boosting/ doping and especially Erythropoietin (EPO) doping has become a fundamental issue in many endurance sports such as cycling, endurance running and cross-country skiing [8-10,12-29]. The tradition of blood doping in modern history dates back to 1960s, when a four times winner of the tour de France cyclist was alleged with blood doping [19]. Nevertheless its widespread use in endurance sports started after the 1968 Olympics in Mexico City, which is situated at a high altitude [18]. It is noteworthy that at higher altitude physiological adaptation in response to hypoxia results in increased red blood cells formation (erythropoiesis), hence higher oxygen carrying capacity in athletes [19,20]. The athletes from high altitude countries succeeded in endurance events in the Mexico Olympics [19]. The benefits of altitude training were acknowledged from this event [20]. However other endurance sports such as cross-country skiing, running, cycling soon adopted a technique to improve performance that was termed as 'blood doping' by the media in 1970s [20-23,25]. Consequently various forms of 'blood boosting' such as autologous (own blood) and homologous (from others) blood transfusion were common practices as the early form of blood doping until the discovery of recombinant variety of erythropoietin (rHu EPO) hormone [17,21,22,25]. It became a common tool in endurance

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sports by the Italian, Americans, Russians, East Germans and Finns [17,21-24]. Some athletes such as the Finnish gold medalist runners in 1972, a Russian distance runner in 1980s and Italian world record holders in 1984 had admitted the use of 'blood doping' techniques [18,24-26]. US cycling team, who won nine gold medals in 1984 Olympics games was alleged with homologous blood transfusion, despite poor performance in the past [19]. Similarly a US Nordic skier also confessed of blood doping in 1987 [24]. More recently, the seven times US winner of the tour de France during 1999-2000, confessed systematic blood doping, EPO, along with other banned substances.

The IOC banned blood doping after the 1984 Olympics [3]. A few years later, the recombinant human variety of EPO (rhEPO) became commercially available after approval by Federal Drug Agency (FDA) for its use in renal patients [17,28,30-33].

Erythropoietin or EPO is a naturally occurring peptide hormone, which stimulates packed cell volume production in the body in response to cellular hypoxia and anaemia [17,28,30]. However in clinical medicine the drug rHu EPO is aimed at treating conditions such as renal failure, malignant and inflammatory diseases by reducing anaemia with fatigue [32]. Its therapeutic effects are erythropoiesis (increased RBCs formation), elevated Haematocrit (Hct) and haemoglobin (Hb) [28-33]. Hence an improvement in the exercise capacity is achieved by increase in the oxygen uptake [30]. However, effect of improved performance soon became the ground for its potential misuse in endurance sports [24-26,30].

Effects of Erythropoietin on Performance

The first study to report the performance boosting effects of blood transfusion and recombinant human erythropoietin came from Ekbolm et al. in 1972 on human volunteers [32]. Its purpose was to analyse effect of the drug on the circulatory adaptation to sub maximal exercise [32]. In his un-blinded experiment, 15 moderately trained subjects were injected with 20-40 IU/kg rHu EPO, three times a week for six weeks [32]. After intervention period, Hct increased from 44.5 % to 49.7 %. There was 10% increase in the Hb from 15.2 g/l to 17.2g/l ($p<0.001$), while oxygen delivery as measured by VO_2 increased 6%, from 4.67l/min/kg to 4.97l/min/kg in the maximal exercise test. Physical performance expressed as time to exhaustion increased by 83 seconds. These results showed substantial increases in performance with autologous transfusion of packed RBCs. However the outcomes must be interpreted with caution, as it was not a double blinded randomized control trial, but a laboratory based study, with small number of subjects of varying aerobic capacity. In contrast, Robertson et al failed to demonstrate improvement in performance with the haematological changes after blood transfusion, despite a 12.8% increase in VO_2 max [33]. He proposed that there is no relationship between submaximal aerobic capacity and artificially induced erythrocythemia, which may suggest that other determinant of endurance exercise must be also be considered. As the EPO-induced haemodynamic effects can be massive, close supervision is necessary during the administration period [34]. A major effect of rHu EPO on hemodynamic was noticed by Ekbolm and his team in form of a significant rise in systolic BP from 177mmHg to 191mmHg at submaximal exercise [32]. Such change in the haemodynamic with the use of EPO has been generally reported in the literature [35]. As is known already that Hct act as a main determinant of blood viscosity [36]. Since the drugs directly elevate the haematocrit level, the developing hyper viscosity will ultimately increase the peripheral resistance. In addition, EPO also reduces plasma volume even before stimulating red blood cell formation, which further aggravates the dehydration in endurance activities [16,37,38]. This is an evident danger in athletes working to boost their RBC mass artificially, and the risk develops rapidly as packed cell volume increases beyond 30 % [16,19,21]. The fatalities of 18 Dutch and Belgian cyclists with very high haematocrit between 1987 and 1990 have never been fully justified [18]. It is mostly believed that blood boosting or EPO use might have triggered hyperviscosity [16,19,18,39-41]. Very thick blood may reduce the peripheral blood flow and increase the cardiac workload [16]. This could also have an opposite effect on the aerobic power, which may deteriorate athletic performance [40].

