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Editorial

*Corresponding author
Florian Simon, PD Dr. med
Department of Vascular and Endovascular Surgery
Heinrich-Heine-University of Düsseldorf
Moorenstr. 5 D-40225 Düsseldorf
Germany
Tel. 49 211 81 7168
Fax: 49 211 81 19091
E-mail: florian.simon@med.uni-duesseldorf.de

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Kidney Ischemia and Reperfusion Injury – Field of Glory or Warterloo for Erythropoietin?

Florian Simon*, Hubert Schelzig and Alexander Oberhuber

Department of Vascular and Endovascular Surgery, Heinrich-Heine-University of Düsseldorf, Germany

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When asking clinicians about their knowledge about Erythropoietin (EPO) most of them would say that it increases Red Blood Cell (RBC) count and can therefore be used to treat anemia, is produced in the kidneys and can be misused as doping agent in sports. The way to reach this today's common knowledge was long and hard. In the year 1667 by giving a lambs blood to an anemic patient and the lucky outcome that the patient felt better afterwards, it became clear that blood could heal.[1] Over two centuries later in a rabbit experimental set-up where plasma was transduced between an anemic and a healthy animal it could be seen that the red blood cell count increased in the anemic one. This gave birth to the thesis that a humeral factor is responsible and was named hemopoietin.[2] Seventy years later this mysterious substance was found by Goldwasser in patients´ urine[3] and was later on cloned by a colleague of him[4] what marked the beginning of EPOs therapeutic career in treating anemia that lasts on until today.

But meanwhile it became clear that there is more to EPO than just to increase red blood cell count. It was found that it also has antiapoptotic, antioxidative and angiogenetic effects that can be used to avoid and treat tissue damage in general.[5,6] This is possible, because of the widespread distribution of the EPO receptor that can mediate non-hematopoietic effects.[7] This is also true for renal tissue where the EPO receptor can be found in the cortex, medulla, papilla, mesangial proximal tubular and medullary collecting duct cells.[8] This means that the kidney tissue might also profit from the antiapoptotic effect of EPO when the kidney is confronted with an Ischemia and Reperfusion (I/R) injury. This scenario might appear during kidney transplantation or during aortic cross clamping as used in aneurysm repair surgery. And indeed experimental data suggest that EPO might protect kidneys in varying species when facing ischemia and reperfusion. In a rat model the animals were subjected to renal ischemia for 45 minutes and received EPO prior to I/R. The renal dysfunction and injury was measured by serum biochemical markers and after death of the animals by histologic evaluation using TUNEL assay and morphological criteria. The authors found that the EPO group had significantly lower serum creatinine levels and that morphological changes of the renal tissue especially of the tubular cells was much less than in the placebo group. Also apoptotic markers like BAX were reduced and the TUNEL assay showed only some positive cells.[9] This effect of renal tissue protection by EPO application was also seen in other rodent models.[10-12] Not only small animal models, but also experimental set-up with large animals that are much closer to clinical reality showed these positive effects. Maio et al.[13] demonstrated that organs obtained subsequent to cardiac death, but treated with EPO, showed improved organ function compared to organs without special treatment. In this context the kidneys were challenged with 30 minutes of warm ischemia and then transplanted after 24 hours of cold storage. Four hours after transplantation organ function was asset and showed significantly attenuated renal/glomerular dysfunction as well as an improved tubular function of the kidneys measured by N-acetyl-beta-D-glucosaminidase (NAG), Aspartate aminotransferase (AST), Glutathione S-transferase (GST), urea and fractional excretion of sodium. Along with improved parameters of inflammation, oxidative

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stress etc. histologic evaluation showed explicit a reduction of the severe acute tubular damage including nuclear condensation, loss of nuclei, cytoplasmic swelling and cellular debris in the tubular lumen.[13] Other working groups could also prove these positive effects of EPO during renal ischemia in large animal models.[14,15] It is recognizable that there was also effort to test EPO in a non-human primate model what shows that EPO is of high interest in protecting kidneys against ischemia and reperfusion. These primates underwent 90 minutes of renal warm ischemia and were observed for further 7 days. EPO was given 5 minutes before clamping and additionally 5 minutes before blood flow was restored. The main findings were that EPO protected the renal tissue and therefore organ function measured by creatinine and blood urea nitrogen, additionally cystatin c and Interleukin-6 (IL-6) levels were improved. The number of apoptotic cells was also lower in the EPO group showing that medical treatment can protect renal cells from programmed cell death caused by ischemia and reperfusion.[16] These findings indicated that EPO might hold the promise many scientists and clinicians were waiting for.

