British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 180–191 180

SYSTEMATIC REVIEW

Systematic review and meta-analysis of clinical outcomes of early caffeine therapy in preterm neonates

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Received 9 December 2015; **Revised** 1 August 2016; **Accepted** 8 August 2016

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Keywords intensive care, meta-analysis, neonatology, pharmacotherapy, systematic review

AIMS

This study evaluated the therapeutic outcomes of early versus late caffeine therapy in preterm neonates.

METHODS

We performed a systematic literature search in PubMed, Embase, CINAHL and CENTRAL from inception to 30 June 2016 to identify studies investigating the use of early caffeine therapy (initiated at less than 3 days of life) in preterm infants. Effect estimates were combined using random-effects meta-analysis. The primary outcomes for this study were bronchopulmonary dysplasia and mortality.

RESULTS

The initial search found 4066 citations, of which 14 studies enrolling a total of 64 438 participants were included. The time of initiation of early caffeine therapy varied from the first 2 h to 3 days postnatal. Early caffeine therapy reduced the risk of bronchopulmonary dysplasia in both cohort studies (RR: 0.80, 95% CI: 0.66 to 0.96) and randomized controlled trials (RR: 0.67, 95% CI: 0.56 to 0.81). In cohort studies, neonates treated early with caffeine also showed decreased risks of patent ductus arteriosus, brain injury, retinopathy of prematurity and postnatal steroid use. However, the mortality rate was increased.

CONCLUSIONS

The findings suggest that early caffeine therapy is associated with reduced incidence of bronchopulmonary dysplasia and may help decrease the burden of morbidities in preterm infants.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Caffeine therapy is commonly used to treat apnoea of prematurity and facilitate extubation in neonates. It is shown to reduce the rates of bronchopulmonary dysplasia, severe retinopathy of prematurity, cerebral palsy and cognitive delay.
- Recent publications suggests that early initiation of caffeine may have incremental benefits on neonatal outcomes.

DOI:10.1111/bcp.13089

WHAT THIS STUDY ADDS

- This systematic review found that early caffeine therapy (initiated <3 days of life) was associated with a significant reduction in the incidence of bronchopulmonary dysplasia compared with late caffeine therapy.

Tables of Links

TARGETS	
G protein-coupled receptors [2]	**Enzymes** [4]
adenosine A1 receptor	cyclic nucleotide phosphodiesterase
adenosine A2a receptor	endoplasmic reticulum
Voltage-gated ion channels [3]	prostaglandin
ryanodine receptor	

LIGANDS	
adenosine	cortisol
caffeine	inositol
cyclic AMP	theophylline
dexamethasone	xanthine

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2–4].

Introduction

Caffeine citrate is one of the most widely used medications in neonatal intensive care units [5]. It is a respiratory stimulant which has well-established therapeutic effects in apnoea and extubation [6, 7]. Over the past four decades, caffeine has been used for the treatment of apnoea of prematurity and facilitates weaning from mechanical ventilation [8, 9]. Despite its widespread use, information regarding optimal time to initiate therapy and appropriate time to discontinue therapy is limited [8].

Recent studies have indicated that early initiation of caffeine therapy is associated with improved neonatal outcomes [10]. We undertook a systematic review and meta-analysis to assess the therapeutic outcomes of early caffeine therapy in preterm neonates. We aimed to extend the knowledge by appraising all the available evidence in clinical studies that evaluated the early use of caffeine (initiated before a postnatal age of 3 days) versus late use of caffeine (initiated on or after 3 days of life).

Methods

The study was conducted and reported following the PRISMA statement [11].

Eligibility criteria

We included all cohort studies, case–control studies and randomized controlled trials which investigated the use of caffeine initiated less than 3 days of neonatal life. Electronic literature searches were performed in PubMed, Embase, CINAHL and CENTRAL from inception to 30 June 2016 without any language restriction using the terms 'infant', 'neonate', 'preterm', 'newborn', 'premature', 'caffeine' and 'methylxanthine'. We also hand-searched the reference lists of all retrieved review papers and primary articles for any additional literature that had not been obtained from our database searches.

Study selection and data abstraction

Titles and abstracts were screened and full texts of relevant articles were retrieved. A standardized form was used to extract information on study demographics, patient characteristics, interventions details, outcomes and adverse events. Any discrepancies were resolved through a consensus discussion. We also contacted seven authors for additional data [12–18] and three responded to our requests [13–15].

Outcomes

The primary outcomes of interest were biparietal diameter (BPD) and mortality. Secondary outcomes included: patent ductus arteriosus (PDA), brain injury, composite outcome of death or BPD, retinopathy of prematurity (ROP), necrotizing enterocolitis (NEC), use of mechanical ventilation, use of surfactant, use of postnatal steroids, discharged receiving oxygen, duration of caffeine treatment, duration of mechanical ventilation, apnoea, tachycardia, bradycardia and hypoxaemia.

Risk of bias and quality assessment

The Newcastle-Ottawa Scale [19] was used to evaluate the risk of bias of case–control and cohort studies while the Cochrane Collaboration's Tool [20] and Jadad Scale [21] were used to assess randomized controlled studies.

