Τεχνολογικό Πανεπιστήμιο Κύπρου

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΤΜΗΜΑ ΝΟΣΗΛΕΥΤΙΚΗΣ

Πτυχιακή Εργασία

ΧΡΗΣΗ ΚΑΦΕΙΝΗΣ ΣΤΑ ΠΡΟΩΡΑ ΝΕΟΓΝΑ:

ΕΠΙΔΡΑΣΗ ΚΑΙ ΑΝΕΠΙΘΥΜΗΤΕΣ ΕΝΕΡΓΕΙΕΣ

Τζώρτζα Σιακίδη

Λεμεσός 2020

ΤΕΧΝΟΛΟΓΙΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΚΥΠΡΟΥ

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ΛΕΜΕΣΟΣ 2020

Πνευματικά δικαιώματα

Θα ήθελα να εκφράσω θερμά την ευγνωμοσύνη και τις ευχαριστίες μου σε όσους βοήθησαν και μου συμπαραστάθηκαν στην εκπόνηση αυτής της πτυχιακής εργασίας. Ιδιαίτερα την επιβλέπουσα καθηγήτρια Δρ. Χριστιάνα Νικολάου για την ευκαιρία που μου έδωσε να ασχοληθώ με ένα πολύ ενδιαφέρον θέμα και για την αμέριστη επιστημονική βοήθεια και καθοδήγηση που μου παρείχε. Την ευχαριστώ θερμά για τις εξαιρετικά ωφέλιμες κριτικές παρατηρήσεις κατά την επεξεργασία της συγκεκριμένης ανασκόπησης. Τέλος θα ήθελα να ευχαριστήσω τις συμφοιτήτριες μου Κυριακή Αγησιλάου και Λάουρα Πάρη για την συνεχή βοήθεια, καθοδήγηση και στήριξη μέχρι την ολοκλήρωση της συγγραφής της εργασίας.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Η καφεΐνη χρησιμοποιείται ευρέως για την πρόληψη της άπνοιας και βοηθάει στην επιτυχή εξώθηση από τον μηχανικό αερισμό. Διευκολύνει τη μετάβαση από επεμβατική σε μη επεμβατική στήριξη και μειώνει τη διάρκεια συνεχούς θετικής πίεσης των αεραγωγών (CPAP) σε πρόωρα νεογνά. Η αποτελεσματικότητα και ασφάλεια της ως προς τις ανεπιθύμητες ενέργειες που προκαλεί, τη θέτουν σε αμφισβήτηση αν πρέπει να χορηγείται σε αυξημένη δόση στα πρόωρα νεογνά.

Σκοπός: Σκοπός της παρούσας εργασίας υπήρξε η διερεύνηση της δράσης της καφεΐνης κατά τη χορήγηση της στα πρόωρα νεογνά και οι ανεπιθύμητες ενέργειες της.

Υλικό και Μέθοδος: Χρησιμοποιήθηκε η μέθοδος αναζήτησης της σχετικής ελληνικής και διεθνούς βιβλιογραφίας σε βάσεις δεδομένων (SCOPUS, MEDLINE, CINAHL) με λέξεις κλειδιά (premature infant or premature neonate or preterm infant or premat*) and (respiratory distress syndrome or respiratory disorder or dyspnoea or apnoea) and (caffeine) and (effects or side effects) σε όλους τους πιθανούς συνδυασμούς.

Αποτελέσματα: Η αναζήτηση κατέληξε σε 16 μελέτες, κατά την περίοδο 2012-2019 που πληρούσαν τα προκαθορισμένα κριτήρια. Μέσα από την αναζήτηση της βιβλιογραφίας διαπιστώθηκε πως η καφεΐνη μπορεί να επιδράσει αποτελεσματικά στην θεραπεία ή πρόληψη της άπνοιας, ωστόσο προκαλεί ανεπιθύμητες ενέργειες οι οποίες δρουν άμεσα ή μπορεί να εμφανιστούν μακροπρόθεσμα.

Συμπεράσματα: Απαιτείται να πραγματοποιηθούν περεταίρω έρευνες ούτως ώστε εξακριβωθεί η ασφάλεια της καφεΐνης και η κατάλληλη δόση η οποία θα είναι αποτελεσματική για την θεραπεία της άπνοιας κατά την προωρότητα η οποία δεν θα επηρεάζει αρνητικά την υγεία του νεογνού.

Λέξεις-κλειδιά: πρόωρο νεογνό, προωρότητα, αναπνευστική δυσχέρεια, σύνδρομο αναπνευστικής δυσχέρειας, δύσπνοια, άπνοια, καφεΐνη, επιδράσεις και ανεπιθύμητες ενέργειες.

ABSTRACT

Introduction: Caffeine is widely used for prevention of apnoea and helps successful extubating from mechanical ventilation. It facilitates the transition from invasive to non-invasive support and reduces duration of continuous positive airway pressure (CPAP) in preterm infants. Its efficacy and safety against the side effects it causes call into question whether it should be given at an increased dose to preterm infants.

Aim: The purpose of the present study was to investigate the effects and side effects of caffeine on premature neonates.

Material and Method: The method used was to search the relevant Greek and international literature in databases (SCOPUS, MEDLINE, CINAHL) with keywords (premature infant or premature neonate or preterm infant or premat*) and (respiratory distress syndrome or respiratory disorder or dyspnoea or apnoea) and (caffeine) and (effects or side effects) in all possible combinations.

Results: The search resulted in 16 studies in the period 2012-2019 that met the predefined criteria. A search of the literature found that caffeine can effectively treat or prevent apnoea but is causes side effects that may appear immediately or occur in the long term.

Conclusions: Further research is needed to verify the safety of caffeine and the appropriate dose that will be effective in the treatment of apnoea of prematurity that will not adversely affect the health of the infant.

Keywords: premature infant, premature neonate, preterm infant or premat *, respiratory disorder, respiratory distress syndrome, dyspnoea, apnoea, caffeine, effects and side effect

ΠΙΝΑΚΑΣ ΠΕΡΙΕΧΟΜΕΝΩΝ

ΚΑΤΑΛΟΓΟΣ ΠΙΝΑΚΩΝ

ΚΑΤΑΛΟΓΟΣ ΔΙΑΓΡΑΜΜΑΤΩΝ

ΣΥΝΤΟΜΟΓΡΑΦΙΕΣ

Στο κείμενο της πτυχιακής χρησιμοποιήθηκαν σημαντικές συντομογραφίες, όπου παρουσιάζονται πιο κάτω συνοπτικά με αλφαβητική σειρά.

c-AMP: intra- cellular cyclic adenosine monophosphate
CPAP: continuous positive airway
EEG: electroencephalogram
FiO2: fraction of inspired oxygen
GA: gestational age
IL-10: interleukin
IQ: intelligence quotient
IV: intravenous
MRI: magnetic resonance imaging
NCPAP: nasal continuous positive airway
NICU: neonate intensive care unit
OR: odd ratio
RDS: respiratory distress syndrome
RScO2: regional oxygen saturation
SaO2: oxygen saturation
TDM: therapeutic drug monitoring
TLR4: tall like receptors 4
TNF-a: tumour necrosis factor alpha
TPN: total parenteral nutrition
ΑΠ: αρτηριακή πίεση
ΒΠΔ: Βρογχοπνευμονική δυσπλασία
ΗΚΓ: ηλεκτροκαρδιογράφημα
ΜΑΠ: μέση αρτηριακή πίεση
ΜΕΝΝ: μονάδα εντατικής νοσηλείας νεογνών
ΝΔ: νευροαναπτυξιακές διαταραχές
ΣΑΔ: συνδρομο αναπνευστικής δυσχέρειας

