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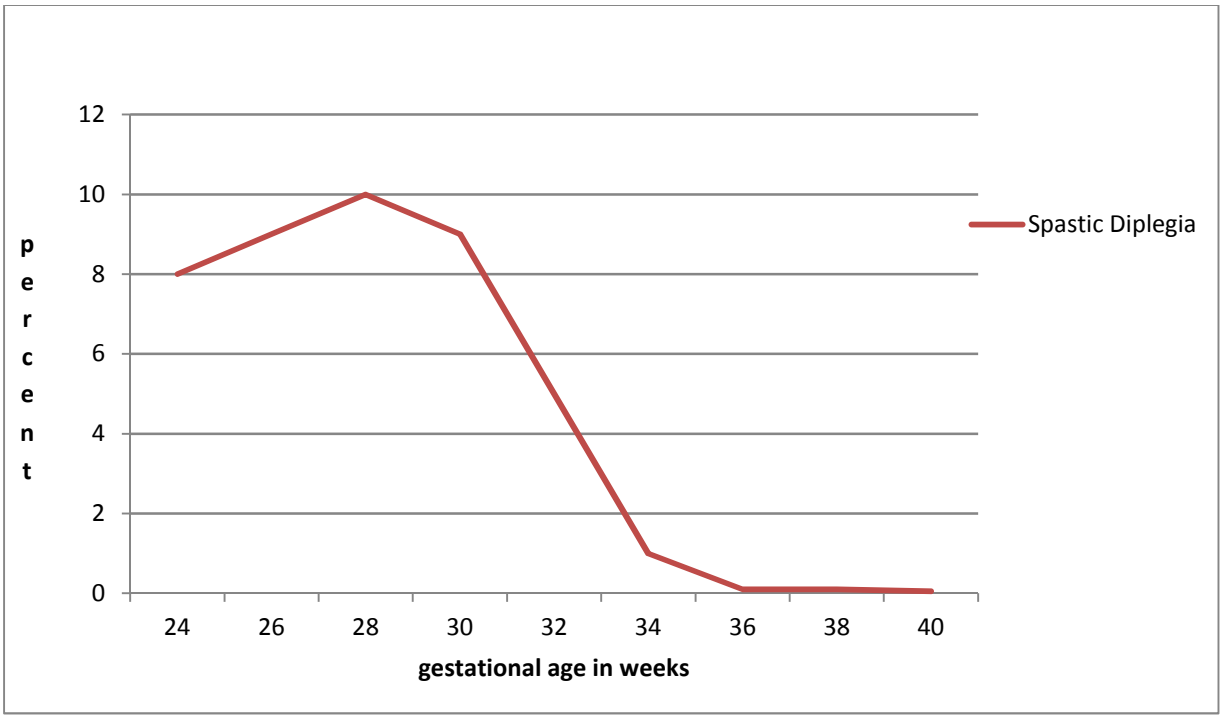
Premature birth has been a well-known phenomenon for many years. The survival of preterm infants has greatly improved, in particular, the infants that are born at less than 1,000 grams. The challenges accompanying the birth of an infant weighing less than 1,000 grams are numerous and include such things as respiratory failure due to surfactant insufficiency, patent ductus arteriosus, intraventricular hemorrhage, renal failure, retinopathy of prematurity, apnea of prematurity, necrotizing enterocolitis, sepsis, and death. As a result, cerebral palsy is a frequent long term outcome (Papageorgiou, Pelausa, & Kovacs 2005). Apnea of prematurity is a condition due to developmental immaturity and was first acknowledged in the late 1960's. Treatment for apnea of prematurity has included mechanical ventilation, theophylline, aminophylline, and most recently caffeine citrate. Recently, it has been noted that there has been a decrease in the incidence of cerebral palsy among extremely low birth weight infants treated with caffeine citrate. Because of the long term benefits of caffeine citrate, it is the drug of choice for treatment of apnea of prematurity (Johnson, 2011).

