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REVIEW

Caffeine therapy in preterm infants

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Abstract

Caffeine is the most commonly used medication for treatment of apnea of prematurity. Its effect has been well established in reducing the frequency of apnea, intermittent hypoxemia, and extubation failure in mechanically ventilated preterm infants. Evidence for additional short-term benefits on reducing the incidence of bronchopulmonary dysplasia and patent ductus arteriosus has also been suggested. Controversies exist among various neonatal intensive care units in terms of drug efficacy compared to other methylxanthines, dosage regimen, time of initiation, duration of therapy, drug safety and value of therapeutic drug monitoring. In the current review, we will summarize the available evidence for the best practice in using caffeine therapy in preterm infants.

Key words: Apnea; Caffeine; Preterm; Methylxanthines

Core tip: Caffeine is among the most commonly prescribed medications in neonatal intensive care units, it has now largely replaced other methylxanthines. Caffeine reduces the frequency of apnea, intermittent hypoxemia, facilitates extubation from mechanical ventilation, and reduces the incidence of bronchopulmonary and patent ductus arteriosus in preterm infants. There are controversies regarding the safety and efficacy of high-dose, early *vs* late administration, duration of therapy, value in older gestational age infants and the value of therapeutic drug monitoring.

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INTRODUCTION

Methylxanthines are among the most commonly used medications in preterm infants[1,2]. They have been used for the treatment of apnea of prematurity (AOP) over the past 40 years[3-8]. Caffeine has now largely replaced theophylline and aminophylline for treatment of AOP because of its wider therapeutic index and longer half-life that allows once daily administration[9]. In the pioneering study "Caffeine for Apnea of Prematurity (CAP) trial"[10], infants who received caffeine had a lower incidence

of bronchopulmonary (BPD) and severe retinopathy of prematurity (ROP). On follow-up at 18 mo, they had a lower incidence of cerebral palsy and cognitive delay. Approximately one-half of this neuroprotective effect was attributed to improved respiratory morbidity, including an approximate 1 wk reduction in the duration of mechanical ventilation[11]. By 5 years of age, the reduction in rates of cerebral palsy with caffeine treatment was no longer statistically significant, but the gross motor function improved and the incidence of developmental coordination disorder was reduced[12,13]. A recent study, demonstrated that early caffeine initiation is associated with reduced neonatal morbidity, including a decreased incidence of BPD and of patent ductus arteriosus (PDA) requiring treatment in very low-birth-weight (VLBW) infants. Many NICUs have changed their practice toward earlier initiation of caffeine therapy[14,15]. Cost-effectiveness analysis showed caffeine to be both cost-saving and beneficial[16]. Moreover, methylxanthines increase the success of extubation of preterm infants within 1 wk of age[17].

MECHANISM OF ACTION

The pharmacological effects of caffeine in AOP include: (1) stimulation of the respiratory center in the medulla; (2) increased sensitivity to carbon dioxide; (3) increased skeletal muscle tone; (4) enhanced diaphragmatic contractility; (5) increased minute ventilation; (6) increased metabolic rate; and (7) increased oxygen consumption[18-20]. Caffeine also stimulates the central nervous and cardiovascular systems, enhances catecholamine secretion, has a diuretic effect, and alters glucose homeostasis[21].

Caffeine acts as a selective adenosine antagonist at the A2a receptors and a non-selective adenosine antagonist at A1 receptor[22,23]. Through this action it modulates many neurotransmitters, such as noradrenaline, dopamine, serotonin, acetylcholine, glutamine, and gamma-aminobutyric acid[24]. It also increases cyclic adenosine 3',5' monophosphate and cyclic guanosine monophosphate leading to bronchodilatation[9,22,25]. Moreover, caffeine enhances peripheral chemoreceptors activity, thus it can terminate apnea and initiate normal breathing[26]. Caffeine may also have an anti-inflammatory action in the immature lung[27]. The benefits of caffeine therapy on respiratory functions increase the success of early nasal-continuous positive airway pressure (CPAP) therapy, facilitate earlier weaning from mechanical ventilation, and reduce ventilator-induced lung injury. This is particularly important in the early neonatal period, when AOP is prevalent and early nasal-CPAP therapy may not be successful in all infants[28-31].

PHARMACOKINETICS

The route of administration of caffeine does not affect its pharmacokinetics as there is almost complete bioavailability after its administration orally or intravenously. Caffeine is absorbed rapidly from the gastrointestinal tract with minimal-to-no first pass metabolism, and its peak plasma concentrations frequently occur in less than one h[20,32,33].

Caffeine is hydrophobic and distributes rapidly without tissue accumulation. It is rapidly distributed into the brain, and in preterm infants the levels of caffeine in the cerebro-spinal fluid approximate the plasma levels. In infants the mean volume of distribution is 0.8-0.9 L/kg compared to 0.6 L/kg in adults[33].

