Pre-emptive morphine during therapeutic hypothermia after neonatal encephalopathy: A secondary analysis

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Abstract

Although therapeutic hypothermia (TH) improves outcomes after neonatal encephalopathy (NE), the safety and efficacy of pre-emptive opioid sedation during cooling therapy is unclear. We performed a secondary analysis of the data from a large multi-country prospective observational study (MARBLE) to examine the association of pre-emptive morphine infusion during TH on brain injury and neurodevelopmental outcomes after NE. All recruited infants had 3Telsa magnetic resonance (MR) imaging, and spectroscopy at 1 week, and neurodevelopmental outcome assessments at 22 months. Of 223 babies recruited to the MARBLE study, the data on sedation were available from 169 babies with moderate (n=150) or severe NE (n=19). Although the baseline characteristics and admission status were similar, the babies who received morphine infusion (n=141) were more hypotensive (49% vs. 25%, p=0.02) and had a significantly longer hospital stay (12 days vs. 9 days, p=0.009) than those who did not (n=28). Basal ganglia/thalamic injury (score $\geq$1) and cortical injury (score $\geq$1) was seen in 34/141 (24%) and 37/141 (26%) respectively, of the morphine group and 4/28 (14%) and 3/28 (11%) of the non-morphine group (p>0.05). On regression modelling adjusted for potential confounders, pre-emptive morphine was not associated with mean (SD) thalamic N-acetylaspartate (NAA) concentration (6.9$\pm$0.9 versus 6.5$\pm$1.5; p=0.97), and median (IQR) lactate/NAA peak area ratios (0.16 [0.12 - 0.21] versus 0.13 [0.11- 0.18]; p=0.20) at 1 week, and mean (SD) Bayley-III composite motor (92±23 versus 94±10; p=0.98), language (89±22 versus 93±8; p=0.53) and cognitive scores (95±21 versus 99±13; p=0.56) at 22 months. Adverse neurodevelopmental outcome (adjusted for severity of encephalopathy) was seen in 26 (18%) of the morphine group, and none of the no-morphine group (p=0.11). Pre-emptive morphine sedation during TH does not offer any neuroprotective benefits and may be associated with increased hospital

stay. Optimal sedation during induced hypothermia requires further evaluation in clinical trials.

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BACKGROUND

Therapeutic hypothermia has become an established therapy for moderate to severe neonatal encephalopathy in high-income countries (Excellence 2010)(NICE Guidance, 2010), following evidence from several major cooling trials that a controlled and moderate reduction of core body temperature is associated with reduced brain injury and improved survival without long-term neurodisability (Gluckman et al. 2005; Shankaran et al. 2005; Azzopardi et al. 2009). However, the administration of opioid sedation during therapeutic hypothermia and its effect on patient outcomes remains controversial.

Although most cooling trials(Gluckman et al. 2005; Shankaran et al. 2005; Azzopardi et al. 2009), except one(Simbruner et al. 2010), did not mandate specified pre-emptive sedation, routine opioid sedation for reducing presumed discomfort during cooling has become a common practice worldwide. In a recent survey of tertiary cooling centres in the UK and USA, over 80% reported pre-emptive opioid sedation during cooling(Markati et al. 2018). Discomfort of cooling therapy and loss of hypothermic neuroprotection without sedation, were the most common reasons for opioid sedation(Markati et al. 2018).

Pre-clinical data on sedation during cooling is limited and conflicting. Thoresen and colleagues (Thoresen et al. 2001) conducted a study using a newborn piglet model for hypoxic injury which demonstrated no significant reduction in neuropathology scores in piglets that were cooled for 24 hours compared to those that were not cooled. This was in contrast with earlier studies using the same model that had demonstrated significant neuroprotection. The authors hypothesised that this difference was due to the piglets in this study not receiving general anaesthesia

during the cooling period and thereby generating a stress response which led to loss of neuroprotection. However, the clinical applicability of this study to human infants is unclear, in particular the differences in thermogenesis pathways, cooling duration and target cooling temperature.

In contrast, Gunn and colleagues (Gunn et al. 1997) reported significant reductions in neuropathology scores in fetal lambs cooled for 72 hours compared to those that were not, without sedation or general anaesthesia.

The secondary analysis of the National Institute of Child Health and Human Development (NICHD) whole-body cooling trial did not show any association of sedation with neurodevelopmental outcome in cooled babies (Natarajan et al. 2018). Worryingly, a combination of opioid sedation and anticonvulsants were associated with worse outcomes. Recent discontinuation of the POPPI trial due to the adverse effects of morphine has raised further concerns about opioid sedation in babies (Hartley et al. 2018).