Data analysis

All results were presented narratively. In studies that had sufficient similarity in terms of population and outcome measurement, a random effects meta-analysis was conducted using results from the intention-to-treat analysis in

randomized studies [22]. For observational studies, the adjusted estimates or crude estimates were used. Results were presented as pooled risk ratio (RR) and 95% confidence intervals (CIs) for dichotomous outcomes, and weighted mean difference (WMD) for continuous outcomes. To determine statistical heterogeneity, the I^2 statistic and Cochran Q-test were used [23]. Publication bias was explored through visual inspection of funnel plots. All analyses were performed using Review Manager (RevMan) software, version 5.3 (Cochrane Collaboration, Oxford, UK).

Results

Study selection and characteristics

The search found 4066 studies and 14 were included in the current review. These comprised six cohort studies [10, 12–14, 24, 25] and eight randomized controlled trials (RCTs) [15–18, 26–29] (Figure 1). The cohort studies included a total of 63 075 neonates with gestational age ranging from 23 to 33 weeks and birth weight between 410 and 2060 g. In the RCTs, a total of 1363 neonates were enrolled with mean gestational age of 26.3 to 32.0 weeks and mean birth weight between 872 and 1800 g.

Seven studies evaluated the use of early *vs.* late caffeine therapy [10, 12–14, 18, 24, 27] and three studies assessed early caffeine use *vs.* placebo [15, 16, 28]. In the remaining four studies, one study each examined: the effects of early caffeine use only [25], early high-dose caffeine *vs.* early standard-dose caffeine [17], early caffeine (<2 h after birth) *vs.* routine caffeine (≥12 h after birth) [26] and caffeine *vs.* theophylline [29]. The time of caffeine initiation varied from the first 2 h to 3 days postnatal age. Dosing regimens ranged from 20 to 80 mg kg^{-1} loading, followed by daily maintenance of 5–10 mg kg^{-1} [15–18, 25–29]. Summaries of the included studies are presented in Table 1 and Supplementary Table S1.

Study quality and risk of bias within studies

The mean Newcastle-Ottawa Scale score was 7.7 and mean Jadad score was 3.6, suggesting that most of the included studies were of high quality (Supplementary Table S2). Most studies also had a low risk of bias, except for the studies by Saeidi and Maghrebi [18] and Skouroliakou *et al.* [29] which had an unclear risk of allocation concealment, blinding and outcome reporting (Supplementary Figure S1 and Supplementary Table S3).

Qualitative results of cohort studies

Four cohort studies reported lower incidence of BPD, less treatment for PDA and oxygen requirement as well as shorter duration of respiratory support in neonates treated with early caffeine [10, 12–14]. However, early caffeine therapy was associated with a longer treatment duration [10, 12–14] and increased risk of NEC [13].