ΑΠΟΔΟΣΗ ΟΡΩΝ

c-AMP: ενδοκυτταρική κυκλική μονοφωσφορική αδενοσίνη

CPAP: συνεχής θετική πίεση αεραγωγού

EEG: ηλεκτροεγκεφαλογράφημα

FiO2: συνολικό κλάσμα εισπνεόμενου οξυγόνου

GA: ηλικία κύησης

IL-10: ιντερλευκίνη

IQ: βαθμός νοημοσύνης

IV: ενδοφλέβια

MRI: μαγνητική απεικόνιση

NCPAP: ρινική θετική πίεση αεραγωγού

RScO2: περιφερικός κορεσμός οξυγόνου

SaO2: κορεσμός οξυγόνου

TLR4: πρωτεϊνικοί υποδοχείς

TNF-a: παράγοντας νέκρωσης όγκου άλφα

1. Εισαγωγή

Πρόωρο νεογνό ορίζεται ως το νεογνό που γεννήθηκε ζωντανό πριν ολοκληρωθούν οι 37 εβδομάδες κύησης. Υπάρχουν υποκατηγορίες πρόωρου τοκετού, με βάση την ηλικία κύησης, ο εξαιρετικά πρόωρος (λιγότερο από 28 εβδομάδες), ο πρόωρος (28 έως 32 εβδομάδες) και ο μέτρια πρόωρος (32 έως 37 εβδομάδες). Υπολογίζεται ότι 15 εκατομμύρια νεογνά γεννιούνται πρόωρα κάθε χρόνο και παρόλο που η συχνότητα πρόωρου τοκετού ποικίλει σημαντικά μεταξύ των χωρών, σχεδόν το 90% αυτών των πρόωρων γεννήσεων παρατηρείται στις αναπτυσσόμενες χώρες της Αφρικής και της Ασίας. Το 2014, το ποσοστό των πρόωρων τοκετών ήταν 10% στις ΗΠΑ, ενώ στην Ευρώπη το 2010 τα ποσοστά πρόωρου τοκετού κυμαίνονταν σημαντικά μεταξύ 5 έως 10,6%. Η Κύπρος χαρακτηρίζεται ως μία με τα υψηλότερα ποσοστό προωρότητας στην Ευρώπη, φθάνοντας το 10,6% και το 18,70% το 2010 και το 2014 αντίστοιχα (Chawanpaiboon *et al.,* 2019) (Yiallouros *et al.,* 2018). Περίπου 1 εκατομμύρια παιδία πεθαίνουν κάθε χρόνο λόγω επιπλοκών πρόωρου τοκετού. Πολλοί επιζώντες αντιμετωπίζουν αναπηρίες κατά τη διάρκεια της ζωής, συμπεριλαμβανομένων μαθησιακών δυσκολιών, οπτικών και ακουστικών προβλημάτων. Σε παγκόσμιο επίπεδο, η προωρότητα είναι η κύρια αιτία θανάτου σε παιδία ηλικίας κάτω των 5 ετών. Οι ανισότητες στα ποσοστά επιβίωσης σε όλο τον κόσμο είναι έντονες. Στις χώρε με χαμηλότερο εισόδημα, κατά μέσο όρο, το 12% των νεογνών γεννιέται πολύ νωρίς σε σύγκριση με το 9% στις χώρες με υψηλότερα εισοδήματα. Υπάρχει μια δραματική διαφορά στην επιβίωση των πρόωρων νεογνών, ανάλογα με το πού γεννιούνται. Για παράδειγμα περισσότερο από το 90% των εξαιρετικά πρόωρων νεογνών (λιγότερο από 28 εβδομάδες) που γεννιούνται σε χώρες με χαμηλό εισόδημα πεθαίνουν μέσα στις πρώτες μέρες της ζωής τους, αλλά λιγότερο από το 10% των εξαιρετικά πρόωρων νεογνών πεθαίνουν σε χώρες υψηλού εισοδήματος. Αυτό συμβαίνει λόγο ανεπαρκούς οικονομικά αποδοτικής φροντίδας, όπως η ζεστασιά, η υποστήριξη του θηλασμού και η βασική φροντίδα για λοιμώξεις και αναπνευστικές παθήσεις. Στις χώρες υψηλού εισοδήματος, σχεδόν όλα τα νεογνά επιβιώνουν. Η μη βέλτιστη χρήση της τεχνολογίας σε περιβάλλον μεσαίας οικονομικής τάξης, αυξάνει το βάρος αναπηρίας στα πρόωρα νεογνά που επιβιώνουν στη νεογνική περίοδο (WHO, 2018)

Ανάλογα με τον βαθμό προωρότητας οι πνεύμονες μπορεί να είναι ανώριμοι κα έτσι δεν εξασφαλίζεται επαρκώς η αναπνευστική λειτουργία. Η ανεπαρκώς ανάπτυξη του

αναπνευστικού συστήματος και των εγκεφαλικών περιοχών που είναι υπεύθυνες για την αναπνοή είναι ένα κοινό ζήτημα στα πρόωρα νεογνά, και κυρίως σε αυτά με χαμηλότερο βάρος γέννησης. Η κατάσταση αυτή έχει ως αποτέλεσμα την εμφάνιση επεισοδίων άπνοιας, που ορίζεται ως η διακοπή της αναπνοής που διαρκεί περισσότερο από 20 δευτερόλεπτα. Κλινικά μαζί με τη διακοπή της αναπνοής μπορεί να εμφανιστεί και βραδύτερος καρδιακός ρυθμός και / ή μείωση της ποσότητας οξυγόνου στο αίμα, κυανώδη τόνος δέρματος και μείωση του μυϊκού τόνου. Γενικότερα όσο χαμηλότερη ηλικία κύησης έχει ένα νεογνό τόσο μεγαλύτερο κίνδυνο έχει να εμφανίσει απνοϊκά επεισόδια, τα οποία γενικά αρχίζουν μεταξύ 2 και 3 ημερών ζωής. Όταν ένα νεογνό εμφανίσει ασθενέστερα απνοϊκά επεισόδια, η αντιμετώπιση επιτυγχάνεται με απτική διέγερση του νεογνού, ενώ σε πιο σοβαρές καταστάσεις απαιτείται φαρμακολογική παρέμβαση με διεγερτικά φάρμακα όπως η καφεΐνη (CHIESI, 2019).

Η καφεΐνη είναι ένα ισχυρό διεγερτικό της κεντρικής αναπνευστικής δραστηριότητας και είναι αποτελεσματικό για τη θεραπεία της άπνοιας του νεογέννητου και την αποφυγή της αποτυχίας αποσωλήνωσης. Η καφεΐνη διεγείρει την αναπνοή και μειώνει την αναπνευστική καταστολή που προκαλείται από την υποξία αυξάνοντας τον μικρό αερισμό και την απόκριση στο CO2 αυξάνοντας επίσης τη δραστηριότητα του διαφράγματος.(Julien, Joseph and Bairam, 2010), (Ballard *et al.*, 2016). Μελέτες δείχνουν την συσχέτιση της καφεΐνης με την πρόληψη της βρογχοπνευμονικής δυσπλασίας (ΒΠΔ), καθώς και με τη μείωση της συχνότητας εμφάνισης άλλων νεογνικών επιπλοκών, όπως το σύνδρομο αναπνευστικής δυσχέρειας (ΣΑΔ), τον ανοικτό βοτάλιου πόρο, την αμφιβληστροειδοπάθεια του προώρου και την ενδοκοιλιακή αιμορραγία (Patel *et al.*, 2013). Ωστόσο η αδενοσίνη ως νευροδιαβιβαστής, είναι υπεύθυνη για τη δραστηριότητα των νευρώνων και μειώνει την προσπάθεια αναπνοής. Η καφεΐνη ως μη ειδικός αναστολέας των υποδοχέων της αδενοσίνης (υποδοχείς Α1 και Α2α) αντιτίθεται άμεσα στο φαινόμενο αυτό με αποτέλεσμα την παρεμπόδιση της αλληλεπίδρασης της αδενοσίνης με τους κυτταρικούς υποδοχείς της, οδηγώντας έτσι σε αυξημένο ρυθμό αναπνοής. Η καφεΐνη έχει επίσης αναφερθεί ότι αυξάνει τις κατεχολαμίνες και την ρενίνη, από περιφερικές και κεντρικές επιδράσεις, προκαλώντας έτσι ταχυκαρδία, αίσθημα παλμών και γρήγορη αύξηση της αρτηριακής πίεσης (Fredholm, 1995).

Ο μηχανισμός με τον οποίο η καφεΐνη βελτιώνει τα αποτελέσματα της νευροαναπτυξιακής εξέλιξης στα πρόωρα νεογνά δεν είναι σαφής. Αρκετές μελέτες έχουν αναφέρει πως η καφεΐνη έχει ευεργετικά αποτελέσματα στον εγκέφαλο, σε αντίθεση με

άλλους που προειδοποιούν για ανεπιθύμητες ενέργειες (Charousová *et al.*, 2017). Σε μια από τις μεγαλύτερες δοκιμές CAP(caffeine for apnea of prematurity) που διεξάχθηκαν, η καφεΐνη συσχετίστηκε με βελτιωμένη λευκή ουσία σε πρόωρα νεογνά (Davis *et al.*, 2010). Ωστόσο δεν είναι γνωστό εάν αυτή η βελτίωση στη δομή του εγκεφάλου επιμένει ή εξασθενεί μακροπρόθεσμα. Σημαντικό να αναφερθεί πως η καφεΐνης μπορεί να προκαλέσει ασβεστιουρία και δημιουργεί αρνητική ισορροπία του ασβεστίου ειδικά μετά από παρατεταμένη χρήση με αντισταθμιστική αύξηση της παραθυρεοειδούς ορμόνης PTH για την ομαλοποίηση του ασβεστίου στον ορό. Αυτό μπορεί να έχει ως αποτέλεσμα τον κίνδυνο για οστεοπενία των πρόωρων νεογνών.

Στις αναπτυσσόμενες χώρες οι αναβαθμίσεις των μονάδων εντατικής νοσηλείας νεογνών αύξησαν το ποσοστό επιβίωσης των πρόωρων νεογνών αλλα παράλληλα αύξησαν τη διάρκεια νοσηλείας και το κόστος. Ως αποτέλεσμα, η φροντίδα των πρόωρων νεογνών να αντιπροσωπεύει μεγάλο ποσοστό του συνολικού κόστους νοσηλείας παγκοσμίως (Cömert *et al.*, 2012). Μια αναδρομική μελέτη που πραγματοποιήθηκε στην Κωνσταντινούπολη έδειξε πως το μέσο συνολικό και ημερήσιο κόστος νοσηλείας ενός πρόωρου νεογνού, έφτανε τα $4187 και $303 αντίστοιχα (Cömert *et al.*, 2012). Όλα αυτά θα μπορούσαν να αποφευχθούν εφόσον τεκμηριωνόταν μέσο μελετών η χρήση της καφεΐνης ως αναγκαία ή αναντικατάστατη απο λιγότερο επιβλαβή φαρμακευτική αγωγή. Η συγκεκριμένη ανασκόπηση είναι σημαντική εφόσον στην Κύπρο δεν πραγματοποιήθηκαν ακόμη μελέτες για τη χορήγηση της καφεΐνης στα πρόωρα νεογνά. Τώρα είναι σημαντικότερο από ποτέ, με την συνεχή αύξηση του ποσοστού πρόωρων γεννήσεων στην Κύπρο, να ενημερωθούν και να εκπαιδευτούν οι επαγγελματίες υγείας που εργάζονται στις ΜΕΝΝ. Η νοσηλευτική παρέμβαση στην αντιμετώπιση προβλημάτων που αφορούν το νεογνό είναι σημαντική και πρέπει να είναι επιστημονικά αποδεδειγμένη. Απαραίτητες προϋποθέσεις για την επίτευξη της ορθής νοσηλευτικής αντιμετώπισης στην ΜΕΝΝ αποτελούν οι σωστές αναλογίες του προσωπικού προς τους ασθενείς και η συνεχής επιμόρφωση του προσωπικού με στόχο την μείωση της θνησιμότητας των προώρων νεογνών, την αποφυγή ανεπιθύμητων ενεργειών από τη φαρμακευτική αγωγή, των επιπλοκών, τη μείωση της διάρκειας νοσηλείας και κατά συνέπεια του κόστους νοσηλείας.