Biotransformation of caffeine occurs in the liver mainly by microsomal cytochrome P450 mono-oxygenases (CYP1A2) and partially by xanthine oxidase. The predominant process of caffeine metabolism in the preterm infant is N7-demethylation, which matures at about the age of 4 mo[31]. The demethylation process is postnatal age dependent, regardless of gestational age or birth weight[31,34-36]. There is a higher rate of caffeine metabolism in female than male neonates[31].

The metabolism of caffeine in the preterm infants is limited by immaturity of the hepatic enzymes. The plasma half-life of caffeine remains prolonged for as long as 38 wk gestation and reaches adult levels at the age of 3 to 4.5 mo[34,37]. Furthermore, the caffeine half-life may be prolonged further in exclusively breastfed infants and infants with cholestatic jaundice[38]. Interconversion between caffeine and theophylline has been reported with a greater rate of theophylline converting to caffeine than caffeine converting to theophylline. Approximately 3%-10% of caffeine converts to theophylline, whereas up to 50% of theophylline converts to caffeine[33,39,40].

In the first weeks of life, caffeine is eliminated mainly by renal excretion[38]. Caffeine elimination is slower in the premature and term neonate, compared with older children and adults, because of immaturity of renal functions. Several factors influence caffeine clearance in neonates including gestational age, post-conceptional age and parenteral nutrition; thus preterm infants receiving parenteral nutrition, may need closer monitoring of plasma caffeine concentrations[38,41]. Renal clearance of caffeine differs between preterm and full-term neonates due to lower glomerular filtration rates (GFR) in preterm infants[36]. The GFR increases rapidly during the first 2 wk of life and then rises steadily until 8-12 mo of age, when adult values are reached[42]. Theophylline has a serum half-life ranging from 24.7 to 36.5 h, and an estimated clearance from 0.02 to 0.05 L/kg per hour in premature neonates, compared with healthy adults, who have an estimated elimination half-life of 6.3 h[43]. On the other hand, caffeine has a longer serum half-life of 101 h in neonates[44], whereas its half-life ranges from 3 to 6 h in adults[43]. Differences in the pharmacokinetics of caffeine and theophylline are shown in Table 1.

CAFFEINE *VS* THEOPHYLLINE

The comparative effectiveness of caffeine *vs* theophylline

Table 1 Pharmacokinetics of caffeine compared to theophylline

	Caffeine	Theophylline
Mechanism of action:		
CNS stimulation	More active	Less active
Cardiac stimulation	Less active	More active
Diuresis	Less active	More active
Loading dose	20 to 40 mg/kg per dose Ⅳ/PO	4 to 8 mg/kg per dose Ⅳ
Maintenance dose	5 to 8 mg/kg per dose once daily Ⅳ/PO	1.5 to 3 mg/kg per dose every 8 to 12 h Ⅳ
Plasma half-life (h)	40 to 230 (mean, 103)	12 to 64 (mean, 30)
Therapeutic level (mg/L)	5 to 25	7 to 12
Toxic level (mg/L)	> 40 to 50	> 20
Adverse effects:		
Cardiovascular	Tachycardia, dysrhythmia	Tachycardia, dysrhythmia
Gastrointestinal	Feeding intolerance, GER	Feeding intolerance, GER
CNS	Jitteriness, irritability, seizures	Jitteriness, irritability, seizures, decreased CBF
Signs of toxicity	Tachycardia, cardiac failure, pulmonary edema, hypertonia, sweating, metabolic disturbances	Tachycardia, agitation, hypokalemia, diuresis, gastric bleeding, seizure
Metabolism	Excreted unchanged or N-demethylation *via* CYP P450 (CYP1A2) liver-methyltransferase pathway	Excreted unchanged or undergoes 8-hydroxylation *via* CYP1A2 and CYP2E1
Inter-conversion	3% to 8% converted to theophylline *via* CYP1A2	25% converted to caffeine *via* methylation
Routine blood level	Not required	Required
Elimination	86% unchanged in urine	50% unchanged in urine
CSF level	Similar to plasma concentrations	Crosses into the CSF
Clearance (L/kg per hour)[9,43]	0.002 to 0.017	0.02 to 0.05

CNS: Central nervous system; CBF: Cerebral blood flow; CSF: Cerebrospinal fluid; GER: Gastroesophageal reflux; GIT: Gastrointestinal tract.

regarding improving respiratory function has been evaluated by several small studies conducted over the past 40 years[45-48]. A meta-analysis of previous trials revealed that caffeine is as effective as theophylline on both apnea/bradycardia with some therapeutic advantages of caffeine over theophylline such as, better enteral absorption, higher therapeutic ratio, and longer half-life as well as less adverse effects such as tachycardia and feeding intolerance[49]. Moreover, caffeine has less plasma concentration fluctuations, and greater central nervous system penetration without producing fluctuations in cerebral blood flow[20]. Furthermore, theophylline therapy has been associated with seizures and hypokalemia in the neonatal population[50]. All the aforementioned benefits of caffeine make it the drug of choice in the treatment of AOP.