This secondary analysis of the Magnetic Resonance Biomarkers in Neonatal Encephalopathy (MARBLE) study (Lally et al. 2018) compared the brain injury and neurodevelopmental outcomes of babies who received pre-emptive morphine sedation during therapeutic hypothermia with those who did not receive morphine. In a sub-group of babies, we examined the total cumulative dose of morphine during cooling therapy and its relationship with whole brain white matter fractional anisotropy.

METHODS

MARBLE was a large, international, prospective, multi-centre study involving 223 encephalopathic babies undergoing therapeutic hypothermia from eight centres in the UK and USA, between January 2013 and June 2016 (Lally et al. 2018). The North London Research Ethics Committee and clinical sites approved the study (11/H0717/6), and informed parental consent was obtained from parents or legal representatives of the infants. The secondary analysis reported here included only babies with moderate or severe encephalopathy as assessed by the National Institute of Child Health and Human Development (NICHD) neurological examination. During the cooling period, the use of pre-emptive morphine or other sedative agents was not mandated and if given, was done so at the discretion of the attending clinician.

All babies had magnetic resonance imaging (MRI) and spectroscopy (MRS) between 4 to 14 days after birth on a 3.0 Tesla scanner using carefully harmonised protocols. Briefly, this included 3D T_1-weighted imaging and 2D axial T_2-weighted imaging, thalamic single voxel spectroscopy, and diffusion tensor imaging(Lally et al. 2018).

The MRS data was analysed centrally by an MR physicist (PJL; 7 years' experience in neonatal MR spectroscopy) and the standard MRI data was reported, masked to clinical outcomes, by a consultant neonatologist (ST; 10 years' experience in neonatal MR imaging) using a ratified scoring system(Rutherford et al. 2010). We used an in-house MR spectroscopy post-processing software for quality assurance and then used LCModel(Provencher 1993) for analysis.

We examined the neurodevelopmental outcome between 20 to 24 months using Bayley Scales of Infant Development exam (Bayley-III, 3rd Edition), and detailed neurological examination. The neurodevelopmental assessments were carried out by trained clinicians blinded to the MR spectroscopy data.

The primary outcome was death or neurodisability defined as either moderate (Bayley-III composite cognitive score 70-84 plus any of: Gross Motor Function Classification System (GMFCS(Palisano et al. 1997)) 2, on-going seizures, or hearing impairment) or severe (Bayley-III composite cognitive score <70, significant hearing or visual impairments or a GMFCS level of 3-5). The secondary outcomes included metabolite peak area ratios and N-acetylaspartate concentrations ([NAA]) derived from thalamic proton MRS, and short-term clinical morbidity.

Initial analyses compared the characteristics of babies given and not given morphine. Categorical variables were compared between the groups using either the Chi-square test or Fisher's exact test. The unpaired t-test was used to compare continuous measures between groups, except for non-normally distributed variables, where the Mann-Whitney was preferred.

Subsequent analyses compared study outcomes between babies receiving and not receiving morphine. Continuous outcomes were analysed using linear regression (with a log transformation if the values were positively skewed). Both unadjusted and adjusted analyses (accounting for possible confounders) were performed. Variables were included as possible confounders in the adjusted analyses if there was any suggestion that they varied between patients with and without morphine. As none of the babies in the non-morphine group had an adverse outcome, the analysis was

performed using exact logistic regression. In a sub-group of babies scanned on a single 3T Philips MR scanner, we examined the association of morphine dose with white matter fractional anisotropy using Tract Based Spatial Statistics(Smith et al. 2006) (TBSS), after adjusting for gestational age at the time of scanning, and the severity of encephalopathy at admission.

RESULTS

Of 223 babies recruited to the MARBLE study, 183 had moderate or severe encephalopathy meeting the NICHD criteria for cooling therapy. Of these, 141 (76%) received morphine infusion for sedation, and 28 (15%) did not (Table 1). Data on sedation were not available in 14 (8%) babies.

Although the baseline characteristics and admission status were similar, the babies who received morphine infusion were more hypotensive (49% vs. 25%, p=0.02) and had a significantly longer hospital stay (12 days vs. 9 days, p=0.009) (Table 1).

Basal ganglia/thalamic injury (score $\geq$1) and cortical injury (score $\geq$1) was seen in 34/141 (24%) and 37/141 (26%) respectively, of the morphine group and 4/28 (14%) and 3/28 (11%) of the non-morphine group (p>0.05). White matter injury (score $\geq$2) was seen in 46/141 (32%) of the morphine and 6/28 (21%) of the non-morphine group (p>0.05). Mean (SD) thalamic [NAA] (6.5 ±1.5 mmol/kg wet weight versus 6.9 ± 0.9 mmol/kg wet weight) and median (IQR) lactate/NAA peak area ratio (0.16 [0.12, 0.21] versus 0.13 [0.11, 0.18]) were also similar in both groups (p>0.05) (Table 2 and **Error! Reference source not found.**).