Έτσι κύριος σκοπός αυτής της ανασκόπησης είναι η περιγραφή της χρήσης της καφεΐνης, η διερεύνηση της επίδρασης της και των ανεπιθύμητων ενεργειών της στα πρόωρα νεογνά.

Θεωρητικό υπόβαθρο

Σε αυτό το σημείο θα δοθούν κάποιοι κύριοι ορισμοί των όρων που χρησιμοποιήθηκαν στην μελέτη.

- Προωρότητα: Η προωρότητα αναφέρεται σε ένα νεογνό που γεννήθηκε πριν να ολοκληρωθούν 37 εβδομάδες κύησης. Κανονικά μια εγκυμοσύνη διαρκεί περίπου 40 εβδομάδες. Ο ακριβής μηχανισμός εκδήλωσης είναι δύσκολα ανιχνεύσιμος διότι το 50% περίπου των συνολικών περιστατικών παρουσιάζονται με άγνωστη αιτία. Σύμφωνα με τον Παγκόσμιο Οργανισμό Υγείας, το 2014 περίπου το 10,6% όλων των γεννήσεων ήταν πρόωρα. Κάθε χρόνο, περίπου 15 εκατομμύρια νεογνά γεννιούνται πρόωρα και αυτός ο αριθμός αυξάνεται. Οι επιπλοκές πρόωρου τοκετού είναι η κύρια αιτία θανάτου σε παιδία ηλικίας κάτω των 5 ετών, τα οποία ευθύνονται για περίπου 1 εκατομμύριο θανάτους το 2015. Τα τρία τέταρτα αυτών των θανάτων θα μπορούσαν να αποφευχθούν με τρέχουσες οικονομικά αποδοτικές παρεμβάσεις. Σε 184 χώρες, το ποσοστό πρόωρης γέννησης κυμαίνεται από 5% έως 18% των γεννηθέντων νεογνών (WHO. 2018). Σε μια έρευνα περιγεννητικής υγείας που πραγματοποιήθηκε στην Κύπρο το 2007 παρατηρήθηκαν αυξημένα ποσοστά πρόωρων τοκετών σε πολύδυμες κυήσεις και με την αύξηση της ηλικίας της μητέρας αυξάνονταν τα ποσοστά πρόωρων τοκετών (Στατιστική υπηρεσία, 2007).

- Άπνοια προωρότητας: Ορίζεται ως η αναπνευστική διακοπή τουλάχιστον 20 ή περισσότερων δευτερολέπτων και συνοδεύεται από πτώση του κορεσμού αρτηριακού οξυγόνου ή βραδυκαρδία. Προκαλείται από ανωριμότητα του κεντρικού ελέγχου του αναπνευστικού συστήματος. Είναι μια κοινή επιπλοκή που επηρεάζει περίπου το 90% των πρόωρων νεογνών που ζυγίζουν κάτω από 1000 γραμμάρια (Eichenwald, 2016).

- Κιτρική καφεΐνη: Η καφεΐνη ανήκει στις μεθυλξανθίνες και είναι διεγερτικό του κεντρικού νευρικού συστήματος, του καρδιακού μυός, είναι διουρητικό, συμβάλλει στη χαλάρωση του λείου μυός, αυξάνει την έκκριση του γαστρικού οξέος και προκαλεί αύξηση των ελευθέρων λιπαρών οξέων και της γλυκόζης στο πλάσμα.

Από τις αρχές της δεκαετίας του 1970, οι μεθυλξανθίνες έχουν χορηγηθεί ως διεγερτικά του αναπνευστικού συστήματος στη θεραπεία της άπνοιας κατά την προωρότητα και θεωρούνται ως η κύρια θεραπευτική επιλογή και είναι μεταξύ των φαρμάκων που χρησιμοποιούνται συχνότερα σε πρόωρα νεογνά. Ωστόσο διαφάνηκε πως μόνο το 20% των πρόωρων νεογνών ανταποκρίνονταν στη θεραπεία (Siu and James, 2010). Η καφεΐνη έχει τώρα αντικαταστήσει σε μεγάλο βαθμό την θεοφυλλίνη και την αμινοφυλλίνη για την θεραπεία της άπνοιας κατά την προωρότητα λόγο ευρύτερου θεραπευτικού δείκτη και μεγαλύτερης διάρκειας ημερισιας ζωής, επιτρέποντας τη χορήγηση της μια φορά την ημέρα (Abdel-Hady, 2015). Επιπρόσθετα η ανάλυση κόστους-αποτελεσματικότητας έδειξε ότι η καφεΐνη είναι τόσο οικονομική όσο και ευεργετική και αυξάνει τα ποσοστά επιτυχίας εξώθησης των νεογνών σε ηλικία 1 εβδομάδων (Kreutzer and Bassler, 2014).

- Οστεοπενία: Η οστεοπενία κατά την προωρότητα χαρακτηρίζεται από μειωμένα αποθέματα περιεκτικότητας σε οστικά μεταλλικά στοιχεία λόγο αυξημένων απαιτήσεων στη νεογνική περίοδο. Φυσιολογικά το ασβέστιο και ο φώσφορος αποκτώνται στο μέγιστο από το έμβρυο κατά τη διάρκεια του τελευταίου τριμήνου της εγκυμοσύνης, έτσι τα πρόωρα νεογνά γεννιούνται με σημαντικά μειωμένα αποθέματα μεταλλικών στοιχείων σε σύγκρισή με τα νεογνά που γεννιούνται φυσιολογικά (Abdallah *et al.*, 2016).

2. Σκοπός

Σκοπός της παρούσας βιβλιογραφικής ανασκόπησης είναι η διερεύνηση των επιδράσεων και ανεπιθύμητων ενεργειών της καφεΐνης σε πρόωρα νεογνά με άπνοια.

Επιμέρους στόχοι:

- Η σύγκριση διαφορετικών δόσεων καφεΐνης στα πρόωρα νεογνά
- Η διερεύνηση της επίδρασης της συσσωρευμένης δόσης και διάρκειας της καφεΐνης σε πρόωρα νεογνά με άπνοια.
- Η διερεύνηση της ανταπόκρισης των πρόωρων νεογνών διαφόρων ηλικιών κύησης κατά την έκθεση τους σε καφεΐνη

Πληθυσμός: Πρόωρα νεογνά (ηλικία κύησης κάτω των 37 εβδομάδων)
Σύγκριση: Με ομάδα εικονικού φαρμάκου ή τα ίδια τα νεογνά σε μεγαλύτερη ηλικία ή διαφορετική δόση καφεΐνης.
Εκβάσεις: Βραχυπρόθεσμες ή μακροπρόθεσμες ανεπιθύμητες ενέργειες και θεραπεία ή μείωση των επεισοδίων άπνοιας.

3. Υλικό-Μέθοδος

Η παρούσα μελέτη αποτελεί συστηματική ανασκόπηση της διεθνούς βιβλιογραφίας με σκοπό την διερεύνηση της επίδρασης της θεραπείας με καφεΐνη και τις ανεπιθύμητες της ενέργειες.

Η ανασκόπηση έγινε στις ηλεκτρονικές βάσεις δεδομένων της Scopus, Medline και Cinahl όπου χρησιμοποιήθηκαν οι ακόλουθες λέξεις κλειδιά και κριτήρια εισδοχής.

Λέξεις κλειδιά:

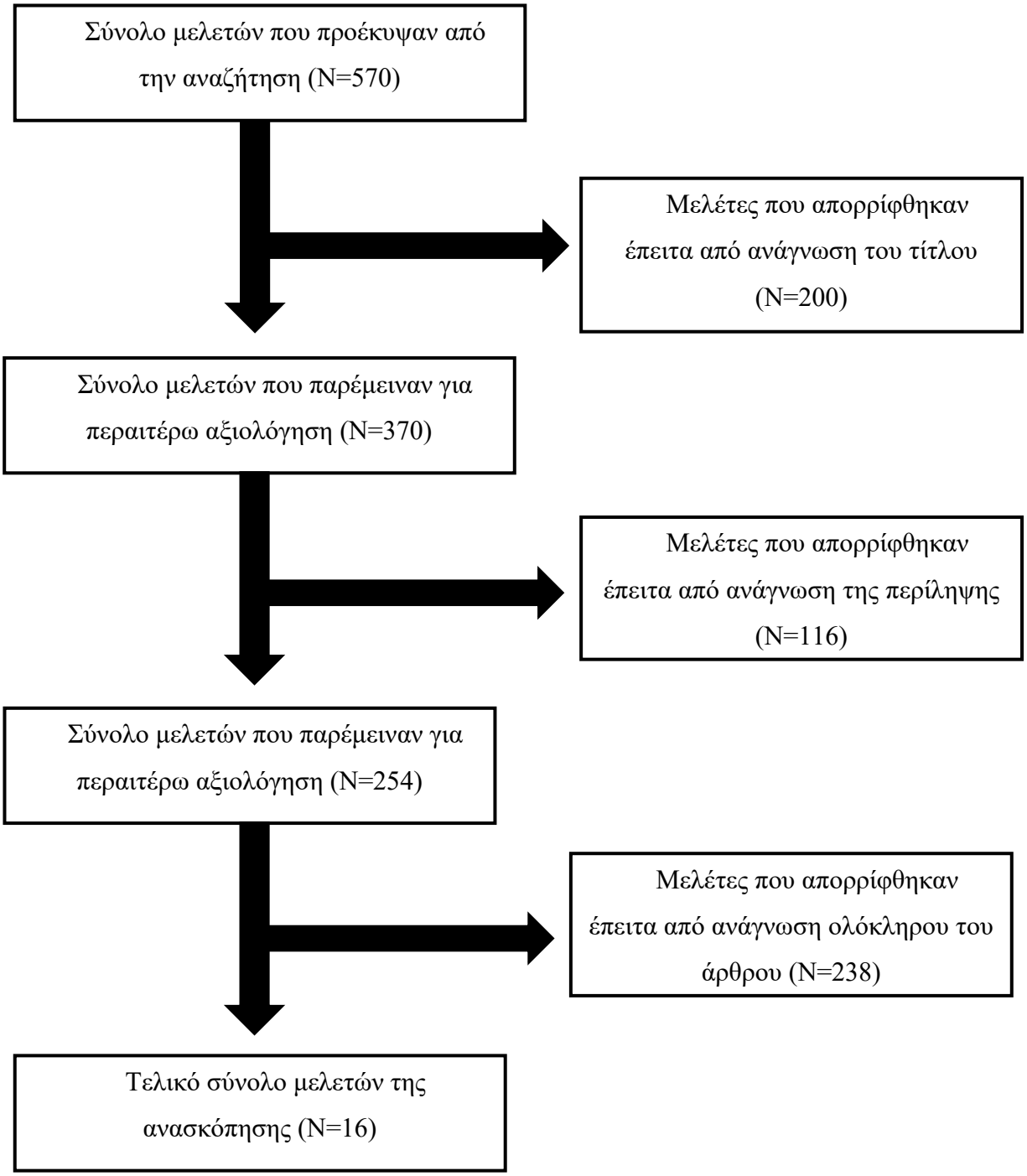
Premature neonate OR Premature infant OR Preterm infant OR Premat* AND respiratory disorder OR respiratory distress syndrome OR dyspnoea OR apnoea AND caffeine AND effects OR side effects.