Definition and Description of the Problem

Apnea of prematurity is defined as a "sudden cessation of breathing that lasts for at least 20 seconds or a shorter duration and is accompanied by bradycardia or cyanosis in an infant younger than 37 weeks' gestational age" (AAP, 2003). If left untreated, apneic episodes will result in recurrent hypoxic events that will increase in frequency and severity. The effects of recurrent hypoxic events include neurodevelopmental impairment, most notably cerebral palsy (Aranda, Beharry, Davis, Natarajan, & Valencia, 2010). Cerebral palsy (CP) is defined as a "chronic disorder of movement or posture of cerebral origin, arising in early life and is not the result of a progressive disorder" (Robertson, Watt, & Yasui, 2007). Cerebral palsy varies in severity but remains one of the most predominant developmental disabilities diagnosed in

children as a result of prematurity. Both spastic diplegia and spastic quadriplegia are types of CP associated with prematurity with varying degrees of predictability. Spastic diplegia is the less predictable type of CP but is the clinical result of periventricular white matter injury from hypoxic-ischemic insults. It is the risk of repeated hypoxic insults associated with apnea of prematurity that caffeine citrate is used to control (Bennett, 2005).

Occurrence of spastic diplegia as related to gestational age (Bennett, 2005)



The quality of life for a child with CP is difficult to determine. Quality of life is subjective for the child and for the family. The type of CP that is strongly associated with prematurity, spastic diplegia, is characterized by increasing neuromotor abnormalities of muscle tone and movement, excessive reflex activity and delayed motor milestones (Bennett, 2005). Extremities with hyperreflexia and hypercontraction are painful (www.nids.nih.gov). The care

involved for children and adult people with spastic diplegia CP include, but is not limited to, physical therapy and occupational therapy, speech therapy, drugs to control seizures, muscle spasms, and alleviate pain, surgery to correct anatomical abnormalities or release rigid muscles, and equipment like braces or orthotic devices, wheelchairs or rolling walkers, and communication aids (www.nids.nih.gov). It is evident that having a child with spastic diplegia is an incredibly difficult journey and one that includes numerous healthcare provider and therapeutic appointments and intense on-going care.

Review of Current Evidence-Based Literature

The current literature was searched for information regarding the use of caffeine citrate in the extremely low birth weight infant (ELBW) and the reduction in neurodevelopmental disabilities, in particular, spastic diplegia cerebral palsy. An electronic search was performed using CINAHL, MEDLINE, and COCHRANE COLLABORATION databases with keywords caffeine citrate, neurodevelopmental disabilities, cerebral palsy, and extremely low birth weight infants. The dates searched were 2000 to 2011.

The Caffeine for Apnea of Prematurity (CAP) Trial was a study done where 2006 infants were enrolled between October 11, 1999 and October 22, 2004 to assess the short term outcomes prior to discharge home of preterm infants that were treated with caffeine citrate vs. a placebo. It was a large, multi-center, randomized, placebo-controlled trial which focused on determining the short-term and long-term outcomes of caffeine therapy for apnea of prematurity (Schmidt et al., 2006). Because of the methodological strengths of the CAP trial and the number of enrolled infants, the same children were followed at 18 to 21 months of age and again at the age 5 years to assess long-term outcomes. The primary long-term outcome of the trial was death before 18

to 21 months or survival with ≥ 1 of these conditions: cerebral palsy, cognitive delay, hearing loss requiring amplification, or bilateral blindness. What was discovered was that caffeine citrate reduced the rate of death before 18 to 21 months and 2 other components, cerebral palsy (4.4% vs. 7.3%) and cognitive delay (33.8% vs. 38.3%) vs. a placebo. These outcomes had a CI of 95% and p values 0.009 for CP. The authors of the study were clear that caffeine improves neurodevelopmental outcomes at 2 years of age and follow-up at 5 years of age will further delineate the positive outcome of caffeine citrate on neurodevelopmental outcome. Information on the 5 year follow-up is not yet available. The CAP trial is the major study establishing the superiority of caffeine citrate for the treatment of apnea of prematurity because of its reported long-term benefits (Schmidt, et al., 2007).