Neurodevelopmental outcomes at 22 months were available in 142 (83%) babies and the outcomes were compared between groups using exact logistic regression. Prior to adjusting for confounding variables, adverse outcomes (moderate/severe disability or death) occurred in 26 (18%) of the morphine group, and in none of the non-morphine group (p=0.05). These results were similar after exclusion of babies with severe encephalopathy. Further analyses adjusted for possible confounding variables. The adjusted results suggested some evidence that an adverse outcome remained higher in the morphine group, but the difference did not reach statistical significance (p=0.11) (Table 2). Furthermore the mean (SD) composite Bayley-III cognitive scores (95±21 versus 99±13), language scores (89±22 versus 93±8) and motor scores (92±23 versus 94±10) were similar in the morphine and non-morphine groups (**Error! Reference source not found.**).

In the sub-group of 34 babies scanned on a single MR scanner, no relationship was observed between the morphine dose and white matter fractional anisotropy, adjusted for the severity for encephalopathy at admission. The total morphine dose given over the first 4 days after birth varied between 0 and 1.8mg/kg, equating to a range of infusion rates between 0 to 25mcg/kg/hour (Figure 3). At 6 hours, 15 (44%) babies and at 24 hours, 20 (59%) babies were receiving a morphine infusion of 10 to 20 mcg/kg/hour. Seven (20.6%) babies at 6 hours and 2 (6%) babies at 24 hours were receiving a morphine infusion rate >20mcg/kg/hour. No relationship was observed between the total morphine dose and any of the composite cognitive, language or motor scores (Figure 4), or white matter fractional anisotropy (Figure 5).

DISCUSSION

In this secondary analysis of a large, prospective, multi-centre observational study, pre-emptive morphine sedation during therapeutic hypothermia was associated with longer hospital stays, but not with brain injury on conventional MR imaging, proton MR spectroscopy thalamic [NAA] and lactate/NAA peak area ratios, or neurodevelopment at 22 months. Whilst data on morphine dosing was collected in only a subgroup of patients, it demonstrated that a large number (59%) of the infants were receiving relatively high doses (>10mcg/kg/hour) at 24 hours. The total morphine dose was not associated with whole white matter fractional anisotropy on tract based spatial statistics.

Pain management has long been a controversial aspect in neonatal medicine. In the 1950s & 1960s, a widespread belief was that neonates were incapable of perceiving pain (Merskey 1970), leading to an unfortunate number of painful procedures, including surgeries, being performed without anaesthesia or sedation until the 1980s (Lippmann et al. 1976). Gradually, it became clear that this belief was incorrect, and that neonates demonstrated clear stress responses during surgery via changes in their endocrinological and metabolic profiles (Anand et al. 1985).

This shift in our understanding of neonatal pain then led to the use of pre-emptive morphine and opioids routinely during ventilation of preterm neonates, with doses as high as 50-100mcg/kg/hour in some studies (Quinn et al. 1992; Quinn et al. 1993). However, the large NEOPAIN trial, in which ventilated preterm neonates were randomly assigned to either placebo or pre-emptive morphine infusions, there were significantly higher rates of severe intraventricular haemorrhage, death and periventricular leukomalacia in the group who received open-label morphine compared to the placebo group (Anand et al. 2004). Thus, a later Cochrane review

concluded there was insufficient evidence to recommend routine use of opioid sedation during ventilation in neonates (Bellù, de Waal, and Zanini 2008). Follow-up studies of those babies routinely sedated for ventilation have also demonstrated significant differences in morphometrics (i.e. smaller head circumference and body weight) and impaired behavioural/social development at school age in those that received pre-emptive morphine compared to those that did not (de Graaf et al. 2011; Ferguson et al. 2012).

A further difficult aspect to pain relief and pain management in neonates is the difficulty of reliably interpreting and classifying the background stress and discomfort during cooling. There are a variety of pain assessment tools available (Lawrence et al. 1993; Krechel and Bildner 1995; Stevens et al. 2014), but they are generally limited to assessment of short-term painful stimuli (acute stress), such as a heel-prick or venepuncture rather than for the assessment of more prolonged pain in neonates, that might be more analogous to the discomfort felt by cooled infants (Hall and Anand 2014). The dissociation of cortical and behavioural pain responses in babies during high stress states add further complexity in quantifying nociception.