Κριτήρια εισδοχής:

- Το δείγμα να είναι σε πρόωρα νεογνά με αναπνευστική δυσχέρεια
- Να χορηγείται καφεΐνη στα πρόωρα νεογνά για διόρθωση της αναπνευστικής δυσχέρειας
- Χρόνος δημοσίευσης μελετών από το έτος 2009-2019
- Να είναι γραμμένες στη ελληνική και αγγλική γλώσσα
- Οι μελέτες να μην είναι συστηματικές ανασκοπήσεις, μεταναλύσεις ή περιπτωσιακές μελέτες.
- Οι μελέτες να μην έγιναν σε πειραματόζωα

Από την παρούσα βιβλιογραφική ανασκόπηση προέκυψαν 570 επιστημονικά άρθρα, από τα οποία απορρίφθηκαν τα 200 λόγο μη συνάφειας του τίτλου με το θέμα. Στη συνέχεια από τα 370 που έμειναν, τα 116 απορρίφθηκαν μετά από ανάγνωση της περίληψης και τα 238 μετά από ανάγνωση ολόκληρου του άρθρου. Έτσι για την συγγραφή της παρούσας συστηματικής ανασκόπησης προέκυψαν δεκαέξι άρθρα. Δεν εντοπίστηκε κάποιο άρθρο γραμμένο στην ελληνική γλώσσα που να πληρούσε τα κριτήρια εισδοχής. Η διαδικασία αναζήτησης παρουσιάζεται στο διάγραμμα 1.

Διάγραμμα 1: Μεθοδολογία αναζήτησης μελετών βιβλιογραφικής ανασκόπησης



Πίνακας 1: Μεθοδολογικά χαρακτηριστικά των μελετών								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα/ Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Schmidt *et al.*, (2012) Αμερική	Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity	Εάν η νεογνική θεραπεία με καφεΐνη έχει μακροχρόνια οφέλη ή νέους φαινομενικούς κινδύνους στη σχολική ηλικία.	Τυχαιοποιημένη ελεγχόμενη δοκιμή	• 833 πρόωρα νεογνά με καφεΐνη και 807 πρόωρα νεογνά στην ομάδα placebo • Σκόπιμη	31 hospitals in Canada, Australia, Europe, and Israel	• Θάνατος πριν 18 μήνες ή επιβίωση με τουλάχιστον 1 βλάβη • Σε 5 χρόνια θανάτου πριν ηλικία 5 ετών ή επιβίωση με 1 ή περισσότερες διαταραχές	• Wechsler Preschool and Primary Scale of Intelligence III. • Child Behaviour Checklist.	1. Τα ποσοστά θανάτου, κινητικής δυσλειτουργίας, προβλήματα συμπεριφοράς, κακή γενική υγεία, η κώφωση και η τύφλωση δεν διέφεραν σημαντικά μεταξύ των δύο ομάδων (p=0,09) 2. Η επίπτωση της νοητικής

								βλάβης ήταν χαμηλότερη στα 5 χρόνια από ό, τι στους 18 μήνες και παρόμοια στις 2 ομάδες (p=0,89)

Πίνακας 2								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα /Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Ulanovsky *et al.*, (2014) Ισραήλ	The effects of caffeine on heart rate variability in newborns with apnea of prematurity	Μελέτη των οξέων επιδράσεων της καφεΐνης σχετικά με τη μεταβλητότητα καρδιακού ρυθμού στα πρόωρα νεογνά που έλαβαν θεραπεία με καφεΐνη με συμβατικές και δυναμικές μη γραμμικές αναλύσεις μεθόδων.	Προοπτική μελέτη	• 21 πρόωρα νεογνά • Σκόπιμη	NICU in Rambam health care campus	• Η ηλικία κύησης κατά την παράδοση • καρδιακός ρυθμός και μη γραμμικά χαρακτηριστικά • Βάρος γέννησης • Χορήγηση επιφανειοδραστικού παράγοντα • Προγεννητικά στεροειδή • μεταγεννητική ηλικία • Φύλο Apgar στα 5 λεπτά	• Philips MP60), cardiac monitor • Apgar score	1. Δεν υπήρξαν μεταβολές στον καρδιακό ρυθμό, την αρτηριακή πίεση ή τον τόνο του αυτόνομου νευρικού συστήματος μετά τη χορήγηση καφεΐνης

Πίνακας 3								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Maitre *et al.*, (2015) Αμερική	Effects of caffeine treatment for apnea of prematurity on cortical speech-sound differentiation in preterm infants.	Η επίδραση σε αντιθέσεις ήχου-ομιλίας σε 45 νεογνά εντατικής θεραπείας, διαστρωματωμένα με αθροιστική έκθεση ως ομάδες μη καφεΐνης, χαμηλής και υψηλής δόσης καφεΐνης	Προοπτική μελέτη παρατήρησης κοορτής	• 45 πρόωρα νεογνά • Σκόπιμη	Monroe Care Jr Children's Hospital (Vanderbilt)	• Εγκεφαλική λειτουργεία • Ανάλυση ομιλίας-ήχου • αναπνευστική σταθερότητα στον αέρα του χώρου χωρίς ανάγκη για ρινική CPAPA ή ρινική κάνουλα	• Geodesic Sensor Net • ηλεκτροεγκεφαλογράφημα (EEG)	1. τα βρέφη στην ομάδα χαμηλής έκθεσης αποδεικνύουν μεγαλύτερη ηχητική διαφοροποίηση από τα βρέφη με υψηλή έκθεση σε καφεΐνη (p=0,02)

Πίνακας 4								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Mohammed *et al.*, (2015) Αίγυπτος	High versus low dose caffeine for apnea of prematurity	Η σύγκριση της αποτελεσματικότητας και ασφάλειας της υψηλής και χαμηλής δόσης κιτρικής καφεΐνης στην άπνοια των πρόωρων νεογνών (AOP) και την επιτυχή εξώθηση τους από τον μηχανικό εξαερισμό.	Τυχαιοποιημένη ελεγχόμενη δοκιμή	• Ομάδες σύγκρισης, 60 πρόωρα νεογνά μεγάλης δόσης καφεΐνης και 60 πρόωρα νεογνά χαμηλής δόσης καφεΐνης • Σκόπιμη	NICU of Mansoura University Children's Hospital	• Αποτυχία αποσωλήνωσης • Συχνότητα άπνοιας • Κατεργαμένες ημέρες άπνοιας • Διάρκεια μηχανικού εξαερισμός (ημέρες) • Διάρκεια CPAP (ημέρες) • Διάρκεια θεραπείας οξυγόνου	Drager monitors	1. Η υψηλή δόση καφεΐνης συσχετίστηκε με σημαντική μείωση αποτυχίας εξώθησης (p <0,05), συχνότητα άπνοιας (p <0,001), καταγεγραμμένες μέρες άπνοιας (p <0,001) 2. Η υψηλή δόση καφεΐνης συσχετίστηκε με

								σημαντική αύξηση επεισοδίων ταχυκαρδίας (p <0,05).

