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RESEARCH ARTICLE

CAFFEINE CITRATE NEUROPROTECTION IN PRETERM BABIES

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ABSTRACT

Caffeine citrate has been implemented to some extent worldwide withinneonatal units for preterm baby's obstructive sleep apnea management. Almost, preterm babies are prone to obstructive sleep apnea, plus elevated death risk or even disabilities. Up to date, caffeine citrate is addressed for preterm babies` apnea targeting to reduce bronchopulmonary dysplasia incidence, as well neurodevelopmental disability at 18-21 months. Caffeine citrate is recognized to havelong-term safety, particularlyrelating to motor, behavioral, and intelligence skills. Prenatal caffeine predisposes to intrauterine growth restriction and small growth for gestational age at birth. Caffeine citratehas a cost-effective pharmacotherapy benefit, in terms of safety, and efficacy for preterm babies' apnea, and modulating rates of bronchopulmonary dysplasia within neonatal intensive care units.

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INTRODUCTION

Worldwide improvements in preterm babies rescue technologies is associated with obvious substantial national improvements for survival rate of critical ill preterm babies that estimated up to nine-million premature babies per year with expected lifelong experiencing neurological and physical disabilities. Up to date, preterm babies` brain injuries revealed lack for its etiologies, pathogenesis, as wellmanagement. Recently, efficient neuroprotective strategies were addressed for covering such lacking (1-3). Moreover, preterm babies` brain damage can be collectively referred to as prematurity encephalopathy. Preterm babies with encephalopathies often recognized with both gray and white matter, and cerebellum affections, plus associated pathological features i.e., oligodendrocyte-maturation disorder, axonopathy, and neuroinflammation; moreover, fractional anisotropy and cortical volume appear to be reduced on magnetic resonance imaging (4). Almost, improving the adverse neurodevelopmental outcomes associated with prematurity is a priority. Despite improved survival of preterm infants, there has not been an equivalent improvement in long term neurodevelopmental outcomes. Motor impairments such as developmental coordination disorder affects 10–72% of extremely preterm survivors (5). Relatively few neuroprotective strategies have been identified. Findings that caffeine used to treat or prevent apnea of prematurity, as compared to placebo, improved survival without neurodevelopmental disability at 18-21 months corrected age in caffeine citrate for prematurity babies obstructive sleep apnea, also bronchopulmonary dysplasia spurred interest in caffeine citrate neuroprotective potential (6). Recent identified evidence indicates that caffeine citraterecognized neuroprotective benefits in premature babies through alleviating hypoxia-induced white matter lesions, in addition efficient in terms of ventilation parameters, as well brain self-regulation. Moreover, caffeine citrate was addressed to minimize brain neurons` apoptosis developing rates, ventricular enlargement, even myelination disorders (7-8). Caffeine citrate meditation as a methylxanthinesstill addressed as the 1st choice for management based on its efficacy, better tolerability and wider therapeutic index as well as longer half-life (9). Up to date caffeine citrate has been named as 'silver or Maic' bullet (10). However, that reported improvements, unless remarkable issues still unsolved regarding caffeine citrate. In this line, current paper was introduced to represent updated pharmacological features, therapeuticeffectiveness and suggested future research, especially regarding neuroprotection in preterm babies.

Caffeine Citrate

Brief hints: The coffee has been known since 15th century, as a rejuvenating drink. By 19th century, it was known that pure

caffeine was extracted from Arabian coffee beans by Friedlieb Ferdlinand Runge (11).

Pharmacological features: The caffeine is a pure form of a white odorless powder with melting point ~235° C. Its basic nature with pKa value nearby 0.6, that classified under an achiral molecule might be synthesized from dimethylurea and malonic acid (12).

