

Tract-based spatial statistics investigation of the effects of hypothermic therapy for neonatal encephalopathy in a South Indian neonatal unit

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Introduction

Diffusion tensor imaging (DTI) analysed by Tract-based Spatial Statistics (TBSS) has proven a viable biomarker for detecting treatment effects in asphyxial neonatal encephalopathy (NE)^[1]. Rescue hypothermic neuroprotection combined with intensive care improves neurological outcomes and reduces brain injury following NE in high-income countries^[2]. The population co-morbidities of infants with NE in low and mid income countries (LMIC) are very different to those of high-income countries; therefore therapeutic hypothermia (TH) efficacy in high-income countries cannot be extrapolated to LMIC^[3]. We assessed the effect of TH on brain tissue injury following NE using DTI-TBSS in a level 2 public sector neonatal unit in South India (Clinical Trial No: NCT01138176).

Patients and methods

The study group consisted of 33 infants (gestational age >36 wk; birth weight >1800 g) diagnosed with NE. 16 subjects were randomly allocated within 6 h of birth to be treated with TH (rectal temperature reduced to 33.5°C for 72 h); the other 17 received standard care. DTI in 21 directions (TR=2800 ms, TE = 94 ms, acquisition matrix 128 x 128, nineteen contiguous 5 mm axial slices, b= 0, 1000) was performed on a 1.5T MR imager (Siemens Medical Systems, Erlangen, Germany). All subjects were scanned aged 7 to 13 d. Median (range) postnatal age at scan was 9.5 (6-13) d in the standard care group and 8 (6-12) d in the TH group. Image analysis used the Oxford Centre for Functional MRI of the Brain (FMRIB) software library (FSL)^[4] incorporating the FMRIB diffusion toolbox (FDT) and TBSS tool^[5]. First the DTI images were corrected for eddy currents and head movement and the diffusion vectors were rotated to account for this. Extra-cerebral tissues were removed using an automatic brain extraction process. Fractional anisotropy (FA) maps were then generated using the FDT tool. The FA maps were aligned to a common space using non-linear registration. By aligning each subject's FA map to every other one in turn it was possible to automatically identify the most representative FA map in the group. This was chosen as the target image for the subsequent registrations. A mean FA map was then generated. This was 'thinned' to create a mean FA skeleton representing the white matter tracts common to all the subjects. Each subject's aligned FA image was then projected onto the skeleton. A skeleton threshold of FA >0.15 was chosen for the statistical analysis. This is low enough to include the major white matter tracts in the damaged neonatal brain but not so low as to include minor tracts in which there tends to be greater cross-subject variability and less effective alignments. A voxel-wise cross-subject analysis was then performed; fully corrected across space using threshold-free cluster enhancement. A probability (p) <0.05 was considered significant. Postnatal age at scan was introduced as a confounding variable into the general linear model thus the results were independent of this factor. As a further step the FA in five portions of the skeleton were measured for each subject. The portions corresponded to the left and right anterior limb of the internal capsule (ALIC), left and right posterior limb of the internal capsule (PLIC) and the corpus callosum.

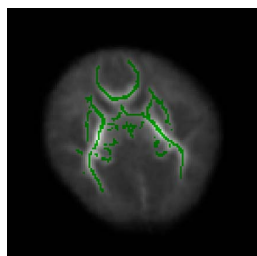
Results

Six infants died before MRI. Two DTI data sets were unusable due to artefacts; the remaining 24 datasets were analysed. The Figure shows the mean FA image for all subjects with the FA skeleton superimposed. According to the voxel-wise analyses there was no significant FA difference between the cooled and non-cooled groups indicating a similar degree of injury to the white matter tracts. There was no significant mean FA difference in the 5 white matter tract areas between TH and standard care groups (see Table).

Discussion

DTI-TBSS indicates that TH did not reduce white matter injury following NE in this population; this may be due to the different population co-morbidities and/or higher incidence of perinatal sepsis. Carefully controlled clinical trials are required before TH is routinely used in clinical practice in LMIC to obtain a better understanding of the injury pattern and aetiology in NE in these settings.

Figure: Mean FA map with FA skeleton overlaid in green. There were no significantly different voxels between the treated and standard care groups p<0.05



	TH (n=12)	Standard Care (n=12)	p-value
Right PLIC	0.342 ±0.042	0.352 ±0.030	0.74
Left PLIC	0.328 ±0.033	0.350 ±0.027	0.51
Right ALIC	0.234 ±0.037	0.252 ±0.025	0.09
Left ALIC	0.217 ±0.037	0.229 ±0.022	0.20
Corpus callosum	0.339 ±0.061	0.346 ±0.041	0.35

Table: Mean FA in selected white-matter areas

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