

Yatsiv I, Grigoriadis N, Simeonidou C, Stahel PF, Schmidt OI, Alexandrovitch AG, Tsenter J, Shohami E. Erythropoietin is neuroprotective, improves functional recovery, and reduces neuronal apoptosis and inflammation in a rodent model of experimental closed head injury. *The FASEB Journal*. 2005;19:1701-1703.

Traumatic brain injury (TBI) is a life threatening condition and is the leading cause of mortality in the young population of industrialized countries. Yatsiv et al. states that the physiology of the brain after TBI is still not well understood and management for it is generally attempting to reduce brain edema, and prevent hypoxia and shock. Recombinant human erythropoietin (rhEpo) has been demonstrated to have anti-inflammatory and antiapoptotic effects on various tissues. The purpose of this study was to observe the cellular and neurobehavioral effects of Epo on rats and mice with TBI.

Each rat and mouse was anesthetized and an incision was made on the head to pull back the skin. A cone was placed on the skull over the left frontal lobe and a weight was dropped on the cone to induce a TBI in the animal. The animals were given oxygen for two minutes and returned to their cages. One hour post injury the animals were given the neurological severity score (NSS) and divided into two groups: vehicle/ control, or rhEpo. Each group received treatments at one hour and 24 hours post injury. NSS measurements were taken in both groups at days 1, 3, 7, 10 and 14. Cognitive function was tested with the object recognition test (ORT) which was used to evaluate the animals' memories. The control and experimental groups were divided so that some animals were tested on day 3 post injury and the other groups were tested day 8. The animals were then given a lethal injection and sections of the injured brain were preserved and studied. Axon damage was assessed by evaluating the density of axons in the damaged tissue and was graded 0-2: 0 for normal density and pathology; 1 for patches of axonal damage and mild axon loss; 2 for extensive axon damage and loss.

Rats and mice treated with rhEpo after TBI had similar neurobehavioral function as the control group 1 hour post injury. However, this group showed better neurobehavioral function beginning on day three and continued to improve more quickly than the control group. Cognitive functions were assessed at 3 days post injury for some animals in which the experimental group demonstrated a better memory, thus higher cognitive function than the control group. At 8 days post injury, no significant differences were found between the groups with the ORT. Upon examination, both groups had similar amounts of axonal loss and injury at 24 hours post injury. However, the experimental animals had a significant increase in the amount of grade 0 axons, and decrease in the amount of grade 2 axons compared to the control group. Both groups had similar amounts of grade 1 axonal damage.

This study is a prospective, controlled, cohort study. The level of evidence for this study according to the AAOS scale is level V since this is an animal study. The strength of recommendation according to SORT is grade C, as this is a low evidence level study which does not allow for strong clinical implications.

While this study has little clinical implication to athletic training since it is an animal study, the issue of TBI damage is relevant to athletes. Many athletes are at risk for TBIs, especially those in full contact sports, such as football and wrestling. While these TBIs may be mild, they still pose a significant risk to the athletes. If Epo proves to reduce detrimental effects of TBIs in humans, it can be administered to athletes who sustain these injuries. The best information for patient education of athletes in the athletic training setting is the introduction. It

should be stressed that after a TBI is sustained much of the tissue is damaged and currently the only approved treatments aim to reduce edema and decrease intracranial pressure. Thus, prevention is key; this will help me stress to athletes to report concussion symptoms immediately and always wear protective equipment.

# Critical Appraisal Checklist

## *Evaluation Criteria:*

*(Score from 0 -2 on all questions using guidelines on pages 2-9)*

### **Study Question**

1. Was the relevant background work cited to establish a foundation for the research question? **2**

### **Study Design**

2. Was a comparison group used? **2**
3. Was patient status at more than one time point considered? **2**
4. Was data collection performed prospectively? **2**
5. Were patients randomized to groups? **2**
6. Were patients blinded to extent possible? **2**
7. Were treatment providers blinded to the extent possible? **2**
8. Was an independent evaluator used to administer outcome measures? **2**

### **Subjects**

9. Did sampling procedures minimize sample / selection biases? **0**
10. Were inclusion / exclusion criteria defined? **0**
11. Was an appropriate enrollment obtained? **0**
12. Was appropriate retention / follow up obtained? **2**

### **Intervention**

13. Was the intervention applied according to established principles? **2**
14. Were biases due to treatment provider minimized (i.e., attention, training)? **2**
15. Was the intervention compared with the appropriate comparator? **1**

### **Outcomes**

16. Was an appropriate primary outcome defined? **1**
17. Were appropriate secondary outcomes considered? **1**
18. Was an appropriate follow-up period incorporated? **2**

### **Analysis**

19. Was an appropriate statistical test(s) performed to indicate differences related to the intervention? **2**
20. Was it established that the study had significant power to identify treatment effects? **1**
21. Was the size and significance of the effects reported? **2**
22. Were missing data accounted for and considered in analyses? **2**
23. Were clinical and practical significance considered in interpreting results? **1**

### **Recommendations**

24. Were the conclusions/clinical recommendations supported by the study objectives, analysis, and results? **2**

**Total Quality Score (Sum of above / 48) = 35 = 72.9%**