However, the results of the above mentioned meta-analysis[49] should be interpreted with caution due to limitations, including small sample size of the included studies; variations in the gestational age, birth weight and clinical status of the infants enrolled in the studies; and absence of data regarding drugs safety and their effects on neurodevelopmental term outcomes. Larger randomized controlled trials (RCTs) enrolling lower birth weight and gestational age infants are highly recommended to demonstrate the effectiveness and safety of varying doses of caffeine compared to theophylline with respect to important clinical outcomes such as safety, growth and long-term effects on neurodevelopmental outcome.

DOSAGE

The current loading and maintenance dosage of caffeine, which have been approved by the Food and Drug Administration (FDA) for treatment of AOP is 20 mg/kg (equivalent to 10 mg/kg of caffeine base) and 10 mg/kg per dose (equivalent to 5 mg/kg caffeine base) once daily, respectively[20,51]. The goal is to achieve a therapeutic blood level of 5 to 25 mg/L of caffeine in preterm infants less than 32 wk post-menstrual age (PMA). However, higher loading and maintenance doses of caffeine have been evaluated in various settings of treatment for AOP and to facilitate of extubation from mechanical ventilation (Table 2). In the CAP trial, Schmidt *et al*[10] used a loading dose of 20 mg/kg and a maintenance dose of 5 to 10 mg/kg per dose once daily of caffeine citrate for treatment of apnea in preterm infants. Prior to the CAP trial, a loading dose of 50 mg/kg caffeine citrate (25 mg/kg caffeine base) was shown to be more effective in reducing apneic episodes within 8 h than a loading dose of 25 mg/kg in preterm infants[48]. Furthermore, a daily maintenance dose of 30 mg/kg caffeine citrate was reported to be administered safely in preterm infants[52].

Steer *et al*[53] found that a high dose regimen of 20 mg/kg caffeine citrate, given 24 h before a planned extubation in preterm infants, reduced the rate of extubation failure compared to a low dose regimen of 5 mg/kg caffeine citrate with no effect on infant mortality, major neonatal morbidity, death, or severe disability. Shah and Wai[54] compared two dosing regimens of caffeine (loading dose of 20 mg/kg over 30 min and maintenance dose of 5 mg/kg per day *vs* loading dose of 10 mg/kg over 30 min and maintenance dose of 2.5 mg/kg per day) in preterm infants less than 34 wk gestation and found that the higher dose caffeine was associated with lower frequency of shallow breathing,

Table 2 Recommended caffeine doses

Trial	Design	Population	Intervention	Outcomes	Main results
Scanlon *et al*[48] United Kingdom	Prospective, randomized, controlled trial	44 preterm infants less than 31 wk gestation	High (loading 25 mg/kg and maintenance 6 mg/kg per day) *vs* low (loading 12.5 mg/kg and maintenance 3 mg/kg per day) caffeine citrate given 24 h prior to extubation	Frequency of apnea	High dose caffeine significantly decreased the frequency of apnea
Steer *et al*[52] Australia	Prospective, randomized, blinded, controlled trial	127 preterm infants less than 32 wk gestation	Three dosing regimens of caffeine citrate (3, 15 and 30 mg/kg) for peri-extubation management of ventilated preterm infants	Successful extubation defined as staying off ventilation for 7 d post-extubation	No statistically significant difference in the incidence of successful extubation however, infants in the two higher dose groups had statistically significantly less documented apnea
Steer *et al*[53] Australia	Prospective, randomized, blinded, controlled trial	234 preterm infants less than 30 wk gestation on mechanical ventilation	High (loading 80 mg/kg and maintenance 20 mg/kg per day) *vs* low (loading 20 mg/kg and maintenance 5 mg/kg per day) caffeine citrate given 24 h prior to extubation	Primary: Successful extubation of mechanically ventilated infants Secondary: Frequency of apnea	High dose caffeine significantly increased the chance for successful extubation, decreased the frequency of apnea and shortened the duration of respiratory support
Shah *et al*[54] Singapore	Prospective, case control trial	Preterm infants less than 34 wk gestation	High (loading 20 mg/kg and maintenance 5 mg/kg per day) *vs* low (loading 10 mg/kg and maintenance 2.5 mg/kg per day) caffeine citrate	Primary: Frequency of apnea, desaturation, and shallow breathing Secondary: Side effect of caffeine, BPD, and ROP	High-dose caffeine significantly reduced episodes of apnea and shallow breathing without side effects
Gray *et al*[125] Australia	Prospective, randomized, blinded, controlled trial	287 preterm infants less than 30 wk gestation exhibit AOP or require mechanical ventilation	Loading dose of 40 mg/kg followed by two maintenance doses of either 20 or 5 mg/kg per day	Primary: Cognitive development at 1 yr of age on the Griffiths Mental Development Scales Secondary: Neonatal morbidity, death and disability, temperament at 1 yr and behavior at 2 yr of age	High maintenance dose was associated with borderline benefit in cognitive outcome without increasing morbidity, temperament or behavior disorders
Mohammed *et al*[55] Egypt	Prospective, randomized, blinded, controlled trial	120 preterm infants less than 32 wk gestation exhibit AOP or require mechanical ventilation	High (loading 40 mg/kg and maintenance 20 mg/kg per day) *vs* low (loading 20 mg/kg and maintenance 10 mg/kg per day) caffeine citrate	Primary: Successful extubation of mechanically ventilated infants Secondary: Frequency and documented days of apnea	High dose caffeine significantly increased the chance for successful extubation, decreased frequency of apnea

