FINAL REPORT

TITLE: INFLAMMATORY RESPONSE IN MAJOR INJURY & RECOMBINANT HUMAN ERYTHROPOIETIN (IRMINE) - A PILOT STUDY

Background

Mortality after major trauma remains high, despite improvements seen in recent years mirroring the innovations developed by the UK's defence medical services (Jansen et al., 2009). Recombinant human erythropoietin (rh EPO) has been used for many years to manage anaemia in chronic conditions. Improved survival was noted in trauma patients enrolled in randomised studies using rhEPO to treat the anaemia of critical illness (Corwin et al., 2007) (Napolitano et al., 2008). The potential physiological benefits of rhEPO are very wide-spread ranging from improved mitochrondrial function, inflammatory/ immune modulation to neuro-protection (Abdelrahman et al., 2004, Corwin et al., 2007, Joyeux-Faure, 2007, Kao et al., 2010, Maiese K et al., 2005). Further studies have shown no demonstrable benefit in terms of neurological recovery in adults with traumatic brain injury. However, again, improved survival was seen (Gantner et al., 2018, Skrifvars et al., 2018). While there are multiple potential routes via which rhEPO could benefit the major trauma patient, no data exists to elucidate which is the most likely.

Methodology

A Phase II Clinical Trial of Investigational Medicinal Product (CTIMP) pilot study was designed and the methodology/protocol revised iteratively during the course of the pilot. A single blind, randomised, placebo-controlled trial compared rhEPO and saline, with clinical and Laboratory based outcomes.

Ethical Considerations & Consent: Due to the nature of major trauma, the patient is often intubated and ventilated as part of their essential treatment. Available evidence indicates that the earlier rhEPO is administered, the more effective it may be. As the safety profile of rhEPO used in these circumstances is very good, it was decided to randomise and administer the first dose of rhEPO/placebo on the basis of presumed consent (French et al., 2017, Mesgarpour et al., 2014). Consent would then be obtained from their next of kin/legal representative and ultimately from the patient once capacity was recovered.

Study Duration: Pilot was intended to last until a maximum of 10 patients have been recruited and followed up for 30 days

Study Centres: Initially Swansea - Intensive Therapy Unit (ITU), Critical Care and Trauma & Orthopaedic departments Morriston Hospital Swansea, and Institute of Life Science 1, Swansea University, joined by Birmingham – Intensive Care Unit (ICU); NIHR Surgical Reconstruction and Microbiology Research Centre; University of Birmingham Research Labs, Institute for Inflammation and Ageing at Queen Elizabeth Hospital, Birmingham.

Approvals were in place for Nottingham (Queens Medical Centre Intensive Care Unit (ICU); and Department of Academic Orthopaedics at Queens Medical Centre) but recruitment was never initiated.

Objectives: The primary objective of this pilot was to test the trial design and logistics, in preparation for a bid for a multi-centre randomised controlled trial.
The secondary objectives were:

a) To determine whether the use of rhEPO reduces organ failure after severe trauma in adults.
b) To understand the effect of rhEPO on the clinical, cellular & biomolecular manifestations of the systemic inflammatory response to injury.
c) To identify whether human haemopoeitic bone marrow responds to rhEPO after severe injury.
d) To determine whether rhEPO is associated with an increase in thromboembolic events despite appropriate standard of care prophylaxis.
e) To determine whether the use of rhEPO reduces 30 day mortality after severe trauma in adults.

Inclusion Criteria: Adult (aged 18-75 years) blunt trauma patients admitted to ITU with injury severity score (ISS) ≥16 & stay expected to last ≥3 days. The initial upper age limit was increased to 75 years in the hope of improving recruitment.

IMP/Placebo: After screening and randomisation***,*** the IMP was prescribed by a doctor on the delegation log between 09:00 and 11:00 on day 1 post admission (rhEPO 40,000 units (Eprex epoetin alfa JANSSEN)/Placebo normal saline 1ml (Fresenius Kabi Ltd). Repeat doses at day 8 and 15 were abandoned after protocol amendment in the light of published evidence indicating a possible survival benefit with a single post-admission dose (Gantner et al., 2018, Skrifvars et al., 2018).

Safety Reporting: The initial approach of reporting all adverse events was modified in line with published recommendations as following major trauma there are multiple well recognised complications which form part of the expected natural history of the disease (Cook et al., 2008). Appropriate preferred terms were identified to assure consistency in reporting.

Statistical Methodology and Analysis; The ability to recruit was be assessed. Daily Denver Multiple Organ Failure Scores (DMOFS) were compared between those randomised to receive rhEPO versus placebo control. Peripheral blood samples from participants were analysed. Comparisons were to be made by a blinded statistician.

Results

Study Duration: The study opened to recruitment in Swansea on 14/11/2016 and randomised 4 patients. Birmingham opened for recruitment on 04/12/2017, randomised 2 patients within 4 days and screened 17 patients.

Swansea Trials Unit handed over trial management to the sponsor on 15/12/2017. Recruitment was halted on 31/12/2017 and the trial closed on 12/07/2018 after the application for EME funding was rejected.

Ethical Considerations & Consent: Of the 6 patients randomised, one was withdrawn as the patient's partner was unable to give consent. In another, an advanced directive came to light and active ITU management and trial involvement was withdrawn.

Primary Objective: The trial design fundamentally worked in terms of potential patients being identified and screened for enrolment. One patient in Swansea was not successfully randomised due to a failure of the randomisation software and backup arrangements. Due to changes in the referral and transfer patterns in South Wales, our ability to recruit locally was severely impaired.