Πίνακας 5								
Συγγραφεις χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Parikka *et al.*, (2015) Φινλανδία	The effect of caffeine citrate on neural breathing pattern in preterm infants	Η επίδρασης της κιτρικής καφεΐνης σε νευρολογικό έλεγχο της αναπνοής, ιδιαίτερα της κεντρικής άπνοιας, σε πρόωρα βρέφη χρησιμοποιώντας το σήμα Edi	Αναδρομική μελέτη	• 17 πρόωρα νεογνά • Σκόπιμη δειγματοληψία	Neonate intensive care unit of Turku University Hospital	• Νευρολογικός έλεγχος αναπνοής πριν και μετά την χορήγηση καφεΐνης • Κεντρική άπνοια	Edi catheter	1. Ο αριθμός άπνοιας συσχετίστηκε με το βάρος γέννησης, p=0,039. 2. Η κιτρική καφεΐνη μείωσε σ τον αριθμό της κεντρικής άπνοιας 5-10 sec σε 30 λεπτά, (ρ = 0.02) 3. Η κιτρική καφεΐνης αύξησε τη δαπάνη ενέργειας του διαφράγματος p=0,004

Πίνακας 6								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα /Δειγματοληψία /Σχεδιασμός μελέτης**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Chavez-Valdez *et al.*, (2016) Αμερική	Mechanisms of modulation of cytokine release by human cord blood monocytes exposed to high concentrations of caffeine	Η επίδραση της καφεΐνης στα επίπεδα των κυτοκινών στο αίμα των νεογνών	Συγχρονική μελέτη	• 19 πρόωρα νεογνά • Σκόπιμη	Johns Hopkins Hospital	• Ηλικία κύησης • Apgar 1 λεπτό • Apgar 5 λεπτά • Επίπεδο καφεΐνης • Μορφή γέννας • Βάρος γέννησης • Φύλο	• ELISA / EIA • Apgar score	1. Η καφεΐνη μείωσε τα επίπεδα TNF-α, cAMP. και IL-10 2. Οι ανταγωνιστές A, 1R, A3R και PDE μείωσαν τον TNP-α αλλά όχι IL-10. 3. Οι συγκεντρώσεις της καφεΐνης σχετίζονται με αύξηση TLR4 ($p<0,001$)

Πίνακας 7								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Yu *et al.*, (2016) Αμερική	Incorporating pharmacodynamic considerations into caffeine therapeutic drug monitoring n preterm infants	Να βρεθεί η σχέση μεταξύ των φαρμακοδυναμικών αποκρίσεων και συγκεντρώσεων ορού καφεΐνης για να ενημερωθεί η χρήση του TDM(θεραπευτική παρακολούθηση φαρμάκων) σε νεογνά	Αναδρομική μελέτη παρατήρησης	• 115 πρόωρα νεογνά • Σκόπιμη	• Utah Valley hospital • Intermountain medical center • McKay-Dee hospital • Primary children's hospital • Dixie regional hospital • Latter-day Saints hospital • American fork hospital • Logan regional hospital	• Φύλο • μεταγεννητική ηλικία κατά την έναρξη ή δοκιμή • Βάρος γέννησης • μετεμμηνορροϊκή ηλικία κατά την 'έναρξη ή δοκιμή • APGAR score 1 min • Apgar score 5 min • Ηλικία κύησης	Apgar score	1. Οι συγκεντρώσεις της καφεΐνης και του καρδιακού ρυθμού συσχετίστηκαν (p<0,005) 2. Δεν παρατηρήθηκαν άμεσες συσχετίσεις μεταξύ αναπνευστικών επιπέδων ή απνοϊκών επεισοδίων και συγκεντρώσεων καφεΐνης 3. Δοσολογία θεραπείας 40 /5 mg οδήγησε σε παρόμοιο ρυθμό

								ενδοτραχειακής επαναδιασωλήνωσης, αυξάνοντας το ποσοστό ταχυκαρδίας σε σύγκριση με την σταθερή δόση 20/5mg/kg (p<0,001)

Πίνακας 8								
Συγγραφείς χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Ali *et al.*, (2018) Καναδάς	Caffeine is a risk factor for osteopenia of prematurity in preterm infants	Η επίδραση της Συσσωρευμένης δόσης και της διάρκειας της καφεΐνης στα πρόωρα νεογνά με οστεοπενία	Αναδρομική περιγραφική μελέτη κοορτής	• 109 πρόωρα νεογνά • Σκόπιμη	Health Scienses centre in Winnipeg, Manitoba	• Ηλικία κύησης • Αριθμός γεννήσεων • Μέσο εβδομαδιαίο βάρος • Ποσότητα φωσφόρου στον ορό • Δόση και διάρκεια καφεΐνης • Διουρητική δόση • Δόση στεροειδών • Βιταμίνη D • Διάρκεια TPN (ημέρες)		1. Η δόση καφεΐνης και η διάρκεια της θεραπείας έδειξαν ισχυρή συσχέτιση με την οστεοπενία του πρόωρου, p<0,001 2. Τα στεροειδή (p=0,038) και η βιταμίνη D (p<0,001) συσχετίστηκαν σημαντικά με οστεοπενία προώρου.

Πίνακας 9								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Amaro *et al.*, (2018) Αμερική	Early caffeine and weaning from mechanical ventilation in preterm infants	Να αξιολογηθεί η επίδραση της πρώιμης καφεΐνης σε ηλικία πρώτης επιτυχούς εξώθησης σε πρόωρα βρέφη	Τυχαιοποιημένη ελεγχόμενη δοκιμή	• 83 πρόωρα νεογνά • Σκόπιμη	• Holtz Children's hospital of Jackson health system • University of Miami Medical center	• Προγεννητικά στεροειδή • Μέση πίεση αεραγωγού σε τυχαιοποίηση • Apgar κλίμακα <5 λεπτά • FiO2 σε τυχαιοποίηση • Ηλικία διασωλήνωσης • Ηλικία τυχαιοποίησης • Εάν έλαβε επιφανειοδραστική ουσία	• Kaplan-Meier log-rank test • Apgar score	1. Η ηλικία στην πρώτη επιτυχή εξώθηση δεν διέφερε μεταξύ της πρώιμης καφεΐνης και της ομάδας ελέγχου, p=0,703 2. 75% έδειξε μια τάση προς υψηλότερη θνησιμότητα σε μία από τις ομάδες και η επιτροπή

								συνέστησε τη διακοπή της δοκιμής 3. Η θνησιμότητα δεν διέφερε σημαντικά μεταξύ των ομάδων. (p=0,222)

Πίνακας 10								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Dix *et al.*, (2018), Ολλανδία	Effects of caffeine on the preterm brain	Να αναλύσει τα αποτελέσματα της καφεΐνης στον νεογνικό εγκέφαλο	Μελέτη παρατήρησης	• 34 πρόωρα νεογνά • Σκόπιμη	Wilhelmina Children's Hospital	• Προγεννητικά κορτικοστεροειδή • Υπερβιλιρουβιναιμία με φωτοθεραπεία • Δημογραφικά χαρακτηριστικά • Επιληπτικές κρίσεις • Apgar score • Περί/ενδοκοιλιακή αιμορραγία • Ένδειξη για καφεΐνη • Αναπνευστική υποστήριξη • ΣΑΔ	• INVOS φασματόμετρο υπέρυθρης ακτινοβολίας • BrainZ aEEG παρακολούθηση • IntelliVue mP70	1. Το rScO2 μειώθηκε σημαντικά 1 ώρα μετά την καφεΐνη και ανακτήθηκε στις 6h με επαναλαμβανόμενη ανάλυση αερίων αίματος, παρατηρήθηκε σημαντική μείωση στο pCO2 μετά την πρόσληψη καφεΐνης (48,66 πριν και 44.90 mmHg μετά, (ρ= 0.02) 2. Άλλες μεταβλητές Doppler,

						• Ηλικία χορήγησης καφεΐνης • Αιμοδυναμική υποστήριξη κατά την θεραπεία		παραμέτρους aEEG και SaO2 δεν επηρεάστηκαν

Πίνακας 11								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα /Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Faramarzi *et al.*, (2018), Ιράν	The efficacy and safety of two different doses of caffeine in respiratory function of preterm infants	Η σύγκριση της αποτελεσματικότητας και ασφάλειας της μονής δόσης καφεΐνης έναντι δύο φορές ημερησίως σε πρόωρα βρέφη με σύνδρομο αναπνευστικής δυσφορίας	Τυχαιοποιημένη κλινική δοκιμή	• 40 πρόωρα νεογνά • Σκόπιμη	Bu-Ali Sina Teaching Hospital, Sari	• Δημογραφικά στοιχεία • Αποτυχία εξώθησης • διάρκεια αναπνευστήρα • Θεραπεία ή αποτυχία με CPAP	Apgar score	1. Ο ρυθμός αποσωλήνωσης (p=0,50), η αποτυχίας CPAP (p=0,70) ήταν χαμηλότερη στη ομάδα διπλής δόσης ημερησίως χωρίς στατιστικά σημαντική διαφορά 2. Τα μέσα SP02 κατά τις πρώτες τρεις ημέρες της θεραπείας με καφεΐνη ήταν υψηλότερα στην ομάδα διπλής δόσης. (p=0,049)

Πίνακας 12								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Huvanandana et al. 2018, Αυστραλία	Cardiovascular impact of intravenous caffeine in preterm infants	Αξιολόγηση της οξείας επίδρασης της ενδοφλέβιας καφεΐνης στον καρδιακό ρυθμό και την μεταβλητότητα της αρτηριακής πίεσης στα πρόωρα βρέφη	Αναδρομική μελέτη κοορτής	• Μελέτησαν 31 πρόωρα βρέφη με δεδομένα αρτηριακής πίεσης και 25 με δεδομένα ΗΚΓ • Σκόπιμη	Westmead Hospital Neonatal Intensive Care Unit	• Καρδιακός ρυθμός • Φύλο • Αρτηριακή πίεση • Διασωλήνωση • Ηλικία κύησης • CPAP • Βάρος σώματος • μη αναπνευστική υποστήριξη • Μεταγεννητική ηλικία • RDS • θάνατος	• ΗΚΓ • NCMS Philips Agilent System monitor	1. Παρατηρήθηκε μείωση στους εκθέτες κλιμάκωσης (a1, a2) της ΜΑΠ και αύξηση της αναλογίας βραχείας (SD1) και μακροπρόθεσμης (SD2) μεταβλητότητας 2. Στη καρδιακή συχνότητα οι αναλύσεις έδειξαν μείωση στο a1 (μέσο (SD) 0,92 (0,21) έως 0,86 (0,21), ρ <0,01) με αυξημένη οσφυαλγία

								3. Μετά την καφεΐνη, η παλμική πίεση beat-to-beat αυξήθηκε (2,1 (0,64) σε 2,5 (0,65) mmHg, p <0,01)