Audran and his co-workers hypothesized that a daily dose of erythropoietin will increase the Hb, RBCs and Hct in a dose-dependent manner and will replicate the situation of (rHu EPO) abuse [42]. Nine trained subjects from various sports were given a daily dose of 50IU /kg rHu EPO for 26 days. The result was 9.3% increase in Hb, 11.5% increase in Hct, and 9.3% increase in VO2 max in the those subjects. However the researcher doubted that higher oxygen capacity in the subjects could also be due to adherence to their exercise-training programme [42]. No doubt several weaknesses were present in the study design. Lack of control group, unblinding, fewer participants and diversity among studied subjects are some of the limiting factors in the above study. Studies on homogenous subjects in terms of sports and training programme, with a skill adjusted control group, are essential to evaluate the impact of rHu EPO on physical performance and cardiopulmonary system. However Birkeland et al. performed a randomized placebo controlled blinded trial on 20 'well-trained' endurance athletes with different sporting background. Moderate doses of EPO 181-232IU/kg/week were given for four weeks. The endurance was measured by the time to exhaustion and the oxygen uptake was demonstrated by VO_2 max. The results showed Hct surged from 42.7% to 50.8% in the EPO group only whereas the aerobic power measured as VO2 max increased from 63.3ml/kg to 68.m1/kg ($p<0.001$) compared to control group. Moreover there was increase in ferritin receptors in the drug-treated group. The time to exhaustion, as a measure for performance extended from 12.8 minutes to 14 minutes ($p<0.007$) on the cycle ergometer. Interestingly the placebo group also showed improvement in time to exhaustion, which although non-significant, shows the importance of blinded study design.

It appears that the drug stimulates the perception of increased physical strength and fitness psychologically among endurance athletes [12] this results in a better commitment to their exercise programme [12]. Although the study shows favourable outcomes, the endurance performance cannot be accurately assessed by 'time to exhaustion' test. In fact the 'time-trial' is very relevant scale for evaluating aerobic performance, because the principle of 'riding to exhaustion' does not reflect the precise measure of performance. In addition, the study also claimed that 10% progress in time to exhaustion is equivalent to four weeks altitude training through an increase in haematocrit [42,43]. It is also seen that the haemoglobin concentration [Hb] is normalized rapidly after discontinuation of EPO [37,38]. However the oxygen transport capacity of the erythrocytes (RBCs) may still remain higher

for few weeks [34,37,38]. The physiological consequence seems to be very limited, as long term EPO treatment did not have any result on the total number of capillaries, nor the type and diameter of the muscle fibres, which means that the influence of EPO on the skeletal system is less obvious [34].

One of the first comprehensive studies to assess the impact of rHu EPO treatment on the respiratory response to exercise came from Wilkerson et al. [44]. In their experiment, 8 healthy individuals received a weekly subcutaneous injection of rHu EPO (150 IU /kg) in a randomized placebo controlled (n=7) trial for four weeks. The rHu EPO treatment group showed a 7% increase in Hb (from 15.8 to 16.9 g /dl; $P < 0.01$) and a 12% increase in Hct (from 43% to 49%; $P < 0.01$). They also demonstrated 7% improvement in peak power output (from 311 to 332 W; $P < 0.05$) in a step and ramp exercises at three different intensities. However no significant changes were noticed in the blood Lactate (LT), end-exercise Heart Rate (HR), and HR dynamics at any of the three intensities studied [44]. Interestingly, there was no change in the pulmonary VO_2 kinetics during the moderate, heavy or extreme step exercise testing.

Perhaps since low to moderate doses of the drug were used in the studies above and it could be assumed that higher doses of EPO would show significant improvement in the exercise physiology in the healthy subjects [44]. Nevertheless Rasmussen et al did not discover any quantifiable effect of EPO on aerobic performance, despite using higher doses [45-47]. 15 healthy volunteers were divided into low dose for 3 months (5000IU/week) and high dose for three (30,000IU) consecutive days in his placebo controlled double-blinded study. His results showed no improvement in exercise capacity, cognitive functions, but the ratings of perceived exertion increased in the EPO treated subjects ($P < 0.05$). Furthermore, EPO did not reduce central fatigue or change cognitive functioning, which may suggest that EPO augments exercise capacity exclusively by increased oxygen delivery to the working muscles [34].

As it is known already that endurance sports rely on oxidative metabolism for its energy demand [40]. It seems obvious that factors associated to oxygen (O_2) transport and its consumption such as maximal oxygen uptake (VO_2 max), are the most important elements of endurance activities, beside lactate threshold and work economy [40]. Most studies investigating the effects of EPO on performance have only evaluated VO_2 max as a measure of aerobic activity [26,32,33,42-47]. When haematocrit is raised from baseline to around 50%, VO_2 max rises exponentially from 7–12% and Hb from 7-11% [32,42-45,47-49]. But the main drawback of the studies above is extrapolation of its results into competitive level endurance sports. As we know, endurance performance depends on various elements [34]. Several differences exist in the genetic makeup, training programme and its intensity in the highly trained athletes compared with other subjects [50]. This limits the interpretation and validity of the results in endurance sports. Moreover, it is unclear whether EPO directly affect other aspects of endurance training alongside VO_2 max or not [34].