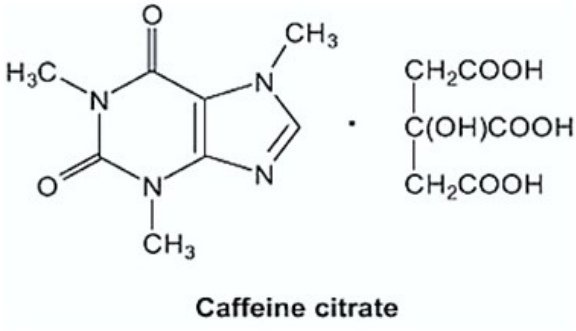

Fig. 1. chemical structure of caffeine (13)

Physiochemical features: The caffeine is a pure form of a white odorless powder with melting point ~235° C. Its basic nature with pKa value nearby 0.6, that classified under an achiral molecule [(1,3,7-trimethylxanthine, $C_8H_{10}N_4O_2$)], (Fig. 1) might be synthesized from dimethylurea and malonic acid (12).

Physiochemical features: Caffeine is rapidly and completely absorbed orally with almost no first pass metabolism. It is metabolized by the enzymes in liver whose maturity progresses with increasing gestational age. In preterm neonates, the predominant process of caffeine metabolism is N7 demethylation, which increases exponentially with postnatal age. The half-life of caffeine in preterm neonates is very long, ranging from 65 h to 102 h. This is maintained even up to 38 weeks until the maturity of hepatic biotransformation (14). The rate of metabolism of caffeine is found to be higher in female than male preterm neonates (13). Peak plasma concentration with both oral and intravenous route is almost the same and is reached within thirty minutes to two hours. The clearance increases non-linearly with increasing post-natal age, reaching a plateau at 120 days, and volume of distribution increases linearly with increasing weight. he bioavailability of oral dose is not disturbed by concomitant feeds. Renal route is the main route of excretion in neonates, where almost 86% of the drug is passed unchanged in urine, whereas in adults only 4% is excreted via renal route. The elimination half-life starts to decrease from birth and reaches the adult values at 60 weeks' post-conception age (13, 16).

Mechanism of action: Firstly, it is the adenosine receptor antagonist, secondly, it is a phosphodiesterase inhibitor, and thirdly, it is an active intracellular calcium mobilizer (13). Adenosine is a purine nucleoside present in the brain whose level rises with inflammation. It has four known receptors – A1 and A2a-b, and A3. These receptors, with their effects upon adenylate cyclase, lead to numerous effects such as central respiratory depression, sedation, anti-diuresis and decreased GFR, smooth muscles constriction and dilation, locomotor activity, etc. Caffeine, a trimethylxanthine, is a known specific inhibitor of at least two of these receptors; A1 and A2a. By blocking these receptors, caffeine manifests the most important pharmacological effects in preterm neonates (16). Caffeine is also an inhibitor of phosphodiesterase and prevents breakdown of cyclic adenosine monophosphate [cAMP]. Increased level of cAMP leads to stimulation of the central nervous system. However, being a weak inhibitor, a much higher concentration of caffeine is required and at therapeutic doses caffeine is unlikely to mediate this effect. Caffeine also binds to calcium channels and releases calcium from intracellular sites. It also inhibits voltage-sensitive calcium channels and may inhibit neurotransmission. However, the dose required for these effects may be in toxic levels (17-18). Further research is warranted into these aspects of mechanism of action of caffeine.

Pharmacological actions: Caffeine stimulates the respiratory center, sensitizing it to hypercapnia. This leads to increase in mean respiratory rate and tidal volume, improved pulmonary blood flow, better carbon dioxide sensitivity and enhanced diaphragmatic function and breathing pattern (16). It acts as a central stimulant as well as a somnolytic agent. The adenosine blocking action of caffeine is also known to secondarily affect several other neurotransmitters in the brain like dopamine, serotonin, noradrenaline, acetylcholine, gamma-aminobutyric acid [GABA], etc. (16).

Caffeine stimulates the myocardium and increases heart rate, cardiac output, stroke volume as well as mean arterial blood pressure. In kidneys, caffeine increases glomerular filtration rate and produces diuresis. This is primarily mediated via its adenosine antagonistic activity in the kidneys. Caffeine also increases basal metabolic rate, enhances catecholamine secretion and alters glucose homeostasis (14).