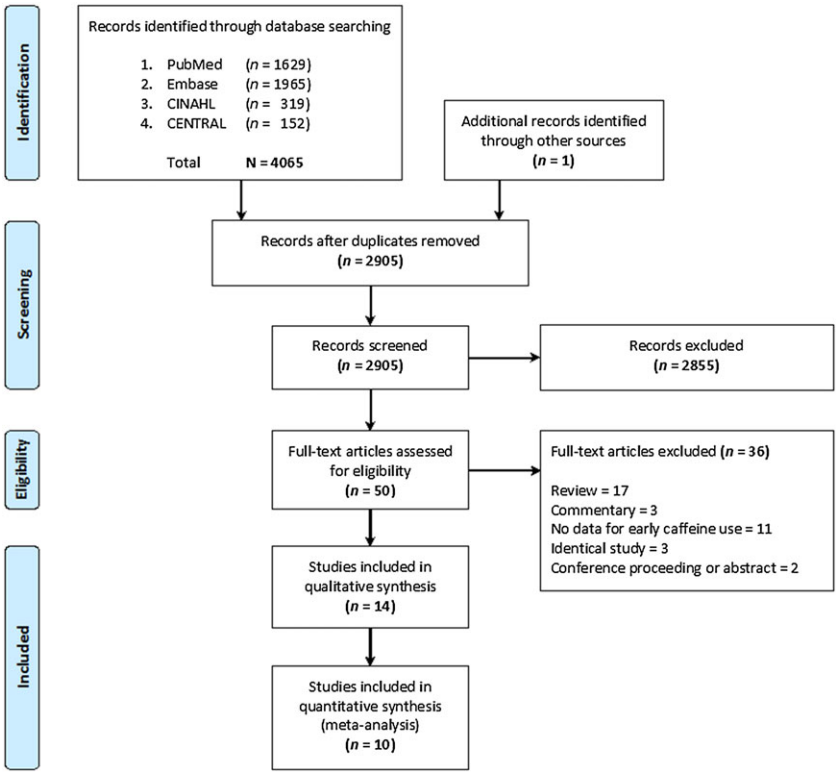


Figure 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

Table 1

Summary of main results of the included studies

Author, country, study period	Regimens	Total no. of patients		Characteristics of patients: Gestational age (weeks)[a]		Characteristics of patients: Birth weight (grams)[a]		Main findings
		I	C	I	C	I	C	
Retrospective cohort studies								
Dobson, USA, 1997–2010 [10]	Caffeine initial dose <3 days of life *vs.* ≥3 days of life	30 891	23 816	28.2 (25.0– 32.0)[c]	27.7 (24.0– 32.0)[c]	1076 (650– 1450)[c]	1009 (560– 1450)[c]	Early caffeine therapy was associated with reduction in BPD, decreased treatment of a PDA and shorter duration of mechanical ventilation
Gupte, USA, 2006–2012 [24]	Caffeine initial dose <3 days of life *vs.* ≥3 days of life	54	67	26.0 (23.0–31.0)[d]	26.0 (23.0–30.0)[d]	800 (410–1210)[d]	822 (520–1440)[d]	Early caffeine therapy was associated with significantly better composite, cognitive, language and motor BSID III scores compared with late caffeine or no caffeine treatment
	No caffeine	39		26.0 (23.0–32.0)[d]		775 (470–1400)[d]		
Lodha, Canada, 2010–2012 [12]	Caffeine initial dose <3 days of life *vs.* ≥3 days of life	3806	1295	28.0 (26.0–29.0)[b]	28.0 (26.0–30.0)[b]	1070 (850–1310)[b]	1050 (790–1360)[b]	Early caffeine therapy was associated with reduction in death or BPD and PDA
Patel, USA, 2008–2010 [14]	Caffeine initial dose <3 days of life *vs.* ≥3 days of life	83	57	27.3 (25.6–28.7)[b]	26.6 (25.3–27.7)[b]	940 (730–1100)[b]	910 (715–1035)[b]	Early caffeine therapy was associated with reduction in death or BPD, PDA requiring treatment and duration of mechanical ventilation
Taha 2014, USA, 2006–2011 [13]	Caffeine initial dose <3 days of life *vs.* ≥3 days of life	1986	965	27.5 ± 2.0	27.2 ± 2.1	938 ± 201	899 ± 216	Early caffeine therapy was associated with reduction in BPD, composite of death or BPD, severe IVH, PDA, length of hospital stay, duration of mechanical ventilation, PMA to room air, first extubation age and discharged home on oxygen
Prospective cohort study								
Hoecker, Germany, 2001 [25]	Nasogastric caffeine citrate 25 mg kg^{-1} load within 24 to 72 h of life	16	NA	31.0 ± 1.2	NA	1400 ± 380	NA	Early high-dose caffeine (25 mg kg^{-1} load) resulted in significant reduction in intestinal

(*continues*)

Table 1

(Continued)

Author, country, study period	Regimens	Total no. of patients		Characteristics of patients: Gestational age (weeks)[a]		Characteristics of patients: Birth weight (grams)[a]		Main findings
		I	C	I	C	I	C	
								and cerebral blood flow velocity, which could increase the risk of NEC, periventricular leukomalacia and haemorrhage
Randomized controlled trials								
Armanian, Iran, 2013–2014 [28]	Intravenous caffeine citrate 20 mg kg^{-1} load within 24 h of life *vs.* placebo	26	26	28.7 ± 2.0	28.6 ± 2.1	967 ± 194	1008 ± 134	Early caffeine therapy was associated with significant reduction in BPD, apnoea, bradycardia and cyanosis
Bucher, Switzerland, 1982–1985 [15]	Intravenous caffeine citrate 20 mg kg^{-1} load at 48 h of life *vs.* placebo	25	25	30.3 ± 1.8	30.4 ± 2.0	1396 ± 296	1321 ± 343	There were no differences between early caffeine and placebo groups in the number of infants with bradycardia, hypoxaemic episodes, use of intermittent positive pressure ventilation or side effects
Davis, USA, Canada, Australia, Europe and Israel, 1999–2004 [27]	Intravenous caffeine citrate 20 mg kg^{-1} load within first 3 days of life *vs.* ≥3 days of life	413	593	27.4 ± 1.7	27.3 ± 1.9	964 ± 186	964 ± 186	Early caffeine therapy was associated with reduction in BPD, PDA ligation and duration of respiratory support
Katheria, USA, 2013–2014 [26]	Intravenous caffeine citrate 20 mg kg^{-1} load within the first 2 h of life *vs.* at 12 h of life	11	10	27.0 ± 0.9	27.0 ± 0.9	1007 ± 169	1005 ± 239	Caffeine given <2 h of life was associated with improved haemodynamics, but did not reduce the need for intubation. There were no between-group differences in BPD, days of oxygen, days of mechanical ventilation, inotropes use, intraventricular haemorrhage and PDA requiring treatment
Levitt, UK, 1981–1983 [16]		27	27		29.0	NR	NR	There were no differences between early caffeine

(*continues*)

Table 1

(Continued)