The question regarding pre-emptive morphine use in therapeutic hypothermia and its relationship with neuroprotection, as touched on above, stemmed from pre-clinical data (Thoresen et al. 2001). However, despite the widespread use of pre-emptive sedation during cooling and some supportive data on potential neuroprotective effects (Angeles et al. 2005), there have been concerns raised about opioid use. The effect of opioid use in normothermic term and preterm infants has previously been assessed both in animal models as well as in infants. Early studies showed that exposure to opioids in the postnatal period resulted in poor brain growth in rats

(Seatriz and Hammer 1993) and more recently, a study by Sabir and colleagues (Sabir et al. 2018) concluded that continuous infusions of high dose fentanyl may lead to apoptosis in the internal granular cell layer of the cerebellum of healthy newborn pigs.

Given the growing concern for use of excessive opioids in normothermic, healthy newborns, there is a pressing need to assess their effects during therapeutic hypothermia. In adults, therapeutic hypothermia is used following cardiac arrest and, as standard, the patients often receive sedation and neuromuscular blockade. However, as discussed in systematic reviews, the exact medications used and the protocol in which they are deployed is widely variable (Chamorro et al. 2010). Adequate therapeutic hypothermia cannot be achieved in adults, children or in newborn piglets without deep sedation and muscle relaxation to suppress shivering. However, newborn infants have non-shivering thermogenesis due to brown fat, and hence sedation and muscle relaxation should not be required to induce hypothermia.

Despite this, a recent survey of sedation practices of the UK cooling centres reported that (Markati et al. 2018) 88% used routine pre-emptive morphine during cooling therapy. Discomfort from cooling (81%) and presumed loss of neuroprotection without sedation (44%) were the commonest reasons given by clinicians for initiating pre-emptive morphine.

Renal and hepatic dysfunction is common following cardiac arrest in adults, and is similarly seen following hypoxic ischaemic encephalopathy in infants(Shankaran et al. 2008). This could lead to prolonged or delayed clearance of opioids(Arpino and Greer 2008; Tortorici, Kochanek, and Poloyac 2007). In adult studies it has also

been shown that hypothermia itself leads to delayed breakdown and metabolism of drugs, thus ultimately changing the drugs' pharmacokinetics. Indeed, this effect has been borne out in a study showing slower rates of morphine clearance in babies undergoing therapeutic hypothermia compared to those treated with normothermia(Frymoyer et al. 2017; Roka et al. 2008). These studies describe possible toxicity in cooled infants at infusions greater than 10mcg/kg/hour.

Furthermore, sedative agents such as opioids are likely to interfere with accurate neurological assessments and may affect interpretation of amplitude integrated electro encephalography (EEG) readings. This, in turn, may cloud the overall clinical picture and delay prognostication (Natarajan et al. 2018). Sedation is also likely to prolong mechanical ventilation and cause haemodynamic compromise(Wassink et al. 2015).

Finally, a recent qualitative study (Craig et al. 2018) has also demonstrated that parents' perceptions of the use of opioids in therapeutic hypothermia are overall negative. Opioids were often given when healthcare professionals perceived the infant to be in discomfort, but many parents felt the assessment of the infant's discomfort was variable and differing from their own perception of their infant. Parents frequently associated morphine use with death or dying, following previous experiences of other loved ones in end of life care. Given the growing evidence that integrated family-delivered care has positive effects on outcomes in babies treated on neonatal intensive care units (O'Brien et al. 2018), the perception and participation of parents is an important aspect to consider when treating with opioids.

Although our study was a large, multi-centre study with carefully harmonised MR and outcome assessments, there are several limitations. Firstly, this was not a randomised controlled trial, and it is possible that the babies who received morphine were sicker than those who did not. However, the results adjusted for the severity of encephalopathy suggested some evidence that an adverse outcome still remained higher in the morphine group, although any difference was not statistically significant (p=0.11).

Secondly, we do not know the exact reason for pre-emptive sedation, and the morphine use was not standardised. It is likely that this was a clinical decision taken by the attending consultant based on the clinical needs, and a retrospective analysis may not have captured all the complex medical needs of the individual babies. Accurate assessments of the safety and efficacy of pre-emptive morphine can be assessed only in double-blind placebo-controlled randomised controlled trials.

Thirdly, we collected the precise dose and duration of morphine only in a small subgroup of babies. We also did not have any data on pain or sedation scores of the babies, and hence are not able to judge if the opioid sedation was appropriate for individual babies. There was no requirement for explicit documentation of reasons behind starting morphine and this was left as a clinical decision to be made by the attending clinicians.