Route and Dose: Caffeine citrate is available in form of oral and injectable 'intravenous or intramuscular, also as caffeine benzoate formulations, its doe is half of caffeine citrate (16). The most popular dosing of caffeine citrate is 20 mg/kg loading and 5 mg/kg of maintenance dose. This standard dosing is known to achieve therapeutic level of eight to 20 mg/L in more than 70% of neonates.Loading dose of up to 50 mg/kg and maintenance dose of up to 20 mg/kg has been shown to be more effective in reducing apneic episodes and facilitating extubation in comparison to standard dose (14).

Interactions: The dependency of caffeine upon cytochrome P450 mono-oxygenase makes it susceptible to interact with those drugs which are a substrate for, or inhibit or induce, this hepatic enzyme. Drugs like ketoconazole and cimetidine inhibit caffeine metabolism and hence lower doses of caffeine may be required while these drugs are being used concomitantly. Anti-convulsant drugs like phenytoin and phenobarbitone, on the other hand, potentiate caffeine metabolism and may necessitate higher doses of caffeine when used together (13-14). The caffeine level can be measured in blood, plasma, serum or urine. The plasma caffeine level in regular coffee drinkers is around two to ten mg/L (13-16). It is a drug with wide therapeutic index and has been shown to be safe even at higher levels of 50 to 84 mg/L. Considering a wide safe margin and minimal adverse effects, regular monitoring of serum level may not be required, unless there is suspicion of toxicity or lack of clinical effects (19-21).

Pharmacological benefits: Caffeine citrate acts as a central nervous system stimulant and hypnotic. Previous studies have shown that caffeine antagonizes the adenosine receptor, as wellespecial functioning via non-specifically antagonizing the adenosine A 1 receptor (A1R) and adenosine A2a receptor (A2aR).Blockade of A1R and A2a indirectly affects other neurotransmitters in the brain, such as dopamine, serotonin, norepinephrine, acetylcholine, and γ-aminobutyric acid (GABA), (13, 23).

Neuroprotection of Encephalopathy Using Caffeine: There is currently no uniform caffeine dosage or administration timing for the neuroprotection of preterm babies`encephalopathy. Several long-term randomized controlled trials have studied the effects of caffeine administration timing on the nervous system of premature infants. A study of very premature infants with a gestational age of <29 weeks showed that the early caffeine group (within 2 hours, 20 mg/kg) in the early postnatal period showed greater circulatory improvement i.e., improved blood pressure and systemic blood flow than the conventional caffeine group within 12 hours, 20 mg/kg (24). The latest study suggested that early caffeine treatment is associated with better neurodevelopmental results. A study compared preterm infants with a gestational age of <29 weeks who were treated with caffeine early medication received within 2 days from birth, and late medication received after 2 days of birth. The incidences of cerebral palsy hearing damage and a Bayley scale cognitive score for infant development of <85 was decreased in the early-caffeine group compared to the late-caffeine group.

These data indicate that early use of caffeine could lead to more beneficial neurodevelopmental outcomes (25). In premature infants with a gestational age of <30 weeks, a study compared neonates who received high-dose caffeine citrate (80 mg/kg, for longer than 36 hours, and the standard dose of caffeine citrate 30 mg/kg, for longer than 36 hours. The incidence of cerebellar hemorrhage (CBH) in the high-dose group increased (36 vs. 10%, p = 0.03), as did the incidence of epilepsy and neurobehavioral abnormalities at full-term (corrected for gestational age), (26-27). However, a more recent study showed no difference in the incidence of CBH between high-dose (80 mg/kg/day) and standard-dose (20 mg/kg/day) caffeine citrate administration in very preterm infants with gestational age <28 weeks. In addition, there was no difference between the two groups at the age of 2 years according to the Neurosensory Motor Development Assessment and Bayley Infant Development Scale III (Bayley III). Although these results have allayed concerns regarding the use of high-dose caffeine in early preterm infants, it is notable that no study has reported the advantages and disadvantages of using high-dose caffeine in preterm infants with small gestational age. Therefore, early high-dose caffeine and its effects on brain injury, such as intraventricular hemorrhage and on long-term neurodevelopmental outcome, need to be determined on a larger scale

Neuroprotective Mechanism of Caffeine: The drug action of caffeine involves three basic mechanisms: it is an AR antagonist, a phosphodiesterase inhibitor, and an active intracellular calcium mobilizer. It interferes with GABA-A receptors, change GABA transport (28), and inhibit the production and activation of prostaglandins (29). Because caffeine has a series of molecular targets in the central nervous system, it is difficult to determine its exact molecular and cellular mechanisms in preventing and treating encephalopathy in premature infants.