Doyle, et al (2010) conducted a study to assess the influence of caffeine citrate on the brain macro or microstructural development in preterm infants. The study included 70 preterm infants with birth weights of less than 1,250 grams who were randomly assigned to either caffeine citrate or a placebo. Subjects received magnetic resonance imaging (MRI) at term equivalent age with a follow-up into early childhood and any white and gray matter were measured and scored. The hypothesis was stated that "caffeine treatment would have a beneficial effect in reducing white matter injury and improving cerebral white matter development in preterm infants". The results of this study initially did not show any difference on the qualitative white or gray matter abnormality score between the caffeine group and placebo group with a $p = 0.59$ for white matter and $p = 0.76$ for gray matter scans. But a subset of infants with Diffusion Tensor Imaging (DTI) showed a clear effect of caffeine exposure with reductions in diffusivity which indicates more mature cerebral white matter organization with a $p = < 0.0001$ that establishes statistical significance. The authors of this study state the use of caffeine

citrate therapy improves cerebral white matter development which is indicative of an improvement in neurodevelopment in the premature infants' brain.

A multi-center, randomized, controlled trial design study was done by the Caffeine Collaborative Group with a total of 287 infants to compare two dosing regimens for caffeine citrate and the long term effects on infant development, temperament, and behavior (Gray, Flanedy, Charles, & Steer, 2010). One group was given a high dose of 80mg/kg for a loading dose and then 20mg/kg maintenance dose once per day and the other group was given a loading dose of 20mg/kg and a maintenance dose of 5mg/kg each day. The results showed no statistical significance between the two dosing regimens for caffeine citrate and the incidence of CP evaluated at 12 months of age with a $p = 0.28$. It showed borderline statistical significance for improved cognitive outcomes at 1 year of age with a p value = 0.048. This study too recognized the significance of caffeine citrate on long-term neurodevelopmental outcomes and was aimed at establishing a standardized dosing regimen for those improved neurological outcomes including decreasing the incidence of CP and cognitive delay among very low birth weight and extremely low birth weight infants.

There was a meta-analysis done by the Cochrane Neonatal Group of six trials that reported effects of methylxanthine treatment for apnea of prematurity. Three trials of caffeine citrate and three trials of theophylline, another methylxanthine used in the treatment of apnea of prematurity, were subject to the review. There were many types of outcomes measured and among the long term outcomes measured were neurodevelopmental outcomes, i.e. cerebral palsy. Stated in this review was the concern of recurrent episodes of apnea of prematurity and the possible harmful effects on the developing brain. All of the studies reviewed showed significantly less apneic episodes with methylxanthine treatment than treatment with a placebo or

no treatment with a CI = 95%. With significantly less apneic episodes it can be extrapolated that there is less harmful episodes on the developing brain of the ELBW infant. In this meta-analysis, the CAP trial was reviewed as well. It was noted that the CAP trial is the only study that specifically examined the long term neurodevelopmental outcomes of premature infants on caffeine therapy. The authors' conclusions in this Cochrane Review state the use of methylxanthine therapy is effective in reducing the number and severity of apneic episodes in premature infants which equates to better neurological protection. It was also reported in this Cochrane Review that caffeine has improved neurodevelopmental outcomes. Thus it would be the preferred therapy for apnea of prematurity (Henderson-Smart & De Paoli, 2011).

Robertson, Watt & Dinu (2009) studied the outcomes for the extremely premature infant by reviewing publications from 2004 to 2007 and outcomes reported at each of their institutions from the previous 30 years. The report demonstrated a reduction in the prevalence of cerebral palsy from 77 per 1000 live births to 40 per 1000 live births in Sweden between the years 1995 and 1998. In Canada during the same time period, the incidence of cerebral palsy rose during the years of 1974 to the early 1990's and then dropped to 19 per 1000 live births. In the United States the same decline was seen and was last reported that 5% of live births resulted in infants with cerebral palsy. And finally they reported the results of the CAP trial reported a decrease of CP to 4.4%. This analysis of previous studies over the prior 30 years and also the reported outcomes from their respective facilities clearly show a decrease in cerebral palsy, among other outcomes, and an increase in impairment-free survivors from 22% of survivors in 1974 to 77% of survivors in 2003. Over the course of the 30 years, the survivors that were impairment-free increased 0.8 per 10 years with a p value of 0.001.

