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Caffeine therapy improves the rate of survival without neurodevelopmental disability in preterm babies

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The earlier a baby is born – any new born less than 37 weeks is considered premature – the more likely serious disabilities will affect the baby, in case he or she manages to survive.

One of the most dangerous conditions affecting premature born babies is apnea of prematurity, because their lungs and central nervous system aren't yet properly developed. Caffeine and other methylxanthines-aminophylline, theophylline- have been administered to these preterm infants for more than 30 years, as respiratory stimulants. However, until now, only a few small, short-term studies evaluated their effect on the preterm brain and other organs. The long-term effect of methylxanthine was uncertain.

The paper here commented is the first large, international, randomized, placebo-controlled trial that studies the impact of methylxanthine on neurodevelopmental disability in early childhood, when administered on preterm babies.

2,006 infants with birth weights of 500 to 1,250g were randomly assigned to receive either caffeine or placebo as therapy for apnea of prematurity. The primary outcome was a composite of death, cerebral palsy, cognitive delay (defined as a Mental Development Index score of <85 on the Bayley Scales of Infant Development), deafness, or blindness at a corrected age of 18 to 21 months.

Of the 2,006 infants enrolled in the study, adequate data for analyzing the primary composite outcome were available for 1,869 (93.2%). Of the 937 infants randomized on caffeine, 377 (40.2%) died or survived with a neurodevelopmental disability, as compared with 431 of the 932 infants (46.2%) assigned to placebo (odds ratio adjusted for center, 0.77; 95% confidence interval [CI], 0.64 to 0.93; P=0.008). Caffeine therapy, as compared with placebo, reduced the incidence of cerebral palsy (4.4% vs. 7.3%; adjusted odds ratio, 0.58; 95% CI, 0.39 to 0.87; P=0.009) and of cognitive delay (33.8% vs. 38.3%; adjusted odds ratio, 0.81; 95% CI, 0.66 to 0.99; P=0.04). The study showed no significant effects on the rates of death, deafness and blindness, as well as height, weight and head circumference at follow-up.

The mechanisms responsible for this neuroprotective effect of caffeine most probably relate to the early discontinuation of positive airway pressure in infants treated with caffeine. Long term ventilation induces lung injuries, responsible for the subsequent development of bronchopulmonary dysplasia. This condition is an important risk factor for neuro developmental disability in early childhood. However, about 45% of the beneficial effect of caffeine on 18-month outcome still remains unexplained; further studies are needed in order to properly understand its complete action. N.B. This group of infants are going to be followed-up to a corrected age of 5 years, in order to asses their further physical and neurological development.

This is the first important study meant to clear the uncertainty concerning the efficacy and safety of methylxanthine therapy in preterm babies suffering from apnea of prematurity. In conclusion, the present trial shows that caffeine reduces the rate of bronchopulmonary dysplasia at almost 2 years in infants with very low birth weight, improving the rate of survival without neurodevelopmental disability.

Comment on the paper:
Schmidt B, Roberts RS, Davis P, et al. – Long-Term Effects of Caffeine Therapy for Apnea of Prematurity *N Engl J Med* 2007; 357:1893-1902