Use of Erythropoietin after solid organ transplantation

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Abstract

Anaemia is common after solid organ transplantation. Although many impressive experimental data about the organoprotective properties of erythropoietin (EPO) have been reported, there are only scant clinical and experimental data about EPO use after solid organ transplantation. Since the treatment targets of anaemia in chronic kidney disease cannot be transferred to organ recipients for several reasons (rejection, immunosuppression, infection), the recommendations for optimal targets in the treatment of anaemia remain uncertain. Moreover, further studies will be necessary to clarify whether EPO administration might have haemoglobin-independent beneficial effects.

Keywords: endothelial progenitor cells; erythropoietin; organ transplantation; organoprotection

Anaemia is a major problem in renal failure patients. It has been possible to correct renal anaemia by administration of recombinant erythropoietin (EPO) for two decades. There are many reports about the importance, clinical significance and impact on patient mortality of EPO therapy when used to correct renal anaemia in dialysis patients [1–3]. Although anaemia is relatively common among post-operative solid organ recipients, clinical data regarding EPO use after transplantation and its association with either graft or patient survival are limited. On the other hand, there are some important points to consider with respect to post-transplantation anaemia. First, in the immediate post-transplant period, severe anaemia might result from perisurgical blood loss, postoperative infection or immunosuppressive therapy. Second, independent of anaemia correction, inadequate tissue perfusion can cause cellular hypoxia and acute tubular necrosis in animal models. Third, after initial assessment of the cause of anaemia according to the NKF guidelines, gastrointestinal blood losses have to be carefully excluded. In addition, there are very impressive experimental data about the (haemoglobin-independent) organoprotective effects of EPO in e.g. the infarcted heart [4,5].

One haemoglobin-independent organoprotective property of EPO could be explained by the fact that EPO increases the number of functionally active bone marrow-derived endothelial progenitor cells (EPC). EPCs promote vascular repair processes. EPCs are normally found mainly in the bone marrow, but may also circulate to the vasculature and be incorporated into sites of active neovascularisation [6]. Clinical studies have demonstrated that EPCs derived from bone marrow predict the occurrence of cardiovascular events, including death from cardiovascular causes. Additionally, the intracoronary transplantation of EPCs may improve left ventricular function after acute myocardial infarction in patients with ischaemic heart disease [7]. Although these data are very impressive, there are only scant reports on the use of the therapy after solid organ transplantation. According the recommendations for anaemia in chronic renal failure (haemoglobin should be 11.0 g/dl or greater), much uncertainty remains about the optimal target haemoglobin level in solid organ transplant, especially since it has been shown that partial correction rather than normalisation of haemoglobin levels should be striven for in dialysis patients. Several factors contribute to the development of anaemia, including immunosuppressive therapy, allograft rejection, infection or anti-infecitve therapy. Therefore, treatment and targets in chronic kidney disease cannot be transferred to the solid organ recipient. In addition, anaemia also depends on the time of observation after transplantation. The reasons above explain why there is neither an accepted definition of anaemia nor an accepted target of treatment in this patient cohort.

Renal transplantation

A short pilot study demonstrated that the subcutaneous administration of EPO is effective for the
correction of anaemia after kidney allograft transplantation [8]. Other small prospective studies [9] have proven the safety of EPO [10]. Nevertheless, renal recovery after transplantation does not seem to be positively influenced by the use of EPO [10]. Besides the potential negative side effects of high or normalised haemoglobin levels, e.g. allograft vascular thrombosis, EPO therapy could potentially provide therapeutic benefits. However, the optimal target haemoglobin value after kidney transplantation has yet to be determined. In experimental ischaemic models, EPO has been shown to exert a protective effect on subsequent ischaemic injury of the kidney [11]. Therefore, further clinical and experimental studies on the use of EPO after kidney transplantation are necessary to investigate its influence in various scenarios, such as an ischaemic trauma.

Heart transplantation

Anaemia is recognised as an independent risk factor for mortality after myocardial infarction. Several studies have demonstrated the benefit of anaemia correction in patients with congestive heart failure [12–16]. However, anaemia does not represent an independent mortality risk factor after heart transplantation, but has been associated with functional renal impairment [17]. Post-operative EPO therapy in this case results not only in increased haemoglobin levels, but also in improved quality of life. In an observational study of 37 anaemic heart transplant recipients, renal failure was the sole cause of anaemia in 31 of the patients. Of the twelve of these patients treated with EPO, 8 showed a significantly improved quality of life [18]. There are surprisingly few published reports investigating the role of anaemia in patient mortality after heart transplantation. In an experimental model of myocardial infarction, it was shown that administration of EPO reduces the ischaemic cardiomyocyte loss by approximately 50%, promotes beneficial remodeling and improves haemodynamic function [19].

Liver transplantation

Despite the reported protective effects of EPO in ischaemia and reperfusion models, to the best of our knowledge, there are only limited reports about the EPO-protective effects in ischaemic animal liver models [20]. This is even more surprising, because ischaemia and reperfusion are major causes of problems in patients undergoing liver transplantation. In an animal model, at least, the administration of EPO a few minutes before ischaemia led to a reduction in liver injury [20].

Although anaemia is also common in patients with chronic liver disease, its exact prevalence and incidence in liver transplant recipients has not yet been investigated. In retrospective studies, approximately 5% of liver transplant recipients were found to have haemoglobin levels of < 9 g/dl, or approximately 30% < 10.5 g/dl [21]. Anaemia was found to be present in 65%, 50% and 53% of patients before orthotopic liver transplantation, 6 months and 12 months later, respectively, in another retrospective analysis. One third of the patients received EPO 6 and 12 months after transplantation [21]. Since there are no evident data about beneficial EPO effects vis-a-vis patient survival, one has to consider that there could also be negative effects with respect to graft functioning.

Conclusion

Despite promising first experimental data regarding the organoprotective properties of EPO, especially in ischaemic animal models, little is known about the usefulness of EPO administration after solid organ transplantation in human subjects. Experimental and clinical studies will be necessary to evaluate the full therapeutic properties, risks and benefits. EPO has been shown to increase haemoglobin, but the optimal target level of haemoglobin is thus far unknown. Therefore, one may only speculate as to whether EPO use furnishes any additional benefits with respect to organ and/or patient survival.

Conflict of interest statement. None declared.

References


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