Evidence-based Neonatology Synopsis

Survival without Disability to Age 5 years After Neonatal Caffeine Therapy for Apnea of Prematurity

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CONTEXT

Caffeine is the respiratory stimulant of choice for the treatment of apnea of prematurity. The international, randomized, placebo-controlled Caffeine for Apnea of Prematurity trial has shown that caffeine therapy reduces the duration of exposure to positive airway pressure and supplemental oxygen and the rates of neonatal morbidities, including bronchopulmonary dysplasia and severe retinopathy of prematurity; improves the rate of survival without neurodevelopmental impairment at 18-21 months of age.\(^1\)

MATERIALS AND METHODS

Multicenter randomized controlled trial in 35 centers in Canada, United States, Australia, Europe and Israel. This follow-up study included long-term data from 31 centers only.

Population

Inclusion
- Infants with a birth weight of 500-1250 g
- Clinicians considered them to be candidates for methylxanthine therapy during the first 10 days of life.

Exclusion
- Dysmorphic features or congenital anomalies likely to affect life expectancy or neurological development
- Patient were unlikely to be available for long-term follow-up
- Previously treated with methylxanthine

Intervention

Caffeine group
- Caffeine citrate intravenous loading dose of 20 mg per kg of body weight. This was followed by a daily maintenance dose of 5 mg per kg
- If apneas persisted, the daily maintenance dose could be increased to a maximum of 10 mg of caffeine citrate per kg per day
- The maintenance doses were adjusted weekly for changes in body weight and could be given orally once an infant tolerated full enteral feedings.

Control

Equivalent volume of normal saline.

Outcomes

Primary

Original study

The primary outcome at a corrected age of 18-22 months is a composite of: Death, cerebral palsy, cognitive delay, deafness or blindness.

Current study

The primary outcome at a corrected age of 5 years is a composite of:
- Death
- Motor impairment (Gross Motor Function Classification System level of 3-5)
• Cognitive impairment (defined as a Full Scale IQ < 70)
• Behavior problems defined as a Total Problem T score of greater than 69 (Child Behavior Checklist)
• Poor general health defined as 1 or more of the following: need for supplemental oxygen, positive airway pressure, feeding through a tube or intravenously, seizures occurring more frequently than once per month, or a recent admission to ICU for complications resulting from a neonatal morbidity
• Severe hearing loss was defined as the prescription of hearing aids or cochlear implants
• Bilateral blindness was defined as a corrected visual acuity less than 20/200 in the better eye.

Other outcomes
Motor performance (Movement Assessment Battery for Children), Visual-Motor Integration, height, weight, and head circumference.

Allocation
• A computer-generated randomization scheme was used to assign infants to the two groups in a 1:1 ratio
• Randomization was stratified by study center and balanced in random blocks of two or four patients.

Blinding
Blinded, families, clinical, pharmacy and research staffs were unaware of group assignment.

Follow-up
Adequate data for the main outcome was available for 84.9% of the children.

RESULTS
Five-year follow-up from 31 of 35 centers; 1932 of 2006 participants (96.3%) had been enrolled in the CAP trial between 1999 and 2004. A total of 1640 children (84.9%) had adequate data for the main outcome at 5 years.

The results for the primary composite outcome and for its components are shown in [Table 1]. The rates of motor impairment, severe cognitive impairment, behavior problems, poor general health, blindness, and deafness were not significantly different between the two groups.

Only two children in each of the two groups died between 18 months and 5 years. A secondary analysis using the full ordinal scale of the GMFCS showed evidence of an improvement in gross motor function associated with caffeine therapy.

Change in motor and cognitive function between 18 months and 5 Years
Rates of moderate and severe cognitive impairments were much lower at 5 years than at 18 months. Only 33 of the 178 children (18.5%) with a Bayley II Mental Development Index less than 70 at 18 months had a Wechsler Preschool and Primary Scale of Intelligence III Full Scale IQ less than 70 at 5 years. On average, a child with a Mental Development Index of 70 at 18 months had a Wechsler Preschool and Primary Scale of Intelligence III Full Scale IQ that was almost 20 points higher at 5 years.

COMMENTARY
In the initial trial the use of caffeine significantly improved the outcome at a corrected age of 18-22 months in terms of composite outcome (death before 18 months and cerebral palsy, cognitive delay, severe hearing loss or bilateral blindness).

In the current study, neurobehavioral, neuropsychological, and motor outcomes were comprehensively evaluated at 5 years of age. In contrast to their earlier results, when the children were 5 years of age, CAP investigators found no effect of caffeine on the primary outcome of death or survival with severe disability, which was defined differently than the main trial as motor or cognitive impairment, behavior problems, poor general health, deafness, or blindness.

In contrast, a secondary analysis of the full range of motor outcomes suggests that the improved motor function

| Outcome                                      | Caffeine group no. total (%) | Placebo group no. total (%) | Unadjusted OR (95% CI) | OR adjusted for center (95% CI) | P value | OR adjusted for center and patient characteristics (95% CI) |
|----------------------------------------------|------------------------------|------------------------------|------------------------|---------------------------------|---------|-------------------------------------------------------------|
| Composite death or disability               | 176/833 (21.1)               | 200/807 (24.8)               | 0.81 (0.95-1.02)       | 0.82 (0.65-1.03)                | 0.90    | 0.86 (0.67-1.09)                                            |
| Death before 5 years                         | 59/867 (6.8)                 | 58/837 (6.9)                 | 0.98 (0.67-1.43)       | 0.98 (0.70-1.43)                | 0.92    | 1.03 (0.69-1.52)                                            |
| Motor impairment                             | 13/803 (1.6)                 | 21/773 (2.7)                 | 0.59 (0.29-1.18)       | 0.59 (0.29-1.18)                | 0.20    | 0.63 (0.31-1.28)                                            |
| Cognitive impairment                         | 38/768 (4.9)                 | 38/750 (5.1)                 | 0.98 (0.62-1.55)       | 0.97 (0.61-1.55)                | 0.89    | 1.11 (0.68-1.80)                                            |
| Behavior problems                            | 42/773 (5.4)                 | 52/748 (7.1)                 | 0.75 (0.50-1.14)       | 0.75 (0.49-1.15)                | 0.18    | 0.78 (0.51-1.20)                                            |
| Poor general health                          | 32/805 (4.0)                 | 33/775 (4.3)                 | 0.93 (0.57-1.51)       | 0.92 (0.56-1.52)                | 0.75    | 0.95 (0.57-1.58)                                            |
| Severe hearing loss                          | 22/798 (2.8)                 | 25/773 (3.2)                 | 0.85 (0.47-1.52)       | 0.85 (0.47-1.52)                | 0.58    | 0.91 (0.51-1.64)                                            |
| Bilateral blindness                          | 7/792 (0.9)                  | 7/763 (0.9)                  | 0.96 (0.34-2.75)       | 0.96 (0.34-2.75)                | 0.94    | 1.04 (0.35-3.02)                                            |
observed at 18-21 months of age in the caffeine group was indeed sustained at 5 years.

The rates of cognitive impairment were much lower at 5 years than at 18 months and similar in the caffeine and placebo groups, which suggest that cognitive delay during the second year of life may not be a lasting outcome after very preterm birth. This study and other studies demonstrate that outcomes up to 2 years after very preterm birth may not accurately predict function later in childhood and how long-term follow-up is essential for reaching accurate conclusions about the efficacy of new therapies in preterm infants.\[a,1\]

Abstracted from
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