Πίνακας 13								
Συγγραφείς χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα/ Δειγματοληψία**	**Χώρος Διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Kelly *et al.*, (2018) Αυστραλία	Caffeine for apnea of prematurity and brain development at 11 years age	Διερεύνηση της σχέσης μεταξύ θεραπείας της νεογνικής καφεΐνης και της δομής του εγκεφάλου σε ηλικία 11 ετών	Τυχαιοποιημένη κλινική δοκιμή	• Ομάδα υπό μελέτη :70 πρόωρα νεογνά Ομάδα σύγκρισης :117 παιδία ηλικίας 11 ετών • Σκόπιμη δειγματοληψία	Royal Women's Hospital Melbourne Australia	• Γέννηση • Κώφωση Κατά την ηλικία των 11 ετών • Τύφλωση • IQ Εγκεφαλική παράλυση • Beery VMI (visual motor integration test) • Movement ABC (assessment battery for children)	• SPM: statistic parametric mapping • Free Surfer • Functional MRI of brain FSL's FIRST tool • SPM's spatially unbiased infra-tentorial template • Tract-Based Spatial Statistics TBSS • MRtrix's fixel-	1. Ελάχιστες ενδείξεις για διαφορές μεταξύ ομάδων στους όγκους εγκεφάλου ή λευκής ύλης σε ηλικία 11 ετών 2. η ομάδα της καφεΐνης είχε μικρότερο μεσολόβιο από την ομάδα του εικονικού φαρμάκο

							based analysis	υ (p=0,003) 3. η καφεΐνη συσχετίστηκε με βραδύτερη ανάπτυξη μεσολόβιου και πιο αργή μείωση αξονικής (p=0,02), ακτινικής (p=0,01) και μέσης διάχυση της λευκής ουσίας (p<0,001)

Πίνακας 14								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Lodha *et al.*, (2018) Αμερική	Does duration of caffeine therapy in preterm infants born =<1250gr at birth influence neurodevelopmental outcomes at 3 years of	Αξιολόγηση της επίδρασης της διάρκειας της χρήσης καφεΐνης σε μακροχρόνιες εκβάσεις νευροαναπτυξιακών σε 3 χρόνια σε πρόωρα βρέφη με βάρος σε βάρος ≤ 1250 g	αναδρομική μελέτη κοορτής	• 448 πρόωρα νεογνά • Σκόπιμη	Foothills Medical Center NICU	• Χαρακτηριστικά μητέρας προγεννητικά • Χαρακτηριστικά νεογνού	Πρωτοβάθμια κλίμακα του Wechsler Intelligence, (WPPSI-III)	Καμία από τις μεταβλητές της μητέρας και παράγοντες κίνδυνου του νεογνού δεν έδειξε στατιστικά σημαντική συσχέτιση μεταξύ της διάρκειας καφεΐνης και βλάβης ΝΔ (p>0,05)

Πίνακας 15								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Fakoor *et al.*, (2019), Ιράν	The effect of venous caffeine on the prevention of apnea of prematurity in the very preterm infants in the NICU	Διερεύνηση των επιπτώσεων της προφυλακτικής καφεΐνης σε άπνοια (βραχυπρόθεσμες συνέπειες)	Κλινική-πειραματική δοκιμή	• 100 πρόωρα νεογνά • Σκόπιμη	NICU department of Shahid Motahhari hospital, Urmia	• Ανάγκη για περιβαλλοντικό οξυγόνο • Ανάγκη για κεφαλίδα • Ανάγκη για NCPAP • Ανάγκη για μηχανικό αερισμό • Περίοδος νοσηλείας	Cardiovascular-pulmonary monitor	1. Με βάση τη δοκιμασία του Fisher, δεν υπήρχε σημαντική διαφορά μεταξύ του περιστατικού της άπνοιας στις δύο ομάδες, p=0,58 2. 10 νεογνά από την ομάδα καφεΐνης και 7 από την ομάδα ελέγχου πέθαναν.

Πίνακας 16								
Συγγραφείς, χρονολογία, χώρα	**Τίτλος**	**Σκοπός**	**Σχεδιασμός μελέτης**	**Δείγμα / Δειγματοληψία**	**Χώρος Διεξαγωγής έρευνας**	**Μεταβλητές**	**Εργαλεία μέτρησης**	**Αποτελέσματα έρευνας**
Lodha *et al.*, (2019), Καναδάς	Early Caffeine Administration and Neurodevelopmental Outcomes in Preterm Infants	Να προσδιοριστεί η σχέση μεταξύ πρώιμων (εντός 2 ημερών από τη γέννηση) έναντι της καθυστερημένης έκθεσης στην καφεΐνη και τα νευροαναπτυξιακά αποτελέσματα στα πρόωρα βρέφη	Αναδρομική μελέτη κοορτής	• 2108 πρόωρα νεογνά • Σκόπιμη	Canadian neonatal network units and then assessed at Canadian neonatal follow up network centers	• Μητρικά χαρακτηριστικά • Χαρακτηριστικά νεογνού	• Bayley-III (νευροαναπτυξιακό εργαλείο) • Score of neonatal acute physiology II	1. Ποσοστά βρογχοπνευμονικής δυσπλασίας, ανοικτού βοτάλιου πόρου και σοβαρής νευρολογικής βλάβης ήταν χαμηλότερες στην ομάδα της πρώιμης καφεΐνης 2. Νευροαναπτυξιακή βλάβη (OR=0,68) και αποδόσεις κλίμακας Bayley Βρεφικού και Βρεφικής Ανάπτυξης Toddler (OR=O,67), ήταν χαμηλότερα στην ομάδα

								πρώιμης καφεΐνης. 3. Οι βαθμολογίες ανάλυσης βάσει ζεύγους έδειξε χαμηλότερες πιθανότητες εγκεφαλικής παράλυσης και προβλημάτων ακοής

4. Αποτελέσματα

Το διάγραμμά 1 δείχνει τα βήματα και τον ακριβή αριθμό των άρθρων που εντοπίστηκαν σε καθένα από αυτά, με σκοπό την επιλογή των τελικών άρθρων που χρησιμοποιήθηκαν στην παρούσα μελέτη. Η αναζήτηση με βάση τις λέξεις κλειδιά που αναφέρονται πιο πάνω οδήγησαν στην επιλογή 16 μελετών που πληρούσαν τα κριτήρια εισδοχής στην παρούσα ανασκόπηση. Επτά από τις μελέτες αναφέρονταν στις επιδράσεις της καφεΐνης στα πρόωρα νεογνά, Επτά από τις δεκαέξι μελέτες επισήμαναν τις ανεπιθύμητες ενέργειες της καφεΐνης και δυο μελέτες αναφέρονταν στις επιδράσεις και ανεπιθύμητες ενέργειες της καφεΐνης στα πρόωρα νεογνά. Τα άρθρα που συμπεριλήφθηκαν στην παρούσα ανασκόπηση είχαν δημοσιευτεί από το 2012-2019. Από το σύνολο των μελετών έχουν διεξαχθεί 6 στην Αμερική, 2 στον Καναδά, το Ιράν και την Αυστραλία, 1 στο Ισραήλ, την Αίγυπτο, την Φιλανδία και την Ολλανδία. Πέντε από τις μελέτες ήταν τυχαιοποιημένες κλινικές δοκιμές, πέντε Κοορτής, δυο μελέτες παρατήρησης, μια συγχρονική μελέτη, μια αναδρομική, μια προοπτική και μια κλινική-πειραματική μελέτη. Στις μελέτες χρησιμοποιήθηκε μεγάλος αριθμός εργαλείων και έγινε διερεύνηση σε πρόωρα νεογνά (<37 εβδομάδες). Οι πιο πάνω πίνακες συνοψίζουν κατά χρονολογική σειρά δημοσίευσης, τα βασικά μεθοδολογικά χαρακτηριστικά κα ευρήματα των μελετών.

4.1 Μεθοδολογικά χαρακτηριστικά των μελετών

Τα μεθοδολογικά χαρακτηριστικά των μελετών που πληρούσαν τα κριτήρια περιλαμβάνουν, τη χώρα προέλευσης και σχεδιασμό των μελετών, το δείγμα, δειγματοληψία, τη διαδικασία και εργαλεία συλλογής των δεδομένων.

4.2 Χώρα προέλευσης και σχεδιασμός των μελετών

Συνολικά δεκαέξι μελέτες πληρούσαν τα κριτήρια για να συμπεριληφθούν στην ανασκόπηση. Τα μεθοδολογικά χαρακτηριστικά τους παρουσιάζονται στους πίνακες στο κεφάλαιο 3. Οι μελέτες καλύπτουν ένα σχετικά ευρύ γεωγραφικό φάσμα και συγκεκριμένα προέρχονται από τον Καναδά (2), το Ιράν (2), το Ισραήλ (1), Αίγυπτο (1), Αμερική (6), Φιλανδία (1), Αυστραλία (2) και Ολλανδία (1). Όλες οι μελέτες ήταν ποσοτικές, πέντε ήταν τυχαιοποιημένες κλινικές δοκιμές ((Faramarzi *et al.,* 2018), (Kelly *et al.,* 2018), (Mohammed *et al.,* 2015), (Amaro *et al.,* 2018), (Schmidt *et al.,* 2012)), πέντε μελέτες κοορτής ((Ali *et al.,* 2018a), (Lodha *et al.,* 2018), (Maitre *et al.,* 2015),

(Huvanandana *et al.*, 2019), (Lodha *et al.*, 2019)), μία προοπτική μελέτη (Ulanovsky *et al.*, 2014), δύο μελέτες παρατήρησης((Yu *et al.*, 2016), (Dix *et al.*, 2018), μια συγχρονική μελέτη (Chavez-Valdez *et al.*, 2016), μία κλινική-πειραματική μελέτη (Fakoor *et al.*, 2019) και μια αναδρομική μελέτη (Parikka *et al.*, 2015).

