REVIEW PAPER

USE OF UMBILICAL CORD BLOOD (UCB) STEM CELLS IN NEONATAL HYPOXIC ISCHEMIC ENCEPHALOPATHY

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A. INTRODUCTION

Despite major advances in recent years in the management of neonatal hypoxic ischemic encephalopathy (HIE), particularly in cerebral cooling, there remains a substantial proportion of such babies who still have adverse outcomes. There had been increasing interests from patient families and clinicians about the possibility of use of umbilical cord blood stem cells, particularly autologous cord stem cells, in neonatal hypoxic ischemic encephalopathy, since the publication of a report by Michael Cotten et al, which demonstrated improved outcomes. [1]

B. OBJECTIVE

Review current literature to determine the scientific validity of using umbilical cord blood stem cells in neonatal HIE, and to provide a recommendation on whether it is standard of care.

C. LITERATURE SEARCH

To determine the scientific merit of using umbilical cord stem cells as compared to placebo or controls in neonates of less than 28 days old with hypoxic ischemic encephalopathy, the following keywords were used: HIE, hypoxic ischemic encephalopathy, stem cell transplantation, stem cell, mesenchymal stem cell, autologous stem cell, umbilical cord blood. Pre-clinical studies, including animal studies, paediatric patients older than 28 days old or adult patients were excluded. Studies on patients with established cerebral palsy were also excluded. Databases accessed included PubMed, EmBASE, CINAHL and Cochrane. The dates accessed were from 12th Nov 2018 – 19th Nov 2018. All language mediums were included. Independent searches were conducted by all 4 members of the workgroup.

Based on the above search, only 1 published study was found to have fulfilled the criteria.[1] This was a phase 1 clinical trial to assess the safety and feasibility of providing autologous umbilical cord blood cells to neonates with HIE. Twenty-three patients were recruited into the intervention arm and they were compared against 82 infants with HIE in the historical control arm. Both groups received therapeutic cooling. After 1 year, the odds ratio (OR) for mortality or Bayley III scores < 85 for infants who received cells compared with no cells was 0.27 with a 95% CI [0.08, 0.92].

D. DISCUSSION

Although the results were promising, with a statistically significant OR of 0.27, 95% CI [0.08, 0.92], Cotten's study is the only study published so far that addressed this issue. This study was also designed as a feasibility study and with report of only

short-term outcome at 1 year of age. Moreover the study was not a randomised-controlled trial. Randomised-controlled trials using either autologous or allogeneic source of cord blood cells are needed especially those that study longer term neurodevelopmental outcomes. Such trials are currently planned or ongoing. [2, 3]

At the current moment, there are a number of unanswered questions regarding umbilical cord blood stem cell transfusions. This include identification of which cell populations or combination of cell populations in UCB that confer therapeutic effect, how to optimize their isolation and delivery, the best route for delivery, determining the optimal dose and number of doses needed and finally, the appropriate time window for administration in order to maximize benefit while minimizing risk.

Additional challenges for using cord blood for this purpose include the recent introduction in evidence-based neonatal practice towards the use of delayed cord clamping at the time of delivery, which could potentially reduce the volume of cord blood available for collection. There is also currently research into umbilical cord milking in infants who had suffered in-utero hypoxia-ischemia. This has the potential to mimic the effect of autologous cord blood cell transfusion and is technically comparatively straightforward. [4, 5]

The use of non-autologous (allogeneic) umbilical cord blood stem cell transfusion has been studied in children with cerebral palsy.[6] It has not been performed in neonates with HIE. The use of allogeneic cells may increase the availability of cord blood cells for use in newborns with HIE.

In conclusion multicentre randomised-controlled trials are needed to address this clinical question. It is unlikely that there will be a clear answer over the next 3 to 5 years.

E. RECOMMENDATIONS

The workgroup concluded that there is insufficient evidence currently to support the routine use of umbilical cord stem cell infusion in neonatal hypoxic ischemic encephalopathy.

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