The next step was to use EPO in real life meaning clinical settings of patients suffering from renal ischemia and reperfusion injury. A typical example for this clinical scenario is the transplantation of a kidney. Aydin et al. showed in the PROTECT study, a 12-month single center kidney transplantation study with high-dose EPO (3.3×10^4 International Units (IU) on 3 consecutive days, starting 3-4 h before the transplantation and 24 h and 48 h after reperfusion) that there was no beneficial effect to be seen. The group examined incidence of primary non-function and delayed graft function as well as duration of delayed function, renal function and proteinuria up to 1 year and thrombotic adverse events. EPO did not only show no beneficial effects but it also increased thrombotic risk events at 1 month and 1 year.[17] Another study dealing with high-dose EPO (3 doses of 40,000 IU) in kidney transplantation documented also no beneficial EPO effects but no increase in negative side effects. Endpoints were kidney function after 6 weeks after transplantation as well as incidence of delayed graft function and kidney function after 12 months. The authors conclude that the treatment with high-dose EPO after kidney transplantation was well tolerated, but had no effect on long-term graft function.[18] Results that were also seen in other studies dealing with high-dose EPO in renal transplantation.[19,20] Another interesting field of clinical use would be the protection of renal organ function after cardiac surgery. Two studies examined EPO effects in this setting. The first one evaluated the effectiveness of EPO (300 IU/kg before surgery) in the prevention of AKI after Coronary Artery Bypass Grafting (CABG). In the EPO group only 8% developed postoperative acute kidney failure compared to 29% in the placebo group. Both serum creatinine and estimated glomerular filtration rate were significantly improved in the EPO group indicating positive effects on organ function in the treatment group. The author's state by themselves that their study is only of small size that should be seen as a pilot trial that needs confirmation in a larger clinical trial.[21] The second study tested two different doses of EPO (40,000 IU *vs.* 20,000 IU) on kidney function after cardiac surgery. The end-points were the change in urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) concentration from baseline, creatinine and cystatine C levels as well as acute inflammatory response (Interleukin 6 (IL-6) and Interleukin 8 (IL-8)). EPO treatment did not significantly modify the levels of the above mentioned parameters. The incidence of acute kidney injury and inflammatory cytokines levels did not differ between groups. Therefore one must say that, although safe, EPO demonstrated neither nephroprotective nor anti-inflammatory properties.[22]

A possible explanation for the ineffectiveness of EPO in clinical trials in comparison to experimental data might be that not enough effort was undertaken to examine side effects arising in older individuals. The authors own working group examined therefore in a large animal model the influence of atherosclerosis on EPO function in kidneys. We could not find any positive effect of EPO after an ischemia/reperfusion period. The reason for that controversal outcome was that the absolute number of EPO receptors in atherosclerotic renal tissue was up to 20 times lower as in the tissue of young and healthy animals.[23]

Regarding all this results, both experimental and clinical, one must say that EPO might not have the effect that everyone desired. When looking at EPO and its effects on renal tissue, future experimental set-ups should take in account that most of the clinical problems are in patients of older age. Therefore we must surely define better experimental set-ups when planning animal models. But EPO is not out of interest only because of its inability to work in atherosclerotic tissue, because there is much to investigate how EPO can help to improve renal function in younger patients e.g. undergoing kidney transplantation or having an ischemic injury after accident. Therefore it is still worth to take a closer look on EPO function and not to give up research on its clinical abilities.

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Author's contribution

Simon wrote article. Schelzig and Oberhuber critically reviewed.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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