BPD: Bronchopulmonary; ROP: Retinopathy of prematurity; AOP: Apnea of prematurity.

apnea, bradycardia and cyanosis without significant increase in the rate of side effects. In a recent RCT, we have found that the use of high loading (20 mg/kg caffeine base) and maintenance (10 mg/kg caffeine base) doses of caffeine was associated with a decreased chance for extubation failure in mechanically ventilated preterm infants and decreased the frequency of apnea without significant side effects[55].

Clinical practice varies considerably between NICUs. Most of NICUs in the US do not exceed a loading dose of 20 mg/kg and a maintenance dose of 10 mg/kg per day of caffeine citrate. Some NICUs outside the US use, maintenance doses as high as 20 mg/kg per day[15]. Until further evidence exists from large, well-designed RCTs and meta-analyses we recommend using the FDA-approved doses of 20 mg/kg and 10 mg/kg per day of caffeine citrate as loading and maintenance doses, respectively.

TIMING OF CAFFEINE THERAPY

Methylxanthines have been used to treat apnea in preterm infants for more than 40 years[3,56]. Subsequent studies reported potential advantages for early therapy, which prompted physicians to initiate methylxanthines as a prophylactic therapy before the occurrence of apnea[7]. Moreover, the initial beneficial neurodevelopmental effect demonstrated in the CAP trial[10,11] re-promoted the use of prophylactic caffeine therapy among different NICUs. In a meta-analysis of two RCTs that included 104 preterm infants, prophylactic caffeine therapy did not decrease the frequency of apnea, bradycardia, or episodes of hypoxemia and did not shorten the duration of mechanical ventilation[57]. However, none of the trials included in this meta-analysis reported long-term outcomes for prophylactic methylxanthine therapy. In a retrospective analysis of a large database including over 29000 VLBW infants from Pediatrix Medical Group, Dobson *et al*[14] found that early initiation of caffeine therapy (within 3 d of life) was associated with a lower incidence of BPD, less treatment of PDA, and a shorter duration of mechanical ventilation.

A recent study[58] demonstrated that early initiation of caffeine therapy (within 2 h of age) in non-intubated preterm infants was not associated with a reduction in the need for intubation or vasopressors by 12 h of age. However, it was associated with improved hemodynamic status as measured by blood pressure and superior vena cava flow. Patel *et al*[59] in a retrospective cohort study including 140 preterm neonates have demonstrated that early caffeine therapy (initiated within 3 d of life) was associated with decreased incidence of the composite outcome of death or BPD adjusted odds ratio (AOR: 0.26, 95%CI: 0.09-0.70), PDA requiring treatment (AOR: 0.28, 95%CI: 0.10-0.73), and duration of mechanical ventilation.

In a large retrospective study that included data from 29 NICUs participating in the Canadian Neonatal Network and conducted over more than 5000 preterm infants less than 31 wk gestation, prophylactic (initiated within 2 d after birth) caffeine therapy was associated with decreased odds of a composite outcome of death or BPD (AOR: 0.81, 95%CI: 0.67-0.98) and PDA (AOR: 0.74, 95%CI: 0.62-0.89) with no difference in mortality (AOR: 0.98, 95%CI: 0.70-1.37), necrotizing enterocolitis (NEC) (AOR: 0.88, 95%CI: 0.65-1.20), severe ROP (AOR: 0.78, 95%CI: 0.56-1.10), or severe neurological injury (AOR: 0.80, 95%CI: 0.63-1.01)[60].

Most of the previous trials were either retrospective data analysis, which could be subject to selection bias, or prospective but not powered or designed to detect short and long-term benefits of prophylactic caffeine therapy. It was also unclear from previous data, whether these beneficial short and long-term effects of caffeine are attributed to a real effect of the drug or due to shortening the duration of mechanical ventilation. Given the uncertainty of the evidence, more RCTs are needed to evaluate the short and long-term benefits of prophylactic caffeine therapy in mechanically ventilated and non-ventilated preterm infants.

DURATION OF CAFFEINE THERAPY

There are no clinical trials to support decisions about when to discontinue caffeine therapy in preterm infants. However, because AOP is not common past 34 wk gestation, caffeine therapy should be continued until preterm infants are 34 to 36 wk corrected gestational age and free of any apnea episodes for at least 8 d[61]. Despite the existence of apnea and sudden infant death syndrome in preterm and late preterm infants after discharge from the NICU[62], continuation of caffeine therapy at home is not recommended.