Finally, we did not have any data on the morphine blood levels. Renal dysfunction in conjunction with cooling therapy might have resulted in toxic morphine levels in some babies where the morphine infusion rates exceeded 10 mcg/kg/hour (Figure 3), thus adversely affecting the outcome (Frymoyer et al. 2017).

Pre-emptive morphine sedation during therapeutic hypothermia is common clinical practice for preventing discomfort during cooling. Our data suggest that such a practice may prolong hospital stay without any additional neuroprotective benefit. Morphine levels should be routinely monitored in babies undergoing cooling therapy. Carefully designed clinical trials, including measurement of serum morphine levels, will help to elucidate the question of toxic accumulation of these drugs during therapeutic hypothermia. This will enable establishment of optimal sedation practices and supportive care during therapeutic hypothermia.

ACKNOWLDEGMENTS

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist

Tables and figure legends

Table 1: Baseline characteristics and clinical course

Table 2. Association of pre-emptive morphine sedation during therapeutic hypothermia with MR spectroscopy biomarkers and neurodevelopmental outcomes, determined using exact logistic regression

Figure 1: Boxplot demonstrating no significant difference in MRS biomarker outcome measures between group receiving morphine and group not receiving morphine.

Figure 2: Boxplot demonstrating no significant difference in neurodevelopmental outcome measures (Bayley III composite scores) between group receiving morphine and group not receiving morphine.

Figure 3: Cumulative morphine dose during therapeutic hypothermia in babies with (dotted lines) and without (solid lines) persistent pulmonary hypertension. Green shade indicates cumulative dose at morphine infusion rate <10 mcg/kg/hour, yellow shade indicates infusion rates 10-20 mcg/kg/hour and red shade indicates >20mcg/kg/hour for the first 72 hours

Figure 4: Relationship between total morphine dose and composite language, motor and cognitive scores on Bayley III

Figure 5: Linear regression of morphine dose with whole brain white matter fractional anisotropy using Tract Based Spatial Statistics (TBSS).

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Table 2: Baseline characteristics and clinical course

	Morphine sedation (n=141)	No morphine sedation (n=28)	P value
Birth weight g, mean (SD)	3434 (569)	3348 (522)	0.4
Gestation weeks, mean (SD)	39.9 (1.5)	39.7 (1.2)	0.5
Cord blood pH, mean (SD)	6.9 (1.9)	6.9 (1.9)	0.6
Cord blood base excess, mean (SD)	-14.7 (7.1)	-15.7 (6.2)	0.5
Apgar 10 minutes, median (IQR)	5.3 (2.2)	5.6 (2)	0.61
Encephalopathy stage at admission			
Moderate, n (%)	123 (87)	27 (96)	0.21
Severe, n (%)	18 (13)	1 (4)	
Clinical course			
PPHN, n (%)	16 (12)	0 (0)	0.08
Pulmonary bleed, n (%)	3 (2)	0	0.6
Anti-convulsant use, n (%)	79/128 (62)	10/19 (53)	0.45
Hypotension, n (%)	68 (49)	7 (25)	0.02
Blood stream positive sepsis, n (%)	10/132 (8)	0/26 (0)	0.37
Hospital stay days, mean (SD)	12 (7)	9 (4)	0.009

SD= standard deviation; IQR = interquartile range; PPHN = persistent pulmonary hypertension

(Severe hypoxemia disproportionate to the severity of lung disease and evidence of a right to left shunt)

Hypotension = Persistent mean blood pressure of < 40 mmHg

Table 2: Association of pre-emptive morphine sedation during therapeutic hypothermia with MR spectroscopy biomarkers and neurodevelopmental outcomes

Outcome	Sedation	N	Mean ± SD	Unadjusted		Adjusted [*]	
				Mean (95% CI)	P-value	Mean (95% CI)	P-value
Bayley cognitive	No	17	99.0 ± 12.5	0	0.43	0	0.71
	Yes	115	94.8 ± 21.1	-4.2 (-14.6, 6.2)		-1.9 (-11.7, 7.9)	
Bayley language	No	15	93.1 ± 8.0	0	0.44	0	0.68
	Yes	111	88.6 ± 22.3	-4.5 (-16.1, 7.0)		-2.2 (-12.8, 8.4)	
Bayley motor	No	17	93.6 ± 10.1	0	0.71	0	0.97
	Yes	115	91.5 ± 22.5	-2.0 (-13.0, 8.9)		0.2 (-9.9, 10.2)	
[NAA]	No	10	6.85 ± 0.85	0	0.52	0	0.97
	Yes	61	6.54 ± 1.49	-0.31 (-1.28, 0.65)		-0.02 (-0.91, 0.95)	
NAA/Cr	No	23	1.61 ± 0.29	0	0.08	0	0.21
	Yes	119	1.50 ± 0.27	-0.11 (-0.23, 0.01)		-0.08 (-0.21, 0.05)	

