

# Caffeine Therapy in Neonatal Intensive Care

## Abstract:

Administration of caffeine is global practice in the prevention of apnoea of prematurity. Apnoea leads to hypoxia, bradycardia and cardiovascular instability. It has significant disease burden in this preterm group. Apnoea of prematurity affects 100% of neonates <28 weeks gestation and approximately 50% of infants 30-32 weeks gestational age. Incidence of apnoea is inversely related to gestational age due to CNS immaturity and the higher rates of respiratory distress and infection in the very low birth weight (VLBW) infant.

Caffeine is a proven therapy in the prevention of apnoea.<sup>3,4</sup> Acting as a respiratory stimulant, caffeine has been coined 'the silver bullet'. Its mechanism of action is thought to be two fold, centrally, as an adenosine receptor antagonist and peripherally, improving respiratory muscle performance eg: diaphragm contractility. Methylxanthines are commenced at the discretion of the paediatrician, with early postnatal therapy assisting higher rates of successful extubation. Dosing regimes are also being trialed but always require an initial loading dose followed by a daily maintenance dose.<sup>6</sup> Administration can be intravenous or oral, with excellent bioavailability with po intake. Discontinuation of caffeine is recommended 5-7 days prior to discharge from hospital, this must be done in a timely manner due to the long half life ( $T_{1/2}$ >100 hours when <38 weeks gestation) of caffeine in the neonate. Xanthine therapy causes an increase in metabolic rate and oxygen consumption of approximately 20%, suggesting that caloric demands may be increased. The potential hazards of caffeine therapy are suboptimal weight gain, dehydration and tachycardia. Central nervous system side effects include irritability, sleeplessness, jitteriness while gastrointestinal side effects are also a potential hazard.

Used in clinical practice since the 1970s, safety of this therapy was tested in Caffeine for Apnoea trial, (CAP trial), a large multicentred randomised control trial comparing caffeine therapy to placebo. The CAP trial demonstrated lower incidence of death or neurodevelopmental disability, of chronic lung disease, cerebral palsy and cognitive impairment in the treatment group. Caffeine reduced weight gain temporarily in the treatment group but growth measures were similar overall. Death, deafness, blindness, necrotizing enterocolitis and cranial ultrasound findings did not differ between groups. No major adverse effects were seen with caffeine. Of particular interest was a reduction in cerebral palsy and cognitive impairment in the treatment group. This was unrelated to the number of apnoeas and desaturations. Therefore many concluded from this study that caffeine had a primary neuroprotective role. Of the patients in the caffeine group with term corrected brain MRI available, Doyle et al demonstrated lower ADC values in the white matter suggesting improved white matter microstructural changes.<sup>8</sup> This has prompted investigators to examine caffeine dosing regimes, could earlier and higher dosing further improve neurodevelopmental outcome?

An article in Jama last month has reported the outcomes of the CAP cohort at 5 years of age. The objective, again, to detect adverse consequences and sustained benefits of caffeine therapy. The benefits of neonatal caffeine were attenuated in the period 18 months to 5 years. Lower rates of moderate and severe cognitive impairment and of cerebral palsy were seen at 5 years than at 18 months. Neonatal caffeine was no longer associated with improved rate of survival without disability in this VLBW cohort. Only slight improvement in motor coordination and visual perception was demonstrated in the caffeine group.

This paper highlights the importance of long term follow up in large randomised control trials in neonatology. It also highlights the potential for improved cognition in early childhood. Does it show that early testing at 2 years can identify inadequacies which can be improved with early intervention strategies? The paper doesn't comment on the uptake of early intervention in the patients with impairment at 18 months and the possible benefits this has during periods of critical development. Although parents and caregivers remained blinded to whether the child was in treatment or placebo group, developmental comparisons between their children, peers and siblings is unavoidable. The majority of the cohort stem from middle class backgrounds, the influence of positive environmental factors to a child with delay should also be taken into consideration. This is assuming a middle class background provides optimal stimulation and educational opportunities for such a child.

It is currently the practice in newborn follow up to correct for gestational age up until the age of 2 years. This correction is applied to growth and developmental milestones. Studies using adjusted ages show that developmental trajectory approximate normative development. Assessments by Allen and Alexander 1990 concluded that 24 months would be an optimal time to identify motor delay, while other investigators suggested adjustment was not necessary beyond 12 months. However more recent and longer follow up studies have supported the concept of transient developmental delay with a potential for 'catch up'. Significant cognitive improvement in VLBW infants has been reported between the ages of 3 and 8 years.<sup>12</sup> Perhaps with the increasing survival of infants from 23 weeks gestation, age adjustments should be considered beyond 2 years. As paediatricians we should screen for disability appreciating the benefits of early intervention, however, developmental delay at a single point of time is not 100% predictive of disability in school aged children and beyond. Can caffeine assist in preventing a developmental lag as oppose to correcting a potential long term deficit?

The initial randomised control trial was undertaken to test the safety of administration of caffeine in the vulnerable preterm infant, and this paper confirms the efficacy and safety of caffeine as a proven treatment for apnoea of prematurity. The lack of adverse side effects in short, intermediate and long term reports is reassuring for caregivers and parents. The research group report significant neurodevelopmental improvement at 18 months corrected gestational age suggesting a primary neuroprotective benefit of caffeine. Retesting at 5 years of age, while trending towards superior results in the caffeine group, did not demonstrate statistically significant benefit to developmental outcome. Results support the concept that outcomes at 2 years corrected gestational age are not reliable end points for follow up studies of VLBW infants. Indeed the study group should be commended for continued long term follow up of the cohort into early childhood and beyond. Of course with rapidly evolving changes in neonatal practices there is reduced relevance in very long term follow up. Details of clinical practice at time of enrolment of the cohort are to be taken in to consideration.

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