In a recent prospective RCT, late discontinuation of caffeine therapy at 40 wk PMA significantly reduced the episodes of IH in preterm infants compared to standard discontinuation at 34-35 wk gestation[63]. Although previous animal and human studies have shown that IH is pro-inflammatory and may result in cardio-respiratory instability, ROP, and neurodevelopmental deficits[64-66]; the clinical relevance of late discontinuation of caffeine therapy beyond 35 wk gestation is yet to be established in further RCTs.

THERAPEUTIC EFFECTS

Apnea of prematurity

AOP is a developmental disorder caused by immaturity of the respiratory control mechanisms[67,68], and consequently exhibited a widely variable incidence according to gestational age and birth weight. It was estimated to occur in virtually all infants born at less than 28 wk gestation or less than 1000 g[69,70], 50% of infants born between 30-32 wk[71], as well as in 50% of infants born at 33-35 wk gestation[72]. In most infants, apneic episodes cease by term gestation[73], though apnea might persist beyond term in the most immature infants born less than 28 wk gestation[74].

In 2012, an updated Cochrane review[75] with an aggregate meta-analysis of five trials (two trials of caffeine) that included 192 preterm infants with apnea, revealed that infants treated with methylxanthine compared with those who received placebo had less apneic events relative risk (RR: 0.44, 95%CI: 0.32-0.60) and less need for intermittent positive pressure ventilation (RR: 0.34, 95%CI: 0.12-0.97). Analysis of the two trials evaluating caffeine use[76,77], also found significantly less treatment failure (RR: 0.46, 95%CI: 0.27-0.78). Although, the CAP trial[10] was included in the updated review, the data from this trial were not pooled with the other studies as it was not primarily designed to evaluate the efficacy of caffeine for alleviation of apnea-related symptoms. In the CAP trial[10], caffeine therapy was associated with younger PMA at last supplemental oxygen use compared to placebo. The earlier weaning from mechanical ventilation with caffeine ultimately

supports a decrease in the frequency of apnea[27].

Of particular interest, in a subsequent report of the CAP trial[10], the reduction of duration of mechanical ventilation was only evident in those who received caffeine in the first 3 d of life[78]. In response to this result, several retrospective analyses comparing early (within 3 d of life) *vs* late start of caffeine therapy were conducted and revealed that the early start of therapy was associated with less incidence of BPD, less treatment of PDA, and shorter duration of mechanical ventilation[14,59,60].

According to the evidence above, caffeine is considered the first-choice drug for treatment of AOP as a result of the better safety profile compared to theophylline, alongside its associated respiratory and neuroprotective benefits.

Prevention of extubation failure

The CAP trial had not directly reported extubation failure rates, but the caffeine group was associated with reduction in PMAs at last use of positive pressure ventilation, and endotracheal intubation[10]. A meta-analysis of six studies reported that prophylactic methylxanthine treatment in intubated preterm infants results in a significant reduction in failure of extubation within 1 wk (RR: 0.48, 95%CI: 0.32-0.71)[17]. Steer *et al*[52] conducted two randomized, double-blind clinical trials comparing different dosing regimens of caffeine commenced in the pre-extubation period. In the first trial, 127 infants born at less than 32 wk were enrolled and randomly assigned to 3 groups according to maintenance dosages of caffeine citrate (3, 15 and 30 mg/kg). Although there was no statistically significant difference in the primary outcome of the failure of extubation between groups, reported apnea episodes were significantly reduced in infants in the 2 higher dose groups. The second trial[53], compared a two dose regimens (20 mg/kg *vs* 5 mg/kg) in 120 preterm with gestational age less than 30 wk, the high-dose regimen was associated with a significant reduction in extubation failure (15% *vs* 29.8%; RR: 0.51, 95%CI: 0.31-0.85) number needed to treat (NNT: 7). The two groups did not differ in infant mortality, major neonatal morbidity, or severe disability at 12 mo corrected age. Furthermore, subgroup analysis based on gestational age revealed that infants born at less than 28 wk gained more respiratory benefit of a higher dose of caffeine as evidenced by a significant reduction of mechanical ventilation duration and more marked reduction of extubation failure rate (NNT: 3). In a recent pilot, randomized, double blinded study comparing two different dosing regimens of caffeine citrate (loading dose, 20 mg/kg; maintenance dose, 10 mg/kg *vs* loading dose, 40 mg/kg; maintenance dose, 20 mg/kg); the use of high, in comparison to low, dose caffeine was associated with a significant reduction of extubation failure among mechanically ventilated preterm infants and fewer apnea episodes[55].

The exact mechanisms of increased chances of successful extubation in association of caffeine are still unclear, however, caffeine may improve respiratory mechanics through mounting central respiratory drive[79,80], improving respiratory muscle strength[81], inducing diuresis and hence improving lung compliance[82].