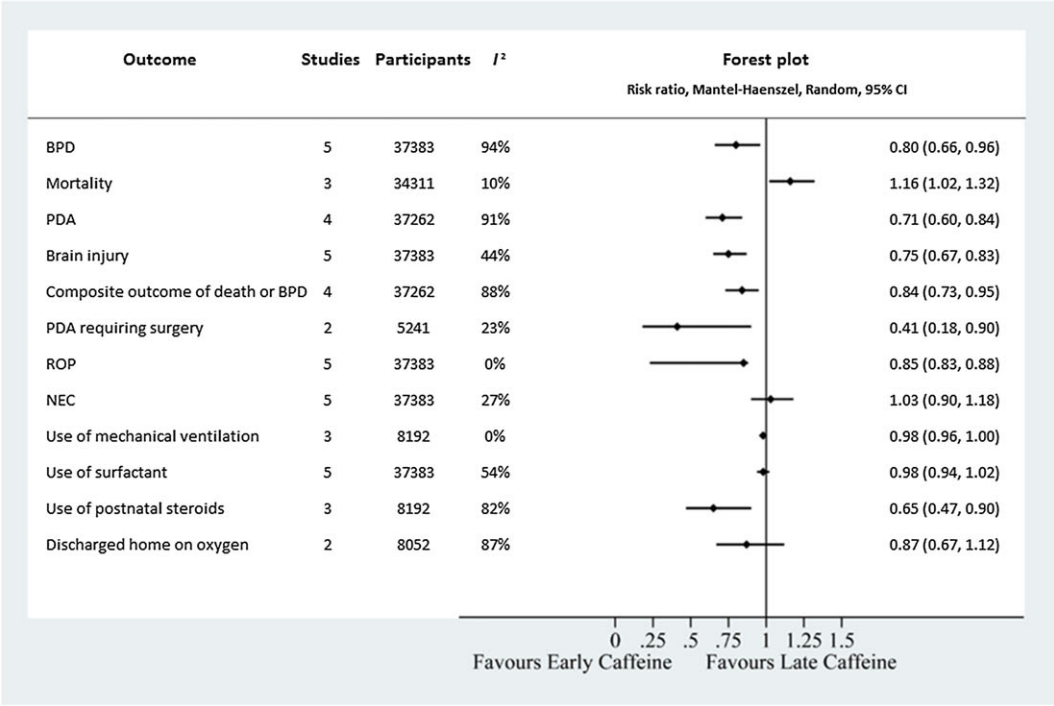
Author, country, study period	Regimens	Characteristics of patients: Total no. of patients I	C	Gestational age (weeks)[a] I	C	Birth weight (grams)[a] I	C	Main findings
	Intravenous caffeine citrate 20 mg kg^{-1} load within the first 24 h of life *vs.* placebo							and placebo groups in the number of infants with apnoea, use of intermittent positive pressure ventilation or side effects
McPherson, USA, 2008–2010 [17]	Intravenous caffeine citrate 40 mg kg^{-1} load within the first 24 h of life *vs.* 20 mg kg^{-1} load within the first 24 h of life	37	37	26.3 ± 1.9	26.8 ± 1.8	872 ± 257	949 ± 245	Early high-dose caffeine (40 mg kg^{-1} load) was associated with increased incidence of cerebellar haemorrhage, more hypertonicity and more deviant neurologic signs at term equivalent age
Saeidi, Iran, 2013–2014 [18]	Intravenous caffeine citrate 20 mg kg^{-1} load within first 3 days of life *vs.* ≥3 days of life	16	20	29.5 ± 2.0		1123 ± 244		Early caffeine therapy was associated with marginal reduction in BPD and significant reduction in apnoea
Skouroliakou, Greece, 2008–2009 [29]	Intravenous caffeine citrate 20 mg kg^{-1} load within first 3 days of life versus theophylline for prevention of apnoea	23	29	30.5 ± 1.8	31.0 ± 2.4	1540 ± 360	1560 ± 300	Early caffeine was associated with no significant increase in apnoea events. There was a significant reduction in the number of apnoea events per day after caffeine administration on days 1–3 as compared with days 4–7
	Intravenous caffeine citrate 20 mg kg^{-1} load within first 3 days of life *vs.* theophylline for treatment of apnoea	10	8	32.0 ± 0.7	29.2 ± 1.7	1800 ± 280	1680 ± 320	

[a]All values are presented as mean ± standard deviation unless otherwise stated.
[b]Values are median (interquartile range).
[c]Values are mean (5th percentile–95th percentile).
[d]Values are median (range).
C, Control group; I, Intervention group; NA, Not applicable; NR, Not reported

Meta-analysis of cohort studies

Meta-analysis of five cohort studies showed that early caffeine therapy reduced the rates of BPD by 20% (95% CI: 0.66–0.96, $P = 0.02$) compared to late caffeine therapy. However, the use of early caffeine was associated with an increased rate of death among infants (RR: 1.16; 95% CI: 1.02–1.32; $P = 0.02$; Figure 2 and Supplementary Figure S2). Analysis of secondary outcomes suggested that early caffeine therapy reduced the rates of PDA (RR: 0.71; 95% CI: 0.60–0.84; $P < 0.001$), brain injury (RR: 0.75; 95% CI: 0.67–0.83; $P < 0.001$), PDA requiring surgical intervention (RR: 0.41; 95% CI: 0.18–0.90; $P = 0.03$), use of postnatal steroids (RR: 0.65; 95% CI: 0.47–0.90; $P = 0.01$; Figure 2 and Supplementary S2) and duration of mechanical ventilation (WMD: −7.50; 95% CI: −10.03 to −4.97, $P < 0.001$; Figure 3). No significant differences were observed in rates of NEC, need for surfactant, mechanical ventilation, home oxygen (Figure 2 and Supplementary S2) and duration of caffeine therapy (Figure 4).