Neuroprotective Mechanism of Caffeine and the Expression and Regulation of Adenosine Receptors: Adenosine is a neuromodulator of which metabolism depends on the synthesis, release, and decomposition of adenosine triphosphate. Known as adenine nucleoside, it exists in all cells and is a component of nucleic acid and energy-carrying molecules (30). In brain tissue, adenosine is mainly produced by neurons and plays an important role in the development of brain injury in immature infants, such as periventricular white matter injury (31).

Expression and Regulation of A1R: Caffeine's inhibition of A1R has opposite effects on embryonic and newborn brains. In the embryonic stage, inhibition of A1R renders cells more susceptible to hypoxia, which adversely affects fetal neurodevelopment and long-term behavior (32). Recent studies have shown that in vitro (33), the expression of A1R is significantly upregulated and the expression of transcription factors of oligodendrocytes is significantly decreased under hypoxia. Caffeine can promote the differentiation and maturation of oligodendrocytes and the expression of myelin-related proteins in vitro by antagonizing A1R.

Expression and Regulation of A2R: Previously, the ability of caffeine to induce central nervous system excitation was mainly attributed to its effect on A1R because the A1R receptor protein is expressed in the brainstem. In addition, adenosine-induced A1R activation was found to have an inhibitory effect on neurons. However, recent studies have shown that A2aR may also be involved. Caffeine-induced central nervous system arousal has been shown to be associated with A2aR (34).

Neuroprotective Mechanism of Caffeine and the Inhibitory Effect on Phosphodiesterase: Caffeine is an inhibitor of phosphodiesterase. This can prevent the breakdown of cAMP. An increase in cAMP availability can stimulate the central nervous system. In addition, cAMP can stimulate lipolysis by triggering the activity of hormone sensitive lipase (HSL), which plays a crucial role in the adrenaline cascade.

It also activates protein kinase A to phosphorylate several enzymes involved in the glucose and lipid metabolisms. Increased lipolysis leads to decreased dependence on glycogen use. Caffeine switches the substrate preference from glycogen to lipids by stimulating HSL activity and by inhibiting glycogen phosphorylase activity, and increases fatty acid oxidation. However, as a weak phosphodiesterase inhibitor, caffeine exerts its effect at much higher concentrations, and it is unlikely that caffeine mediates this effect at standard doses in newborns (13).

Neuroprotective Mechanism of Caffeine and the Regulation of Intracellular Calcium: Caffeine can bind to calcium channels to release calcium from cells, while inhibiting voltage-sensitive calcium channels and thereby inhibiting neurotransmission. However, the dosage required for these effects may be at a toxic level. In addition, A1R can

mobilize intracellular calcium ($Ca2^+$) transmission through the inositol triphosphate receptor (IP3R). Under physiological conditions, sleep deprivation induces forebrain basal cholinergic release to stimulate A1R, leading to IP3R activation and transcription factor changes (35). Under pathological conditions such as hypoxia, abnormal adenosine increase may lead to excessive activation of A1R and a subsequent imbalance of IP3R and $Ca2^+$ signals. Excessive $Ca2^+$ release can directly lead to $Ca2^+$ overload during hypoxia (36-37) and is considered another important mechanism affecting the activity of astrocytes, microglia, and oligodendrocytes.

Neuroprotective Mechanism of Caffeine and Interference with the GABA Receptor. In addition to antagonizing AR, inhibiting phosphodiesterase, and promoting intracellular calcium release, caffeine also has other biological effects, such as interfering with the GABA-A receptor and changing GABA transport (29). Conversely, caffeine affects the release of various neurotransmitters by blocking ARs, such as norepinephrine, dopamine, acetylcholine, serotonin, glutamate, and GABA (13). Other studies have shown that the migration and entry of GABA neurons into the hippocampal circuits of caffeine-administered mouse offspring during pregnancy and lactation are delayed in the 1st week after birth (14). The adult offspring of these mice showed decreased GABA neurons, increased excitability of the neural network, susceptibility to epilepsy, and some cognitive deficit. These effects suggest that rodents exposed to caffeine during pregnancy and lactation may produce offspring with neurodevelopmental deficits. Animal models of fetal drug exposure to caffeine have consistently revealed impaired GABA neurodevelopment (38).