Aranda et al (2010) reviewed the literature specifically discussing the effects of caffeine citrate on the premature infants' long-term morbidities. Caffeine is labeled the "silver bullet" in neonatology in their review stating that not only does it affect long-term neurological outcomes, it positively affects other outcomes such as chronic lung disease and retinopathy of prematurity. Again, the CAP trial was the major supporting study regarding neurodevelopmental long-term outcomes in ELBW infants.

In 2010, Dukhovny et al and the CAP trial group did a retrospective economic appraisal using the data from the CAP trial (n= 1869) to evaluate the cost per survivor without neurodevelopmental impairment. The findings in this reflective evaluation was the mean cost per infant in the caffeine group was $124,466 and in the placebo group $133,505, a difference of $9,039 over the course of the infants hospitalization. They concluded that caffeine is a "win-win" therapy for the infant lowering their chance of significant neurodevelopmental disabilities and economically, lowering the cost of the course of care for a premature infant requiring NICU care.

Recommendations in Treatment of Apnea of Prematurity

The defining recommendations for treatment of apnea of prematurity are still in the developmental stage and more studies are needed for clarification. It is clear that AOP is a disorder that is common in infants born before 37 weeks gestation and its incidence is inversely related to their gestational age, with the earlier and smaller the infant the more likely the occurrence of AOP (Bennett, 2005). The current research supports beginning methylxanthine treatment within the first seven days of life even for infants on mechanical ventilation. Caffeine citrate is favored due to its once daily dosing, wider therapeutic window, lower risk of toxicity,

and ease of switching from intravenous to oral dosing with the equal bioavailability for both (Johnson, 2011).

A cost comparison was also done between caffeine citrate and aminophylline, another medication frequently used in the treatment of AOP, using prices from three local pharmacies including two hospital based pharmacies and a retail pharmacy. There are many factors that affect the cost of each of these medications. Included in those factors are frequency of dosing and monitoring needs to assure the efficacy of the medication. When comparing cost per dose, aminophylline was less expensive than caffeine. When comparing the other influential cost factors, caffeine is more cost effective. Caffeine citrate requires once daily dosing with no required lab work follow-up. Aminophylline requires three times daily dosing with weekly lab draws to monitor serum therapeutic levels. The lab assays are $50 to $100 each, with recommendations for a minimum of weekly testing. With that information available, caffeine citrate is recommended as the drug of choice for the treatment of AOP.

Patient and Family Counseling and Education

When a family is planning the birth of a baby, having a premature infant is not anticipated. The experience of having a premature infant in the NICU is likened to a rollercoaster. Families are frequently faced with difficult decisions when it comes to the course of care for their child. Educating families on the condition of apnea of prematurity is imperative and as a part of the education on the condition should be the treatment modalities available which include caffeine citrate and aminophylline. The route of administration, the frequency of administration along with the side effects, both short-term and long-term, of the medications

should be included. And an important aspect of the information given to families is the most current research available on the use of each medication.

Families need to be included in the decision making for care of their child. Education and counseling gives them the tools to do that effectively and most comfortably. It is the practitioners role to provide the education needed so the families can be a part of the course of treatment for their child so they can be empowered, not disabled, by the experience of having a child in the NICU.

Conclusion

Apnea of prematurity is a disorder of immaturity that has an incidence of almost all infants born at less than 1000 grams, extremely low birth weight. The treatment of apnea of prematurity (AOP) has evolved since the late 1960's when it was first recognized as has much of neonatal medicine (Johnson, 2011). Neurodevelopmental disability, most notably cerebral palsy, continues to be the most frequent disability in preterm infants. Although there are different etiologies of cerebral palsy, recurrent hypoxic injury to the developing brain is a contributing factor to the later development of CP. Reducing the incidence of recurrent hypoxic events in the premature infant will improve the rate of CP diagnosed in early childhood (Bennett, 2005). Caffeine citrate has emerged as the favorable medication in the care of premature infants with its cost effectiveness, low occurrence of side effects, and strong evidence of its improvement in the incidence of neurodevelopmental impairment.

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