The logistics of IMP supply, packaging and blinding of clinical staff worked well both in Swansea and Birmingham.

a) The Denver Multiple Organ Failure score was calculated daily for each patient but no inferences can be made regarding any impact of rhEPO (Hutchings et al., 2017).
b) Similarly, there is insufficient data to determine any impact of rhEPO on the clinical, cellular & biomolecular manifestations of the systemic inflammatory response to injury.
c) Only one bone marrow aspirate was obtained and hence no inferences can be made whether rhEPO alters bone marrow activity after severe injury.
d) No thromboembolic events were recorded on the relevant CRF, nor as SAEs .
e) The 30 day mortality for patients remaining in the study was zero.

Discussion

The fundamental goal of the Pilot Study was to generate data which would support an application to EME to fund a major multicentre randomised trial. This was unsuccessful.

In hindsight, attempting recruitment at all in the Swansea site was more or less fruitless and an argument could be made for this never having been attempted, although quite how the Pilot would have launched at all in those circumstances would be difficult to envisage.

A large amount of time was spent on the reporting of well-recognised complications of major trauma, when these data would be collected on CRFs and reported as part of the outcomes of the study. This was rectified with further protocol amendment.

However, the patients who were recruited were ultimately very positive about their involvement in the study. The consent process was revised so that if the next on kin/legal representative was unable to give consent, then data and sample collection stopped. The proviso to then approach the patient for consent once they had regained capacity was clarified. Although blood samples would not have been possible, the data to calculate the Denver Multiple Organ Failure Score would still be available.

Due to the delays in launching due to approvals and paucity of recruitment, the initial invited full EME application was never submitted and unfortunately a revised application was rejected. The reviewers felt that a study specifically to look at survival was justified, but clearly this could not be hosted in Swansea.

REFERENCES

ABDELRAHMAN, M., SHARPLES, E. J., MCDONALD, M. C., COLLIN, M., PATEL, N. S. A., YAQOOB, M. M. & THIEMERMANN, C. (2004) Erythropoietin Attenuates the Tissue Injury Associated With Hemorrhagic Shock and Myocardial Ischemia. *Shock,* 22, 63-69.

COOK, D., LAUZIER, F. O., ROCHA, M. G., SAYLES, M. J. & FINFER, S. (2008) Serious adverse events in academic critical care research. *Canadian Medical Association Journal,* 178, 1181-1184.

CORWIN, H. L., GETTINGER, A., FABIAN, T. C., MAY, A., PEARL, R. G., HEARD, S., AN, R., BOWERS, P. J., BURTON, P., KLAUSNER, M. A., CORWIN, M. J. & GROUP, E. P. O. C. C. T. (2007) Efficacy and safety of epoetin alfa in critically ill patients. *The New England journal of medicine,* 357, 965-76.

FRENCH, C. J., GLASSFORD, N. J., GANTNER, D., HIGGINS, A. M., COOPER, D. J., NICHOL, A., SKRIFVARS, M. B., IMBERGER, G., PRESNEILL, J., BAILEY, M. & BELLOMO, R. (2017) Erythropoiesis-stimulating Agents in Critically Ill Trauma Patients: A Systematic Review and Meta-analysis. *Annals of surgery,* 265, 54-62.

GANTNER, D. C., BAILEY, M., PRESNEILL, J., FRENCH, C. J., NICHOL, A., LITTLE, L. & BELLOMO, R. (2018) Erythropoietin to reduce mortality in traumatic brain injury: a post-hoc dose-effect analysis. *Annals of surgery,* 267, 585-589.

HUTCHINGS, L., WATKINSON, P., YOUNG, J. D. & WILLETT, K. (2017) Defining multiple organ failure after major trauma: A comparison of the Denver, Sequential Organ Failure Assessment and Marshall scoring systems. *The Journal of Trauma and Acute Care Surgery,* 82, 534-541.

JANSEN, J. O., THOMAS, R., LOUDON, M. A. & BROOKS, A. (2009) Damage control resuscitation for patients with major trauma. *BMJ,* 338, 1436-1440.

JOYEUX-FAURE, M. (2007) Cellular Protection by Erythropoietin: New Therapeutic Implications? *Journal of Pharmacology and Experimental Therapeutics,* 323, 759-762.

KAO, R. L. C., XENOCOSTAS, A., RUI, T., HUANG, W. & MARTIN, C. M. (2010) The Effect of Erythropoietin on Microcirculation Perfusion and Tissue Bioenergetics of the Small Intestine in a Hemorrhagic Shock and Resuscitation Rat Model. *The Journal of Trauma and Acute Care Surgery,* 68, 1342-1348 10.1097/TA.0b013e3181d27dbe.

MAIESE K, LI F & Z., C. (2005) New avenues of exploration for erythropoietin. *JAMA: The Journal of the American Medical Association,* 293, 90-95.

MESGARPOUR, B., HEIDINGER, B. H., ROTH, D., SCHMITZ, S., WALSH, C. D. & HERKNER, H. (2014) Safety of off-label erythropoiesis stimulating agents for critically ill patients. *The Cochrane Library*.

NAPOLITANO, L. M., FABIAN, T. C., KELLY, K. M., BAILEY, J. A., BLOCK, E. F., LANGHOLFF, W., ENNY, C. & CORWIN, H. L. (2008) Improved Survival of Critically Ill Trauma Patients Treated With Recombinant Human Erythropoietin. *The Journal of Trauma and Acute Care Surgery,* 65, 285-299 10.1097/TA.0b013e31817f2c6e.

SKRIFVARS, M. B., FRENCH, C., BAILEY, M., PRESNEILL, J., NICHOL, A., LITTLE, L., DURANTEA, J., HUET, O., HADDAD, S. & ARABI, Y. (2018) Cause and Timing of Death and Subgroup Differential Effects of Erythropoietin in the EPO-TBI Study. *Journal of neurotrauma,* 35, 333-340.