In highly trained endurance athletes, the VO_2 max can range between 60-80 ml/kg/min [51]. This indicates that elite level athletes already have a higher baseline value as they have trained extensively to achieve this level [50,51]. With the time, the VO_2 max reaches a plateau and other aspects of aerobic activities (such as lactate threshold and work economy) improve constantly with the training [50]. Wilkerson and his partners didn't show any improvement in the VO_2 kinetics (the rate at which the VO_2 max rises after the onset of prolong activity) [43]. This may suggest that oxygen supply might be sufficient and it may be determined by some other factors such as oxidative metabolic enzymes [34,44]. In contrast, in a study a placebo controlled trial reported a 7% increase in dynamic response of VO_2 (pulmonary VO_2 kinetics) to sub maximal exercise in endurance-trained athletes during ergometer exercise at 65% VO_2 [45]. However one possible reason for the discrepancy between the results could be due to the type of subjects selected. It is established by research that the VO_2 kinetics vary significantly within the subjects as a study on endurance runners and sprinters have detected a faster VO_2 kinetics in the endurance athletes than sprinters at the elite level ($p<0.05$) [46]. The most potent stimulus to VO_2 kinetics of oxygen is endurance-training exercises [49] (Figure 2). It not only augments the oxygen supply to the muscle but also develop the ability of the working muscle to utilize the oxygen delivered [49,50]. This is proven by a study that 6-weeks endurance-training programme significantly reduced the time constant from 32 sec to 23 sec ($p<0.001$) there was 30-60% increase in time-to-exhaustion and elevation in blood lactate ($p<0.001$) during successive high intensity exercise, hence improved VO_2 kinetics [49]. Such beneficial effect would likely to discourage the short-cut methods such as the use of prohibited substances and techniques [49].

The functional advantage of blood doping practices is dependent on the level of the increase in RBC mass [10]. This suggests that athletes with the lowest normal Hb concentration would have the greatest conceivable benefit [10]. But gain in performance cannot be justified for its abuse in sports due to a number of reasons. Firstly, the Hct does not reflect aerobic performance, as highly or over trained athletes usually have low Hct, due to training induced 'hemodilution' [34,36]. Secondly, neither did these trials explore the health risk of rHu FPO abuse in endurance sports, nor did they investigate the hemodynamic changes on the cardiovascular system of the participants [34]. Although these experiments were cautiously performed to avoid possible detrimental effects, still the findings of some negative effects such as hypertension, increased exertion, or reduction in maximum heart rate were not investigated in some of the above studies [32,34]. More over some studies have reported EPO-induced arterial and cerebral vasoconstriction and at higher doses, it elevates Blood Pressure (BP) at rest and also during exercise [34,35]. Other studies have reported two fold risk of hypertension with 10% rise in haematocrit [48]. Hence in competitive sports, prolonged EPO abuse can lead to several potential risks for the athletes, not only due to secrecy of such practices, but other risks such as infection, thromboembolic events and even death [16,35,41]. Such drastic consequences have been reported in a lab study on rats [16]. Due to elevated Hct, hypertension, increased RBC mass, there was sudden cardiac death in rats during the study [16]. The autopsy revealed left ventricular hypertrophy, congestion in brain due to rHu EPO treatment and maximum exercise [16]. Similarly in a case report of a 26-year-old cyclist, who presented with chronic headaches and photophobia for two months, admitted the use of 200 IU of rHu EPO and growth hormones [41]. His brain MRI showed cerebral sinus thrombosis and obstruction of the superior and transverse sagittal

sinus. These results suggest that the mortality risk can be higher with the rHu EPO abuse and other banned drugs [4,16,18].

Conclusion

The studies showed significant improvement in Hb, VO_2 max and packed cell volume after using rHu EPO or blood transfusion technique. Hence there was increase in time to exhaustion and better aerobic performance in the healthy trained and untrained subjects. Thus, there is a strong evidence to indicate that rHu EPO increases exercise performance by mechanisms no other than improving oxygen carrying capacity of the blood. Such physical performance is also achievable through endurance training. However such studies motivates athlete to rely on 'doping cocktail' for quicker results. This comes with a heavy price, as mortality risk is higher due to drug abuse [16,18,41]. Unfortunately there is a lack of vital information on the hazards of illegal use of rHu EPO in sports. Also, the favourable effects of rHu EPO in elite endurance athlete still remain unclear. There is shortage of the information on the mechanism by which rHu EPO causes serious complications such as MI, stroke, seizure, hypertension, thromboembolism, congestive heart failure and even death that has been associated with the rHu EPO abuse. Blood transfusion has gained popularity in endurance competitions due to the difficulty in detection. It should be the responsibility of the athletes, coaches and team doctors to discourage such artificial methods of performance enhancement, which not only disturb the natural haemostasis of the body, but also distort the image of the sports. Future long-term studies are needed to explore the harmful effects of rHu EPO abuse and its prevalence in athletes.

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