(A) Retrospective cohort studies



(B) Randomised controlled trials

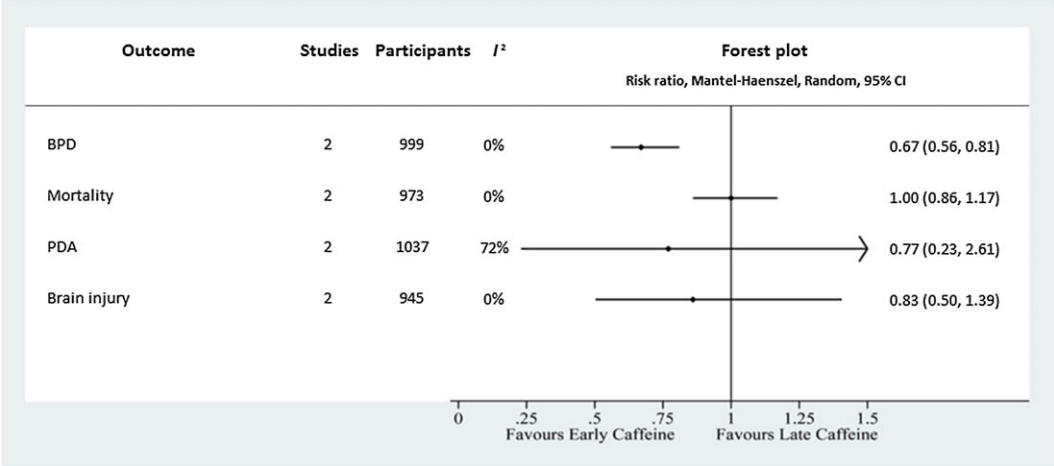


Figure 2

Outcomes of retrospective cohort studies and randomized controlled trials evaluating early (initiation <3 days of life) *vs.* late caffeine therapy (initiation ≥3 days of life) [5 cohort studies *vs.* 2 RCTs]

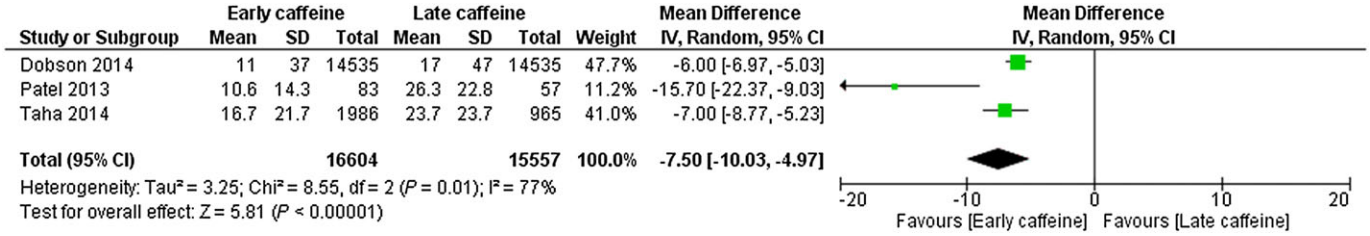


Figure 3

Forest plot of duration of mechanical ventilation in retrospective cohort studies evaluating early (initiation <3 days of life) *vs.* late caffeine therapy (initiation ≥3 days of life)

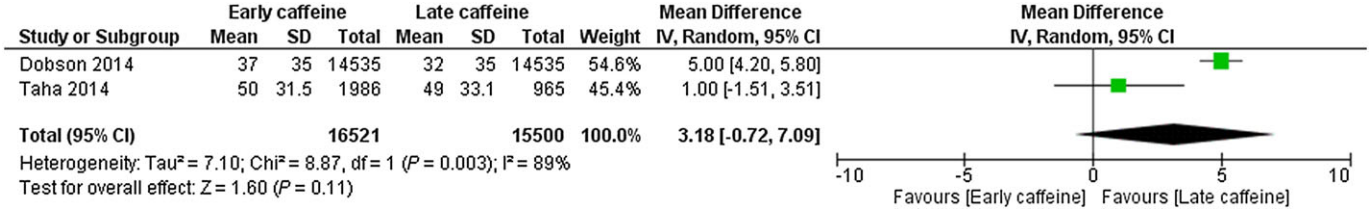


Figure 4

Forest plot of duration of therapy with caffeine in retrospective cohort studies evaluating early (initiation <3 days of life) *vs.* late caffeine therapy (initiation ≥3 days of life)

Qualitative results of randomized controlled trials

Early caffeine therapy was associated with a shorter duration of respiratory support and reduction in BPD, cerebral palsy, PDA ligation, intracranial haemorrhage, apnoea, death and complications such as intraventricular haemorrhage (IVH), asphyxia and NEC [18, 27]. In three studies evaluating early caffeine *vs.* placebo, two studies found no differences in apnoea events, hypoxaemia and bradycardia [15, 16], while one study reported early caffeine was associated with significant reduction in apnoea, bradycardia, cyanosis and BPD [28].