Outcome	Sedation	N	Median [IQR]	Unadjusted		Adjusted (*)	
				Ratio (95% CI)	P-value	Ratio (95% CI)	P-value
Lac/NAA	No	23	0.13 [0.11, 0.18]	1	0.09	1	0.20
	Yes	119	0.16 [0.12, 0.21]	1.30 (0.96, 1.76)		1.22 (0.90, 1.65)	
Outcome	Sedation	N	Number (%)	Unadjusted		Adjusted (*)	
				OR (95% CI)	P-value	OR (95% CI)	P-value
Adverse neuro outcome	No	17	0 (0%)	1	0.05	1	0.11
	Yes	125	26 (21%)	6.15 (0.99, ∞)		4.94 (0.72, ∞)	

(*) Adjusted for PPHN, hypotension and encephalopathy severity score at admission.

Figure 1: Boxplot demonstrating no significant difference in MRS biomarker outcome measures between group receiving morphine and group not receiving morphine.
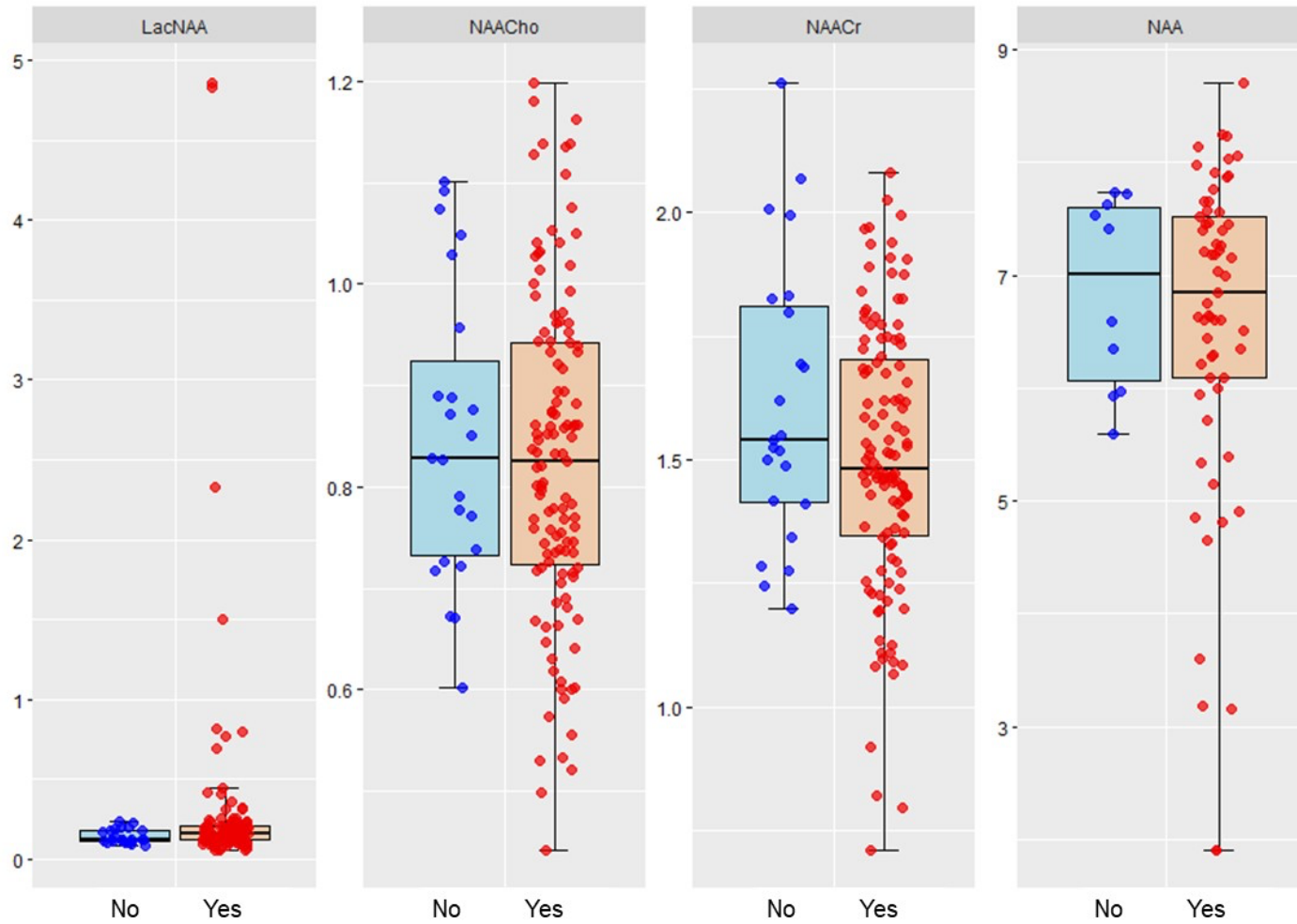
Figure 2: Boxplot demonstrating no significant difference in neurodevelopmental outcome measures (Bayley III composite scores) between group receiving morphine and group not receiving morphine.
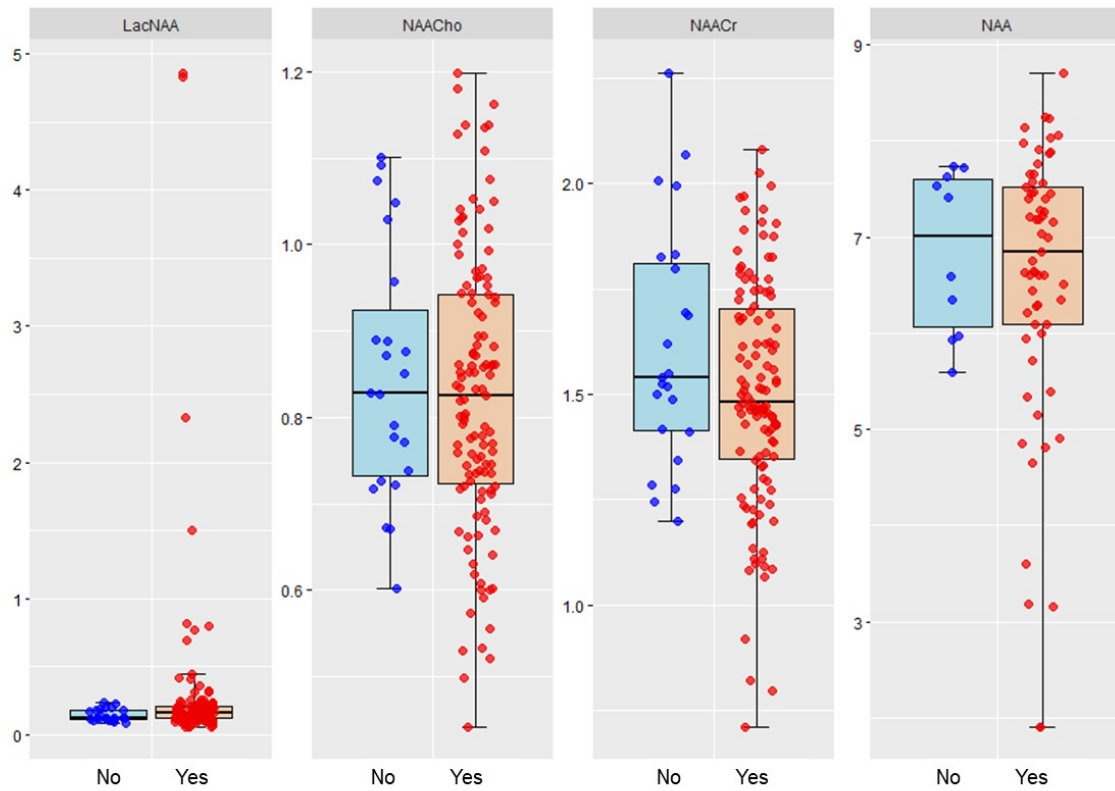
Figure 3: Cumulative morphine dose during therapeutic hypothermia in babies with (dotted lines) and without (solid lines) persistent pulmonary