4.3 Πληθυσμός μελετών

Όλες οι μελέτες είχαν δείγμα πρόωρα νεογνά <37 εβδομάδων τα οποία παρουσίαζαν άπνοια ή αναπνευστικές δυσχέρειες και χρειάζονταν καφεΐνη. Τρείς μελέτες είχαν ως ομάδα σύγκρισης παιδία ηλικίας 3, 5 και 11 χρονών αντίστοιχα ((Lodha *et al.*, 2018), (Schmidt *et al.*, 2012), (Kelly *et al.*, 2018)). Τα νεογνά συμμετείχαν στις μελέτες έπειτα από γραπτή συγκατάθεση των γονέων και εφόσον πληρούσαν τα κριτήρια. Δυο μελέτες οι Faramarzi *et al* .,2018 και Mohammed *et al.*, 2015 σύγκριναν δυο διαφορετικές δόσεις καφεινης. Η μελέτη των Maitre *et al.*, 2015 σύγκρινε τρείς ομάδες νεογνών, μία χωρίς καφεινη , μια με μειωμένη δόση και μια με ψηλή δοση καφεινης σε αντίθεση με την μελέτη των Lodha *et al.*, (2019) όπου έγινε σύγκριση νεογνών με πρώιμη χορήγηση καφεΐνης και καθυστερημένη χορήγηση. Στη μελέτη των (Fakoor *et al.*, 2019) και (Amaro *et al.*, 2018) συγκρίθηκαν ομάδα καφεΐνης και εικονικού φαρμάκου ενώ οι μελέτες των Ulanovsky *et al.*, (2014), Dix *et al.*, 2018 και Parikka *et al.*, 2015, μελέτησαν τα νεογνά πριν, κατά την διάρκεια και μετά την χορήγιση της καφεινης. Στη μελέτη κοορτής των Huvanandana *et al.*, (2019) οι ομάδες σύγκρισης αφορούσαν νεογνά με δεδομένα αρτηριακής πίεσης και ηλεκτροκαρδιογραφήματος, ενώ στην μελέτη των Ali *et al.*,(2018) συμμετείχαν νεογνά με ακτινολογικά δεδομένα. Τέλος στις μελέτες των Yu *et al.*, (2016) και Chavez-Valdez *et al.*, (2016) πάρθηκαν αναλύσεις αίματος από τα νεογνά.

4.4 Δείγμα και δειγματοληψία

Όσον αφορά το είδος της δειγματοληψίας σε όλες τις μελέτες χρησιμοποιήθηκε σκόπιμη δειγματοληψία, εφόσον για την ασφαλή συμμετοχή των νεογνών υπάρχον συγκεκριμένα κριτήρια αποκλεισμού. Ως προς το δείγμα σχεδόν όλες οι μελέτες δεν ξεπερνούσαν τον αριθμό δείγματος πέραν των 250 λόγο ηλικίας των νεογνών, εκτός από δύο μελέτες, στις οποίες συμμετείχαν πολλά νοσοκομεία έτσι το δείγμα κυμαινόταν στα 2000 πρόωρα νεογνά (Lodha *et al.*, 2018, Schmidt *et al.*, 2012).

4.5 Διαδικασία συλλογής δεδομένων

Στις πλείστες μελέτες οι συμμετέχοντες προσεγγίστηκαν αμέσως μετά την γέννηση τους εφόσον πληρούσαν τα κριτήρια και οι γονείς εγκρίναν τη συμμετοχή τους, εκτός από μια των Ali *et al.*,(2018), όπου η συλλογή των δεδομένων άρχιζε εφόσον τα νεογνά συμπλήρωναν τουλάχιστον 12 ημέρες νοσηλείας. Η συλλογή των δεδομένων γινόταν κατά τη διάρκεια της νοσηλείας των νεογνών στο νοσοκομείο. Σε μια από τις μελέτες οι γονείς έπρεπε να συμπληρώσουν ένα ερωτηματολόγιο για την συμπεριφορά (Schmidt *et al.*, 2012). Όσον αφορά τις μελέτες που επαναξιολογήθηκαν τα νεογνά σε μεγαλύτερη ηλικία επανεισάχθηκαν στο νοσοκομείο για την συλλογή των δεδομένων.

4.6 Εργαλεία συλλογής δεδομένων

Αρχικά να αναφερθεί πως η κλίμακα Apgar, χρησιμοποιήθηκε σε πέντε από τις δεκαέξι μελέτες (Faramarzi *et al* .,2018, Amaro *et al.*, 2018, Ulanovsky *et al.*, (2014, Yu *et al.*, (2016), Chavez-Valdez *et al.*) για την αξιολόγηση της φυσιολογικής λειτουργιας του νεογνού. Εξι μελέτες χρησιμοποίησαν διάφορα είδη μονιτορ για την παρακολούθηση των ζωτικών λειτουργιών των νεογνών (Philips MP60, Drager monitor κτλ.) Η μελέτη των Parikka *et al.* 2015, χρησιμοποίησε το Edi monitor για τη μέτρηση της ηλεκτρικής δραστηριότητας του οισοφάγου. Οι Schmidt *et al.*, (2012) χρησιμοποίησαν το Wechsler Preschool and primary scale of intelligence III, και οι γονείς συμπλήρωναν το Child behavior checklist για εντοπισμό συμπεριφορικών προβλημάτων. Στη μελέτη των Chavez-Valdez *et al.*, (2016) χρησιμοποιήθηκε το εργαλίο ELISA για μέτρηση των συγκεντρόσεων TNP-a και IL-10. Οι Huvanandana *et al.*, (2019) χρησιμοποιησαν το NCMS monitor και το ΗΚΓ. Για την εγκεφαλική λειτουργία οι Dix *et al.*, (2018) χρησιμοποιησαν το BrainZ aEEG και για τις φυσιολογικές παραμέτρους και το περιφερικό

κορεσμό οξυγόνου, τα INVOS και mP70. Οι Maitre *et al.*, (2015) για την παρακολούθηση του εγκεφάλου χρησιμοποίησαν το ΗΕΓ και το Geodesic sensor net. Οι Lodha *et al.*, 2018 χρησιμοποίησαν τα εργαλεία Score of neonatal acute physiology II και Bayley-III το δευτερο χρησιμοποίησαν και οι Amaro *et al.*, (2018;). Οι εγκεφλικοί όγκοι στη μελέτη των Kelly *et al.*, (2018) αξιολογίθηκαν με τα εργαλεία, SPM, Free surfer, functional MRI of brain FSL's, FIRST tool, SPM's spatially unbiased infra-tentonal templete, TBSS και το MRtrix's fixel-based analysis.

4.7 Κύρια ευρήματα

Γενικό εύρημα της ανασκόπησης ήταν πως η καφεΐνη είναι αποτελεσματική στην πρόληψη και θεραπεία της άπνοιας κατά την προωρότητα, ωστόσο είναι πιθανό να επιφέρει βραχυπρόθεσμες ή μακροπρόθεσμες ανεπιθύμητες ενέργειες. Έγινε προσπάθεια ομαδοποίησης των αποτελεσμάτων των δεκαέξι μελετών που πληρούσαν τα κριτήριά και παρουσιάζονται πιο κάτω σύμφωνα με την επίδραση της καφεΐνης στα πρόωρα νεογνά με άπνοια και τις ανεπιθύμητες της ενέργειες.

4.7.1 Επίδραση καφεΐνης

4.7.1.1 Δράση καφεΐνης στο αναπνευστικό σύστημα

Η αναδρομική μελέτη των Parikka *et al.*, (2015), που διεξάχθηκε στην Φιλανδία, πήρε δείγμα 17 πρόωρα νεογνά και διερεύνησε την επίδραση της καφεΐνης στον νευρολογικό έλεγχο της αναπνοής κατά την κεντρική άπνοια. Τα αποτελέσματα έδειξαν πως ο αριθμός των επεισοδίων άπνοιας συσχετίστηκαν με το βάρος γέννησης των πρόωρων νεογνών, μειώθηκε ο αριθμός κεντρικής άπνοιας σε περίοδο 30 λεπτών και αυξήθηκε η δαπάνη ενέργειας του διαφράγματος με στατιστικά σημαντική διαφορά ($p=0,004$). Η τυχαιοποιημένη ελεγχόμενη δοκιμή των Mohammed *et al.*, (2015), διεξάχθηκε στην Αίγυπτο με δείγμα 60 πρόωρα νεογνά χαμηλής δόσης και 60 πρόωρα νεογνά ψηλής δόσης καφεΐνης για να συγκρίνει την αποτελεσματικότητα και ασφάλεια της ψηλής δόσης και χαμηλής δόσης κιτρικής καφεΐνης κατά την άπνοια και την επιτυχή εξώθηση από τον αναπνευστήρα. Βρέθηκε στατιστικά σημαντική μείωση της αποτυχίας εξώθησης σε μηχανικά αεριζόμενα νεογνά ($p<0,05$), συχνότητα άπνοιας ($p<0,001$), και των καταγεγραμμένων ημερών άπνοιας ($p<0,001$) κατά τη χορήγηση ψηλής δόσης καφεΐνης. Μια κλινική πειραματική δοκιμή που διεξάχθηκε στο Ιράν από τους Fakoor *et al.*, (2019), διερεύνησε την επίδραση της προφυλακτικής καφεΐνης κατά την άπνοια. Δεν υπήρξαν

σημαντικές διαφορές μεταξύ της καφεΐνης και της ομάδας εικονικού φαρμάκου, ωστόσο η περίοδος νοσηλείας ήταν μικρότερη στην ομάδα που λάμβανε καφεΐνη (p=0,02). Η δεύτερη μελέτη που διεξάχθηκε στο Ιράν, η οποία ήταν τυχαιοποιημένη κλινική δοκιμή των Faramarzi *et al.,* (2018), πήρε δείγμα 40 πρόωρα νεογνά και σύγκρινε την αποτελεσματικότητα και ασφάλεια της μονής δόσης καφεΐνης ημερησίως σε πρόωρα νεογνά με ΣΑΔ. Τα αποτελέσματα έδειξαν πως η διπλή δόση ήταν πιο αποτελεσματική εφόσον μείωσε την αποτυχία αποσωλήνωσης και CPAP χωρίς όμως στατιστικά σημαντική διαφορά. Επίσης στην ομάδα της διπλής δόσης, ο κορεσμός σε οξυγόνο ήταν πιο ψηλός με p=0,049.