Meta-analysis of randomized controlled trials

Pooled analysis from two studies showed that early caffeine therapy was associated with a 33% reduction in BPD (95% CI: 0.56–0.81; $P < 0.001$; Figure 2 and Supplementary Figure S3). No benefits were noted for the other outcomes, including death, PDA and brain injury (Supplementary Figure S3). Similarly, no differences in clinical outcomes were observed with the use of early caffeine *vs.* placebo (Figure 5 and Supplementary Figure S4).

Subgroup and sensitivity analyses

To determine the source of heterogeneity in the cohort studies comparing early *vs.* late caffeine, we stratified the results according to study location. Subgroup analysis showed that study location had little effect in reducing the heterogeneity. Sensitivity analysis also demonstrated no significant differences in outcomes (Table 2). Visual inspection of funnel plots suggested little evidence of asymmetry (Supplementary Figure S5 and Supplementary Figure S6).

Discussion

To date, only a few therapeutic options have been shown to be beneficial in BPD, including vitamin A, caffeine, dexamethasone, hydrocortisone, inositol and clarithromycin [30, 31]. In this study, we found that the use of early caffeine therapy was associated with a relative reduction in the rates of BPD by up to 30%. This was noted in our analysis of both cohort studies as well as RCTs. This is in agreement with results from the Caffeine for Apnea of Prematurity (CAP) study which showed that early caffeine was associated with a 37% reduction in BPD compared to a 13% reduction when treated later with caffeine [27]. Findings from this study also concur with a recent publication which reported early caffeine was associated with improvements in BPD, PDA, brain injury and ROP, with no increased risk of NEC [32].

Results from the meta-analysis of cohort studies also showed that early caffeine was associated with a 29% decrease in the incidence of PDA and had 59% less need for surgical closure of PDA compared to late caffeine. However, no such benefit was noted in the meta-analysis of randomized trials. Post-hoc analysis of the CAP study reported that early caffeine accounted for a 78% decline in PDA ligation (RR: 0.22; 95% CI: 0.12–0.41) *vs.* placebo, as compared to 57% (RR: 0.43; 95% CI: 0.30–0.64) in the late caffeine group [27]. The CAP trial also reported that caffeine therapy was associated with a reduction in PDA requiring treatment compared to placebo (RR: 0.76; 95% CI: 0.67–0.87) [33].

The decrease risk of BPD in the early caffeine group may be due to infants receiving earlier extubation and shorter duration of mechanical ventilation. Several reviews have shown that the use of non-invasive respiratory support decreases the need for invasive mechanical ventilation and the combined

