Hyperbaric oxygen with cord blood transplants: Filling the donor gap

Aljitawi OS, Paul S, Ganguly A, Lin TL, Ganguly S, Vielhauer G, Capitano ML, Cantilena A, Lipe B, Mahnken JD, Wise A, Berry A, Singh AK, Shune L, Lominska C, Abhyankar S, Allin D, Laughlin M, McGuirk JP, Broxmeyer HE. (Division of Hematologic Malignancies and Cellular Therapy; Hematology and Transplantation Translational Research Laboratory; Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, Kansas; Division of Hematology/Oncology and Bone Marrow Transplantation Program, University of Rochester Medical Center, Rochester, New York; Department of Urology, University of Kansas Medical Center, Kansas City, Kansas; Department of Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, Indiana; Cardiovascular Research Institute, Department of Biostatistics, Department of Radiation Oncology, Department of Emergency Medicine, University of Kansas Medical Center, Kansas City, Kansas; Cleveland Cord Blood Center, Cleveland, Ohio; Department of Biomedical Engineering, Case Western Reserve University, Cleveland, Ohio, USA.) Erythropoietin modulation is associated with improved homing and engraftment after umbilical cord blood transplantation. *Blood* 2016;**128:**3000–10

SUMMARY

Delayed engraftment represents one of the most important limitations of umbilical cord blood transplantation (UCBT).[1] To overcome this limitation, Aljitawi *et al.*'s paper, comprising both preclinical experiments and a first-in-humans prospective clinical study, explores a new way to accelerate engraftment in these patients. The hypothesis is that erythropoietin has a negative impact on stem cell homing and engraftment into the bone marrow niche. Since erythropoietin can be downregulated by hyperbaric oxygen (HBO) therapy, HBO may represent a way to accelerate engraftment in UCBT.

Previously, this group had successfully shown in a series of murine experiments that engraftment, as well as immune reconstitution from human CD34+ UCB cells, was significantly better if the mice were exposed to HBO with their transplants.[2] The current paper builds on these findings. The preclinical part of the paper aims to delineate the mechanisms by which HBO enhances engraftment. First, the researchers established the presence of erythropoietin receptors on a subset of CD34+ human UCB cells by flowcytometry and western blot. Further, a functional interaction between erythropoietin and erythropoietin receptors was demonstrated by reduced erythroid differentiation in the presence of RNA interference against the expression of the erythropoietin receptor gene. Subsequently, in a series of experiments performed on CD34+ cells migrating along a stromal cell-derived factor-1 gradient, they showed that erythropoietin inhibits migration of cells along the gradient. They also showed that this inhibition is mediated through erythropoietin–erythropoietin receptor interactions.

The negative relationship between HBO exposure and serum erythropoietin levels was shown in a murine model. They also showed that HBO-treated mice have a higher proportion of CD34+ cells in the marrow 3 hours after transplantation. This difference could be abrogated by erythropoietin treatment after HBO exposure. In a simulated marrow environment, it was shown again that erythropoietin inhibits both migrations as well as myeloid differentiation of CD34+ cells.

Based on these preclinical experiments, a clinical, prospective, interventional, single-arm study was planned. Patients aged 17–70 years undergoing UCBT were recruited. In addition to the routine UCBT process, patients received a single session of 90 minutes of HBO therapy 6 hours before stem cell infusion. The primary outcomes were safety and tolerability, and the secondary outcomes were rates of neutrophil and platelet engraftment.

Fifteen patients were recruited with a median age 44 years. All underwent UCBT for malignant indications, mostly (12/15) for acute myeloid leukaemia. HBO was remarkably well tolerated with no grade III–IV toxicities attributable to the procedure. A few events of uncertain relation to HBO (self-resolving subcutaneous nodules and self-resolving shoulder pain) were noted. When compared to historical cohorts, rates of neutrophil engraftment were faster by around one week, although statistical significance was not achieved possibly due to the small number of patients (Table I). All 15 patients in the cohort

TABLE I. Median (range) day of neutrophil and platelet engraftment compared to historical cohorts

Item	Hyperbaric oxygen (*n*=9 for RIC, *n*=6 for MAC)	Historical control (*n*=27 for RIC, *n*=21 for MAC)
Neutrophil (RIC)	7 (6–17)	14 (5–28)
Neutrophil (MAC)	24.5 (16–45)	33 (13–71)
Platelet (RIC)	32 (0–85)	38 (0–112)
Platelet (MAC)	54.5 (30–84)	50 (29–161)

MAC myeloablative conditioning RIC reduced-intensity conditioning

achieved platelet engraftment compared to only 69% in the historical cohort. Even red blood cell recovery was faster in the HBO-exposed cohort. Survival at day 100 was 100% compared to 76% in the historical cohort.

COMMENT

The chance of finding a matched-related donor for patients requiring allogenic haematopoietic stem cell transplantation is only 25% per sibling. For those who do not have a matched-related donor, the options include matched-unrelated donors, UCBT and haplo-identical donors.[3] In India, finding an appropriate matched-unrelated donor is difficult due to the limited size of domestic registries.[4,5] Haplo-identical transplants are technically difficult and are associated with higher rates of graft failure and graft-versus-host-disease, although progress has been made in this field.[6] In this context, UCBT is a good option for India. However, UCBT is associated with delayed engraftment and a higher risk of graft failure.[1] If this limitation could be overcome, UCBTs would become substantially safer.

A number of ways to achieve this have been explored. These include collecting larger units (placental perfusion), double UCBT, *ex vivo* stem cell expansion or manipulation, double transplants (UCBT with matched-unrelated donor or haplo-identical transplantation), using non-myeloablative conditioning, use of cytokines, intrabone infusions or mesenchymal stem cells.[7] These modalities suffer from limitations such as technical difficulty, high cost and infrastructural requirements, and inferior patient safety.

HBO is a well-established procedure that was developed almost 80 years ago.[8] Typical HBO protocols deliver 100% oxygen at pressures of up to 3 atmospheres. HBO has several distinct advantages over other modalities discussed above.[9] First, the intervention is relatively easy to do. Second, clinically significant toxicity is uncommon and generally self-limited, especially with short protocols as used in the current study. Third, HBO has a large number of established indications (e.g. carbon monoxide poisoning, decompression sickness, anaerobic infections, air embolism, etc.), and existing HBO facilities can be used for UCBT with no need for any modification.

Since the present study has small numbers and a historical cohort, a larger, randomized controlled trial is likely to answer the definitive question on the role of HBO in UCBT. If the benefits shown in the present study are confirmed, HBO would represent a major advance in the field of UCBT, allowing application of the procedure to greater number of patients with significantly less morbidity and mortality. Moreover, since the underlying principles are unlikely to be restricted to UCB cells, there are potential applications of matched related or unrelated donor and haplo-identical transplants as well. These developments are eagerly awaited.

Conflict of interest. None declared

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