Postoperative apnea

Preterm infants, who undergo general anesthesia for surgical procedures may exhibit postoperative apnea episodes. The risk of postoperative apneas is increased in babies who previously experienced apnea[83,84], younger PMA[84,85], BPD[84] and pre-operative anemia[86]. Henderson-Smart *et al*[87] conducted a meta-analysis of three trials that compared administration of caffeine during or immediately after induction of anesthesia, with placebo, as prophylaxis for postoperative apnea. Results revealed that caffeine use was associated with significant reduction of postoperative apnea and bradycardia (RR: 0.09, 95%CI: 0.02-0.34). Therefore, use of caffeine to prevent postoperative apnea in infants born prematurely is recommended; however, more studies are warranted to resolve if all preterm infants should receive caffeine adjunctive to general anesthesia or only those with one of the previously mentioned risk factors.

Bronchiolitis-related apnea

Infants with bronchiolitis may exhibit episodes of apnea, which may require assisted ventilation. Infants who were born prematurely and those less than two months old are more vulnerable to bronchiolitis-related apnea[88]. Two case reports involving a total of 3 infants, who were born preterm and presented with bronchiolitis-related apneas, showed improvement of apnea after aminophylline therapy[89,90]. Furthermore, two retrospective reviews showed that caffeine use in those infants may be associated with significant reduction of need for mechanical ventilation[91,92]. So an appropriately powered RCT evaluating efficacy and safety of caffeine as a treatment of bronchiolitis-related apnea is needed.

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) is a common complication in preterm infants, which may be associated with significant mortality[93], alongside deleterious long-term pulmonary[94,95] and neurodevelopmental morbidities[96,97]. One of the major findings for the secondary short-term outcomes of the CAP trial is significant reduction of BPD incidence in infants who received caffeine (36%) *vs* (47%) in the placebo group (OR: 0.63, 95%CI: 0.52-0.76; $P < 0.001$). This decrement of BPD rates was attributed in part to a shorter duration (about 1 wk) of endotracheal intubation and positive pressure ventilation in the caffeine-treated patients compared with the controls[10]. Notably, the short-term respiratory benefits of caffeine were most significant when treatment was started in the first 3 d of life[78].

Recently, in a large multicenter cohort study using data of 62056 VLBW infants, the use of early caffeine therapy within the first three days of life was associated with a lower incidence of BPD compared with later use (23% *vs* 31%, OR: 1.23, 95%CI: 1.05-1.43)[14]. Another two retrospective reports revealed similar results[60,98]. A clinical trial is currently conducted by Bancalari to evaluate short-term respiratory benefits of early caffeine use commenced within the first five days of life in mechanically ventilated preterm infants born less than 31 wk of gestation (ClinicalTrials, gov, NCT01751724).

The pulmonary protective effects of caffeine in neonates may be, at least partly due to reduction of pulmonary inflammation[99], as evidenced by inhibition of proinflammatory cytokines in both *in vitro* and *in vivo* clinical studies[100-103]. In addition, accumulating evidence has established beneficial effects of caffeine on pulmonary mechanics. In animal models with respiratory distress syndrome, early caffeine therapy in combination with prophylactic surfactant was associated with reduced airway resistance, enhanced lung compliance, and improved ventilator efficiency index within the first 24 h after birth[29]. In agreement with this, human studies reported upgrading of pulmonary function parameters following caffeine administration as exhibited by improved minute ventilation[18], decreased total lung resistance[28], and increased respiratory muscle contractility[19,81].

Intermittent hypoxemia

Intermittent hypoxemia (IH) is defined as brief, repetitive episodes of decreased hemoglobin oxygen saturation from a normoxic baseline followed by reoxygenation and return to normoxia. IH occurs frequently in preterm infants, even until term-equivalent age and after cessation of any clinically apparent apnea-associated symptoms[63,104]. Severe and frequent episodes of decreased hemoglobin oxygen saturation in early infancy have been shown to increase the risk of later neurodevelopmental impairments[105,106]. Furthermore, Di Fiore *et al*[66] reported a significant association between IH and severity of ROP.

A recent prospective, multicenter RCT enrolled 105 infants, who were born less than 32 wk gestation and formerly treated with caffeine, were randomly assigned to either extended caffeine treatment compared to usual caffeine discontinuation. The results revealed significant reductions in IH at 35 and 36 wk PMA with prolonged caffeine treatment[63]. However, further studies are needed to evaluate the optimum dosing regimen of caffeine required to alleviate IH and long-term effects of extended use.

PDA

The post-hoc analysis of the CAP trial revealed that infants in the caffeine group were significantly less likely to require pharmacological treatment for PDA closure compared with infants in the control group (29% *vs* 38% adjusted OR: 0.67, 95%CI: 0.54-0.82). In addition, caffeine therapy was associated with reduced risk of surgical ligation of PDA (adjusted OR: 0.29, 95%CI: 0.2-0.43)[10]. Furthermore, evidence from retrospective studies found that early caffeine therapy within the first 3 d of age was associated with significant reduction of incidence of PDA requiring treatment compared with later initiation of therapy[14,59,61].