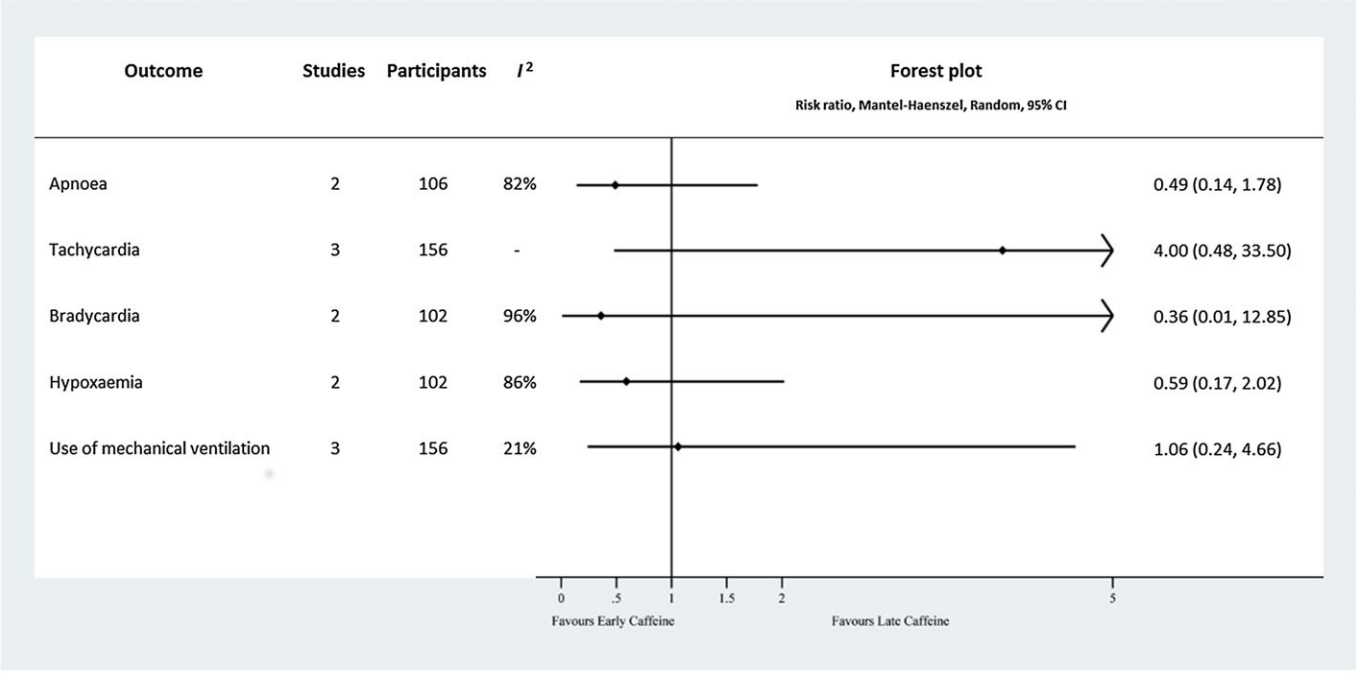


Figure 5

Outcomes of randomized controlled trials evaluating early caffeine therapy (initiation <3 days of life) *vs.* placebo

Table 2

Results of subgroup and sensitivity analysis for primary outcomes

	Number of studies	Fixed-effects model		Random-effects model	
		Effect measure (95% CI)	Heterogeneity, I^2	Effect measure (95% CI)	Heterogeneity, I^2
All studies					
BPD					
Odds ratio	5	0.71 (0.68–0.74)	92%	0.70 (0.53–0.93)	92%
Risk ratio		0.78 (0.76–0.81)	94%	0.80 (0.66–0.96)	94%
Mortality					
Odds ratio	3	1.18 (1.07–1.32)	7%	1.17 (1.03–1.33)	7%
Risk ratio		1.18 (1.06–1.30)	10%	1.16 (1.02–1.32)	10%
Subgroup analysis (Risk ratio)					
BPD					
Studies conducted in US	4	0.74 (0.72–0.77)	51%	0.75 (0.68–0.82)	51%
Studies conducted in Canada	1	1.04 (0.96–1.13)[a]	NA	1.04 (0.96–1.13)[a]	NA
Mortality					
Studies conducted in US	2	1.22 (1.09–1.36)	0%	1.22 (1.09–1.36)	0%
Studies conducted in Canada	1	0.98 (0.76–1.27)[a]	NA	0.98 (0.76–1.27)[a]	NA

[a] P value > 0.05
NA, not applicable

outcome of death or BPD [34, 35]. Our review found similar findings, with a lower percentage of infants in the early caffeine group required mechanical ventilation (RR: 0.98; 95% CI: 0.96–1.00) and shorter duration of mechanical ventilation (absolute mean difference: 7.50 days shorter in early caffeine group, $P < 0.001$), which could lead to improvements in chronic respiratory and neurological outcomes in the premature neonates. While we observed encouraging

results in BPD and PDA, no significant benefits in terms of mortality or major disabilities were noted with the use of early caffeine therapy. In fact, we noted that there was an increased in absolute risk of mortality with early caffeine therapy (4.7% *vs*. 3.9%).

The exact effects of caffeine on ductus contractibility remain controversial. Caffeine's ability to improve the infant's overall pulmonary mechanics may possibly make clinicians less concerned about the persistence of a PDA shunt and initiation of an intervention [36]. Thus far, there have been no animal studies specifically testing the effects of early (prophylactic) caffeine on preterm ductus arteriosus. Caffeine has been postulated to directly affect several of the signalling molecules that are involved in ductus constriction: it increases the concentration of cyclic adenosine monophosphate by inhibiting cyclic nucleotide phosphodiesterase [37], it releases calcium ions from the endoplasmic reticulum by binding to the ryanodine receptor [38], it inhibits both prostaglandin production [39] and activity [40], and blocks adenosine activity by binding to its A1 and A2a receptors [41]. Other potential mechanisms include diuresis, improved blood pressure and cardiac output and altered fluid balance [42]. Therefore, the role of early caffeine in PDA needs to be elucidated in the near future.

In the current study, we also noted a high level of statistical heterogeneity for several variables in the cohort studies. To determine the source of heterogeneity, we stratified the studies by location, as we believed that there might be differences in level of care by neonatologist in different countries [43]. Indeed, several reports have suggested that there were differences in the survival rates and morbidity of extremely preterm infants [44, 45]. Another possible reason is the presence of survival bias. The overall rates of survival of extremely preterm infants within 24 h after birth are frequently low [44]. Thus, it was possible that infants in the early caffeine group had a higher risk of mortality, which may explain the findings of increased mortality. Similarly, as these studies were observational in design, it could not control for any variations in the predefined study cohorts. Survival rates of neonates also varied significantly depending on the concurrent lifesaving treatment that the infants were receiving. A previous study in the United States highlighted that differences in hospital practices regarding the initiation of active treatments in extremely preterm infants contributed to a large portion of between-hospital variations in survival among such patients [46]. Our review also found no evidence of major adverse effects with the use of early caffeine, except for studies by McPherson *et al*. [17] and Hoecker *et al*. [25] which had used higher loading doses of caffeine. This was similarly reported in a recent Cochrane review on prophylactic methylxanthine for the prevention of apnoea in preterm infants [16].