Use of Caffeine for Its Neuroprotective Effect in Prematurity: The neuroprotective strategies for premature infants with encephalopathy include administration of neuroprotective and functional recovery agents. Caffeine is considered to have direct neuroprotective effects in rodents (39) and direct and indirect neuroprotective effects in preterm infants, including decreasing apnea, reducing brain damage, and promoting brain-function recovery. Therefore, we believe that caffeine can exert neuroprotective effects in premature infants and that it is a candidate drug for the promotion of encephalopathy recovery in this patient population.

Effect of Caffeine on the Neurodevelopment of Premature Infants

Potential Direct Effect: Clinical studies have also confirmed that caffeine has a protective effect on the development of the nervous system of premature infants and can promote functional recovery after injury. Although the CAP trial did not assess the direct effects of caffeine on neurodevelopment, reduction of AOP-related events and of intermittent hypoxia can help improve neurodevelopment (16), suggesting that caffeine has a positive effect on neurodevelopment. The CAP trial found that caffeine treatment in premature infants with apnea can confer neurodevelopmental benefits (cognitive delay and cerebral palsy) in the early stages of development, but also has a beneficial impact on long-term neurological development. In a long-term study conducted by Schmidt et al. early administration of caffeine to premature infants with apnea improved the survival rates and decreased the incidence of cerebral palsy and cognitive delay during a 18- to 21-month follow-up period (6). Although the neurodevelopmental advantage was not statistically significant at 5 years of age (40), during follow-up at 11-12 years, motor impairment was reduced in relation to caffeine treatment. These results reflect the potential long-term neurodevelopmental benefits of caffeine in preterm infants (41).

Potential Indirect Effect: Long term mechanical ventilation itself is a strong risk factor for adverse neurodevelopmental outcome (cerebral palsy and a Bayley scale cognitive score for infant development of <85) at 18 months of age (42). In the CAP trial, infants with a shorter duration of positive pressure ventilation days had less dyskinesia (40).In very preterm infants who survived to 36 weeks of corrected gestational age, prolonged hypoxemia episodes in the first 2–3 months after birth were associated with adverse outcomes at 18 months (43). Prolonged caffeine treatment can reduce recurrent hypoxemia events in these preterm infants (44). Studies have shown that administering caffeine within 48-72 h after birth can reduce the occurrence of physiological patent ductus arteriosus (45) and the demand for surgery. Therefore, caffeine can normalize cerebral blood flow by stabilizing the fluctuation of systemic blood pressure, thus conferring a neuroprotective effect in premature infants. In conclusion, the beneficial effects of caffeine on cardiopulmonary physiology in stabilizing systemic and cerebral hemodynamics and its ability to alleviate hypoxic respiratory depression may play an indirect role in neuroprotection.

CONCLUSION

This article reviewed the data available on the effects of caffeine on encephalopathy in prematurity. Clinical studies have shown that caffeine has a beneficial effect on the immature brain; this effect depends on the age at start of administration, the regular dose of caffeine administered, the neurodevelopmental stage at the time of administration, and the duration of exposure. Caffeine has a beneficial effect on the premature infant. Although animal experiments have suggested that higher doses of caffeine may be more beneficial, these results should still be cautiously considered. Therefore, in future preclinical studies, more attention must be paid to assessing the effects of different doses of caffeine on the structure and function of the developing brain and to determine the maximum dose and the best administration window for neuroprotection in premature infants. Regarding the mechanism of action of caffeine, the current focus is on its antagonism of ARs. Few studies have examined the exact molecular and cellular mechanisms of caffeine in preventing and treating encephalopathy in premature infants, and some neuroprotective effects cannot be explained by changes in A1 and A2a receptors alone. Whether caffeine has other mechanisms of action that aid in the neuroprotective effect of encephalopathy in premature infants requires further research and discussion.

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