The beneficial effects of caffeine on PDA may be attributed to favorable hemodynamic changes, including increase in cardiac index, stroke volume, and heart rate, alongside its diuretic and prostaglandin antagonistic properties[107-109]. Also, caffeine use was reported to be associated with increased blood pressure with no significant changes of systemic vascular resistance[107].

Neuroprotective effects

Animal studies found that adenosine A1 receptors activation contributed to hypoxia-induced periventricular white matter injury[110-112]. In agreement with this, caffeine administration in hypoxia-exposed neonatal pups was associated with enhanced myelination and reduced ventriculomegaly[110,111,113]. Moreover, caffeine potentiates neural plasticity at the level of N-methyl-D-aspartate receptors with documented altered morphology of neural synapses and increased size of dendritic spines[114,115]. However, other animal studies raised concerns about long-term consequences of exposing the growing brain to caffeine. Silva *et al*[116] reported that maternal caffeine consumption in rodents during pregnancy and lactation may have adverse effects on the neural development and adult behavior of their offspring. Also, postnatal caffeine treatment of neonatal mice was associated with altered astrocytogenesis[117].

Several studies evaluated short-term neurological effects of caffeine use in preterm infants. Two observational studies reported enhanced cerebral cortical activity in the brains of preterm infants treated with caffeine[118,119]. Also, caffeine-treated preterm infants exhibited improved measures of auditory processing[120]. Studies assessing the effect of caffeine on sleep organization in preterm infants exhibited contradictory results[26,121,122]. However, in a recently published study, evaluation of sleep architecture of 201 children aged 5-12 years who were previously enrolled in the CAP trial revealed no long-term effects on sleep duration or sleep apnea during childhood[123].

The CAP trial[10] found a higher patient survival rate without neurodevelopmental disability (cognitive delay, cerebral palsy, severe hearing loss or bilateral blindness) at a corrected age of 18 to 21 mo in infants within the caffeine group compared with those in the placebo group (59.8% *vs* 53.8%; adjusted OR: 0.77, 95%CI: 0.64-0.93, P = 0.008). Of note, caffeine use nearly halved the rate of cerebral palsy[11]. Subsequent follow-up of 1640 of infants enrolled in the CAP trial, at the age of 5 years, demonstrated no significant difference between the two groups in the combined outcome of death or severe neurodevelopmental impairment (78.9% *vs* 75.2% adjusted OR: 0.82, 95%CI: 0.65-1.03)[78].

Although, by 5 years of age, there was no significant difference in rates of cerebral palsy between both groups, there was a significant reduction of the incidence of developmental coordination disorder in the caffeine treated group (11.3% *vs* 15.2% adjusted OR: 0.70, 95%CI: 0.51-0.95)[13]. The authors attributed the improvements in motor function to improved cerebral white matter micro-structural development as demonstrated in magnetic resonance imaging (MRI) done at term equivalent age[124].

Gray *et al*[125] randomized 287 infants to receive one of two maintenance-dose regimens of caffeine citrate (20 *vs* 5 mg/kg per day). The results of their trial revealed no significant difference in adverse outcomes related to temperament and behavior at 1 and 2 years of age. In addition, infants in the higher-dose group exhibited a trend towards higher cognitive scores at 1 year of age.

Cerebral blood flow

Methylxanthines are non-specific inhibitors of A1 and A2a adenosine receptors, therefore, attenuates adenosine induced vasodilation that can potentially impair cerebral blood flow. Such effect has been reported in adults[126]. Hoecker *et al*[127,128] found that caffeine citrate administration at a loading dose of 50 mg/kg in preterm infants; either as a single or divided doses; was associated with significant reduction of cerebral blood flow. Another trial revealed a significant reduction in the cerebral oxygenation, and cerebral blood flow velocities 1 h after administration of 20 mg/kg loading dose of caffeine citrate with partial recovery at 4 h[129]. However, there were no documented changes of cerebral hemodynamics in preterm infants after the administration of the maintenance dose of caffeine citrate (5 mg/kg once a day)[130].

ROP

In the CAP trial, ROP detection rates did not differ significantly between both groups[10], however fewer infants in the caffeine group exhibited severe ROP compared to the control group (5.1% *vs* 7.9%; adjusted OR: 0.61, 95%CI: 0.42-0.89)[11]. The authors attributed that to the shorter duration of positive airway pressure and supplemental oxygen in caffeine-treated patients. In addition, improvement of IH episodes associated with caffeine use may decrease the severity of ROP[63].