Strengths and limitations

Our study offers several strengths. We used broad inclusion criteria to make the results more generalizable to clinical practice. Because most retrospective cohort studies gave insufficient details about the criteria and dosing regimens of caffeine therapy, we also included randomized trials and prospective cohort studies to gather additional information. This enabled us to integrate data from studies reporting the effects of timing of caffeine therapy as observational studies may furnish additional information, for instance specific study populations, neonatal morbidity, hospital course and mortality, which were usually unavailable in RCTs. We also conducted a comprehensive literature search and considered studies reported in languages other than English. The study followed methodological standards as recommended by the PRISMA guidelines [11].

Our review has several limitations, pertaining to the body of evidence itself, which may affect data interpretation and direction for future research. In the primary cohort studies, although adjusted analyses had been conducted, we could not ascertain whether the authors had considered all pertinent predictors of neonatal morbidity and mortality, or whether even optimal adjustment would allow effective comparisons between the treatment and control groups. Another concern was that the findings may be subject to reporting bias and publication bias, which are often difficult to detect in systematic reviews of observational studies.

We were also unable to extract information on the rationale of how infants were randomized to early or late caffeine in the cohort studies. It was possible that neonates were given caffeine therapy later because they had less severe respiratory distress syndrome, and thus a lower risk of significant PDA. This may explain why there was a benefit in PDA outcome among patients given early caffeine in the cohort studies, but not in randomized controlled studies.

In most of the RCTs included in the current study, the sample sizes were small. As such, we decided to include the post-hoc analysis from the CAP study in our meta-analysis as it provided us with additional data unavailable from most other studies. Nevertheless, a major limitation was that the data of early *vs*. late caffeine was secondary and lacked appropriate randomization. Given the uncertainties of the evidence, our findings should be interpreted with caution.

Implications

Our review suggests that early caffeine therapy is beneficial compared to late caffeine therapy in reducing the incidence of BPD. However, the evidence is sparse in support of the effects of early caffeine in reducing the rates of death, PDA, brain injury and ROP. As such, future research is needed to investigate the benefit and safety of standard-dose early caffeine prophylaxis and its associated short- and long-term consequences. At present, a randomized placebo-controlled trial is in progress at the University of Miami to examine whether caffeine therapy initiated during the first 5 days of life reduces the duration of mechanical ventilation in premature infants of 23–30 weeks' gestation [47]. In addition, Wayne State University is undertaking a randomized placebo-controlled trial to ascertain the effects of early caffeine (initiated within 24 h of life) on death and BPD among very low birth weight infants less than 28 weeks' gestation [48].

When convincing results are available, a formal cost-effectiveness analysis will be the next logical step. In the interim, we suggest that clinicians make individualized decisions about treating preterm infants using early caffeine therapy on the basis of parental preference and own clinical judgement in line with the most recent data available regarding survival and morbidity.

Conclusions

The available evidence suggests that early caffeine initiated within the first 3 days of life is associated with a significant reduction in the rate of BPD in very and extremely preterm neonates. Given the paucity of evidence for neonatal pharmacotherapies, caffeine appears to be a potential therapy for BPD prevention, and optimizing the timing of treatment by earlier initiation may yield additional therapeutic benefits over its conventional use for the treatment of apnoea of prematurity. Further large-scale meticulously designed trials are necessary to confirm its therapeutic advantages before routine use is recommended.

Competing Interests

There are no competing interests to declare.

Contributors

Both authors conceptualized, designed the study and acquired the data. They also drafted and critically revised the manuscript. SWHL is the guarantor of the manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

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Figure S1 Assessment of risk of bias according to a recommended tool for randomized controlled trials by the Cochrane Handbook for Systematic Reviews of Interventions. (A) Risk of bias summary showing review authors' judgments about each risk of bias domain for eight randomized controlled trials; (B) Risk of bias graph showing each risk of bias domain presented as percentages across the studies

Figure S2 Forest plots of clinical outcomes of retrospective cohort studies evaluating early (initiation <3 days of life) *vs*. late caffeine therapy (initiation ≥3 days of life)

Figure S3 Forest plots of clinical outcomes of randomized controlled trials evaluating early (initiation <3 days of life) *vs*. late caffeine therapy (initiation ≥3 days of life)

Figure S4 Forest plots of clinical outcomes of randomized controlled trials evaluating early caffeine therapy (initiation <3 days of life) *vs*. placebo

Figure S5 Funnel plots of primary outcomes in retrospective cohort studies. Vertical line represents the combined effect observed in the analysis

Figure S6 Funnel plots of primary outcomes in randomized controlled trials. Vertical line represents the combined effect observed in the analysis

Table S1 Definitions of outcome variables of included studies

Table S2 Quality of included studies using the Newcastle-Ottawa Scale for cohort studies

Table S3 Quality of included studies using the Jadad Scale for randomized controlled trials