hypertension. Green shade indicates cumulative dose at morphine infusion rate <10 mcg/kg/hour, yellow shade indicates infusion rates 10-20 mcg/kg/hour and red shade indicates >20mcg/kg/hour for the first 72 hours
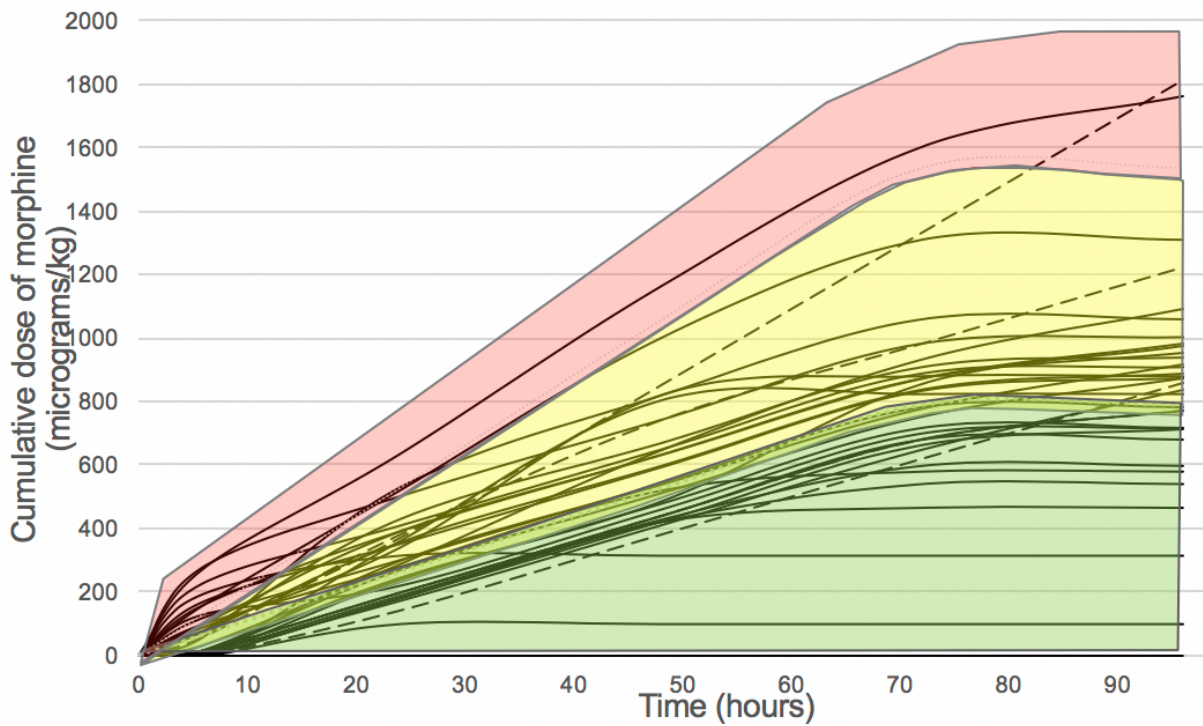
Figure 4: Relationship between total morphine dose and composite language, motor and cognitive scores on Bayley III
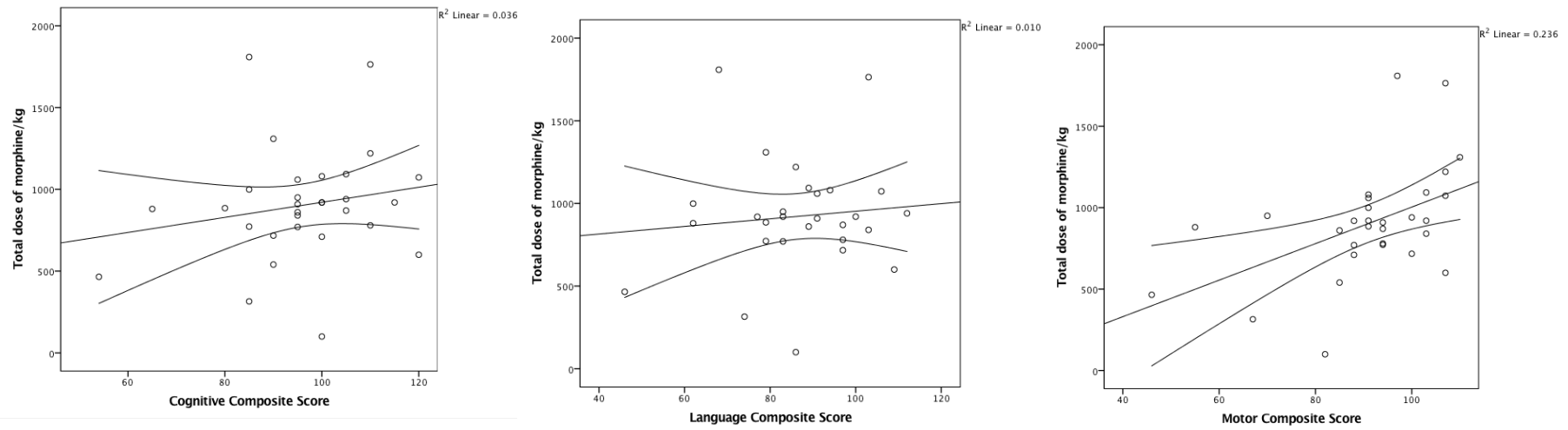
Figure 5: Linear regression of morphine dose with whole brain white matter fractional anisotropy using Tract Based Spatial Statistics (TBSS).