Growth

The CAP trial revealed that infants in the caffeine group gained less weight than those in the control group during the first 3 wk after randomization[10]. However, follow-up of infants at 18 to 21 m showed no long-term difference in weight gain among infants in both groups[11]. Moreover, Bauer *et al*[131] reported increased energy expenditure (2.1 to 3 kcal/kg per hour) and oxygen consumption (7 to 8.8 mL/kg per minute) in caffeine-treated preterm infants compared with baseline measurements. Also, caffeine use was associated with less weight gain during the four-week study period and infants receiving caffeine required a lower incubator temperature to maintain a normal body temperature[131]. In a recently published clinical trial comparing two dosing regimens of caffeine citrate in preterm infants (loading dose, 20 mg/kg; maintenance dose, 10 mg/kg *vs* loading dose, 40 mg/kg; maintenance dose, 20 mg/kg); we reported no significant difference in weight gain between both groups. In agreement with this, Steer *et al*[53] have conducted a study comparing maintenance caffeine doses of 5 and 20 mg/kg per day and found no difference in the overall weight gain between both groups, however infants who received higher dose required longer time to regain birth weight.

Renal

Caffeine exerts a diuretic effect through increasing creatinine clearance, as an indicator of GFR, within 12 h of administration[108]. Also, methylxanthines use was reported to be associated with increased urinary calcium excretion[132]. However, caffeine did not alter serum calcium, phosphorus, sodium, or potassium concentrations[9].

Gastrointestinal

AOP and gastroesophageal reflux (GER) are relatively common in preterm infants, however, there is no evidenced temporal relationship between both conditions[133,134]. Mehtylxanthines may aggravate reflux through delayed gastric emptying and decreasing tone of lower oesophageal sphincter[135,136], they also increase gastrin secretion[137]. Clinical trials did not find aggravation of GER symptoms in caffeine-treated preterm infants[138].

Caffeine citrate administration in preterm infants at a loading dose of 25 to 50 mg/kg were reported to be associated with a reduction of mesenteric blood flow velocities[119,127,128,139], whereas a single 20 mg/kg intravenous loading dose of caffeine citrate did not cause significant changes in superior mesenteric artery flow velocities. In the CAP trial, there were no significant differences in the rates of NEC between both groups[10]. In a recent RCT study, we reported no increment in the rates of NEC in preterm infants after receiving a loading dose of caffeine citrate of 20 mg/kg per day followed by maintenance doses of 10 mg/kg per day compared to standard-dose regimen[55].

Anti-inflammatory effect

The immunomodulatory effects of caffeine may be related to blocking of adenosine receptors located on the surface of immune cells and subsequent up-regulation of Toll-like receptors[140]. Chavez Valdez *et al*[103] had conducted an observational study to determine cytokine level changes in 26 caffeine-treated preterm infants. Results revealed that caffeine levels within the therapeutic range (10-20 mg/L) were associated with a decrease in interleukin-6, tumor necrosis factor-α (pro-inflammatory cytokines) levels, and an increase in interleukin-10 (anti-inflammatory cytokine) levels. However, caffeine levels outside the therapeutic range

were associated with a proinflammatory profile.

ADVERSE EFFECTS

Caffeine has various dose-related side effects on different systems. Accidental administration of high dose caffeine in preterm infants was associated with tachycardia, tachypnea, agitation, irritability, tremor, hypertonia, and tonic-clonic movements representative of seizure activity[141]. The CAP trial and its subsequent reports of outcomes did not reveal any significant short or long-term adverse effects of caffeine therapy in the NICU[10,11]. In the RCTs using high-dose caffeine therapy, the initial slow rate of growth[53] and clinically insignificant tachycardia[55] were the only reported side effects. Metabolic acidosis and hyperglycemia have been reported in acute caffeine toxicity and accidental overdose[141,142].

THERAPEUTIC DRUG MONITORING

Most published researches do not support routine therapeutic drug monitoring (TDM) when caffeine is given at standard doses, as the majority of neonates were found to have plasma concentrations within the recommended therapeutic range (5.5-23.7 mg/L)[51,143,144]. However, TDM may be necessary when higher doses are used or toxicities are suspected[143].

ECONOMIC IMPACT OF CAFFEINE THERAPY

A recent study evaluated the cost per survivor without neurodevelopmental impairment in patients enrolled in the CAP trial (n = 1869); caffeine was found to be a cost-saving therapy compared with the placebo. This effect is mainly caused by the reduced number of days on mechanical ventilation[16]. However, this study has some limitations which may affect the precision of these results such as the existence of retrospective analysis of cost-effectiveness data. In addition, certain resource utilization data were not evaluated adequately in the CAP trial such as costs of inter-hospital transport, post-discharge use of drugs, and other outpatient healthcare services. Moreover, consensus panels recommended that outcomes measured should be expressed in terms of quality-adjusted life-years rather than biological outcomes used in the CAP trial, such as the survival without neurodevelopmental impairment. Finally, they applied Canadian costs from a single center although the trial was an international multicenter trial involving 9 countries.

CONCLUSION

Caffeine is the preferred first-line of treatment of AOP as it has a wider therapeutic range and is associated with less adverse events compared to theophylline. Further RCTs are needed to assess the safety and efficacy of high-dose caffeine especially on long-term neurodevelopmental outcomes, early prophylactic *vs* late caffeine therapy, which gestational age candidate for prophylactic therapy, duration of caffeine therapy, and efficacy of caffeine therapy in infants older than 34 wk gestation.

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