4.7.1.2 Δράση καφεΐνης στην εγκεφαλική λειτουργία

Μια αναδρομική μελέτη κοορτής των Lodha *et al.,* (2019), πήρε δείγμα 2108 νεογνά από διάφορες ΜΕΝΝ στον Καναδά και διερεύνησε τη σχέση μεταξύ πρώιμης και καθυστερημένης δόσης καφεΐνης με την νευρολογική ανάπτυξη των πρόωρων νεογνών. Στην ομάδα της πρώιμης δόσης τα ποσοστά ΒΠΔ, ανοικτού βοτάλιου πόρου και σοβαρής νευρολογικής βλάβης ήταν χαμηλότερα, όπως και οι αποδόσεις στη κλίμακα Bayley. Ακόμη, στην ομάδα πρώιμης καφεΐνης, οι αναλύσεις αντιστοίχισης με βάση τις βαθμολογίες τάσης εμφάνισαν χαμηλότερες πιθανότητες εγκεφαλικής παράλυσης και προβλημάτων ακοής. Κατά την ανάλυση των αποτελεσμάτων της καφεΐνης στον νεογνικό εγκέφαλο 34 πρόωρων νεογνών της μελέτης παρατήρησης των Dix *et al.,* (2018) που διεξάχθηκε την Ολλανδία, παρατηρήθηκε ότι το rScO2 μειώθηκε σημαντικά μια ώρα μετά την καφεΐνη και μετά από επαναλαμβανόμενη ανάλυση αερίων αίματος, παρατηρήθηκε σημαντική μείωση του CO2 (p=0,02). Η τυχαιοποιημένη μελέτη των Schmidt *et al.,* (2012), στην Αμερική πήρε δείγμα 1640 πρόωρα νεογνά και είχε κύριο σκοπό την διερεύνηση της καφεΐνης, εάν έχει μακροχρόνια οφέλη ή φαινομενικούς κινδύνους στη σχολική ηλικία. Τα αποτελέσματα δεν έδειξαν σημαντική διαφορά στα ποσοστά θανάτου, κινητικής δυσλειτουργίας, προβλήματα συμπεριφοράς, κακή υγιεινή, κώφωση ή τύφλωση μεταξύ των δύο ομάδων (p=0,09) και η επίπτωση της νοητικής βλάβης ήταν χαμηλότερη στα 5 χρόνια απ’τι στους 18 μήνες και παρόμοια στην ομάδα καφεΐνης και του εικονικού φαρμάκου (p=0,89).

4.7.1.3 Δράση καφεΐνης στο καρδιαγγειακό σύστημα

Μια προοπτική μελέτη που διεξάχθηκε στο Ισραήλ των Ulanovsky *et al.,* (2014), πήρε δείγμα 21 πρόωρα νεογνά και μελέτησε τις οξείες επιδράσεις της καφεΐνης σε σχέση με τον καρδιακό ρυθμό. Δεν υπήρξαν μεταβολές στον καρδιακό ρυθμό, αρτηριακή πίεση και τον τόνο του αυτόνομου νευρικού συστήματος ,μετά τη χορήγηση της καφεΐνης. Παρόμοιο σκοπό είχε και η μελέτη κοορτής των Huvanandana *et al.,* (2019) στην Αυστραλία με δείγμα 31 πρόωρα νεογνά με δεδομένα αρτηριακής πίεσης και 25 με δεδομένα ΗΚΓ, όπου τα αποτελέσματα έδειξαν μείωση στους δυο εκθέτες κλιμάκωσης (a1, a2) της ΜΑΠ και στη καρδιακή συχνότητα οι αναλύσεις έδειξαν μείωση στο 1a ($p<0,01$).

4.7.2 Ανεπιθύμητές ενέργειες καφεΐνης

4.7.2.1 Νευροαναπτυξιακά

Πιο πάνω έγινε αναφορά στις μελέτες που διερευνήσαν την θετική επίδραση της καφεΐνης στο νευρικό σύστημα, ωστόσο η τυχαιοποιημένη μελέτη των Kelly *et al.,* (2018) που διεξάχθηκε στην Αυστραλία, διερεύνησε την σχέση της θεραπείας με καφεΐνη σε 70 πρόωρα νεογνά και τις δομής του εγκεφάλου σε 117 παιδία ηλικίας 11 ετών, η οποία δείχνει το αντίθετο. Δηλαδή η ομάδα της καφεΐνης είχε μικρότερο μεσολόβιο από την ομάδα του εικονικού φαρμάκου ($p=0,003$) και συσχετίστηκε με βραδύτερη ανάπτυξη του μεσολόβιου και πιο αργή μείωση της αξονικής ($p=0,02$), ακτινικής ($p=0,01$) και μέσης διάχυσης της λευκής ύλης ($p<0,001$). Η μελέτη κοορτής των Maitre *et al.,* (2015) στην Αμερική με δείγμα 45 πρόωρα νεογνά, διερεύνησε την επίδραση διαφόρων δόσεων καφεΐνης σε αντιθέσεις ήχου-ομιλίας. Με αποτέλεσμα τα νεογνά στην ομάδα της χαμηλής δόσης αποδεικνύουν μεγαλύτερη ηχητική διαφοροποίηση στις συλλαβές (da-ga) από τα νεογνά με την υψηλή έκθεση σε καφεΐνη ($p<0,001$). Ακόμη μια μελέτη κοορτής των Lodha et al., (2018) στην Αμερική, πήρε δείγμα 448 πρόωρα νεογνά και αξιολόγησε εάν υπάρχει συσχέτιση μεταξύ της διάρκειας της χρήσης καφεΐνης και των νευροαναπτυξιακών επιδράσεων σε ηλικία 3 ετών. Τα αποτελέσματα έδειξαν ότι η διακοπή της καφεΐνης μεταξύ 15-30 ημέρες μετά την γέννηση συσχετίστηκε με τη μικρότερη συχνότητα εμφάνισης βλάβης νευροαναπτυξιακά σε νεογνά <1250γρ. Αν και η καφεΐνη έχει αποδειχθεί ότι προστατεύει την ανάπτυξη του εγκεφάλου, η μελέτη αυτή δεν βρήκε καμία σχέση μεταξύ παρατεταμένης διάρκειας καφεΐνης (>30 ημέρες) και επιβίωσης χωρίς βλάβη.

4.7.2.2 Οστεοπενία

Η αναδρομική μελέτη κοορτής που διεξάχθηκε στον Καναδά από τους Ali *et al.*, (2018), πήρε δείγμα 109 πρόωρα νεογνά με σκοπό την διερεύνηση της επίδρασης της δόσης και διάρκειας της καφεΐνης στα πρόωρα νεογνά με οστεοπενία. Τα αποτελέσματα έδειξαν πως η δόση και διάρκεια της καφεΐνης έχουν ισχυρή συσχέτιση με την εμφάνιση οστεοπενίας κατά την προωρότητα ($p<0,001$).

4.7.2.3 Θνησιμότητα

Η τυχαιοποιημένη μελέτη των Amaro *et al.*, (2018) που πραγματοποιήθηκε στην Αμερική, πήρε δείγμα 83 πρόωρα νεογνά και αξιολόγησε την επίδραση της πρώιμης καφεΐνης σε ηλικία πρώτης επιτυχούς εξώθησης. Τα αποτελέσματα δεν έδειξαν στατιστικά σημαντική διαφορά στην θνησιμότητα μεταξύ των δυο ομάδων ωστόσο λόγο μιας ενδιάμεσης ανάλυσης το 75% έδειξε μια τάση προς υψηλότερη θνησιμότητα σε μια από τις ομάδες, έτσι η επιτροπή ασφάλειας και παρακολούθησης δεδομένων συνέστησε τη διακοπή της δοκιμής.

4.7.2.4 Ταχυκαρδία

Η τυχαιοποιημένη μελέτη των Mohammed *et al.*, (2015), σύγκρινε την αποτελεσματικότητα και ασφάλεια της ψηλής και της χαμηλής δόσης κιτρικής καφεΐνης κατά την άπνοια και την επιτυχή εξώθηση από τον αναπνευστήρα. Παρόλο που έδειξε πως η ψηλή δόση μείωσε την αποτυχία εξώθησης, τη συχνότητα και τις καταγεγραμμένες ημέρες άπνοιας, ωστόσο συσχετίστηκε με σημαντική αύξηση των επεισοδίων ταχυκαρδίας ($p<0,05$). Παρόμοια αποτελέσματα έδειξε και η μελέτη κοορτής των Huvanandana *et al.*, (2019), οπου παρόλο που είχε πτώση στην ΜΑΠ, ωστόσο η παλμική πίεση beat to beat αυξήθηκε με $p<0,01$ και σημειώθηκε αυξημένη οσφυαλγία.

4.7.2.5 Ανοσοποιητικό σύστημα

Μια συγχρονική μελέτη που διεξάχθηκε στην Αμερική των Chavez-Valdez *et al.*, (2016), πήρε δείγμα 19 πρόωρα νεογνά και διερεύνησε την επίδραση της καφεΐνης στα επίπεδα κυτοκινών στο αίμα των νεογνών. Τα αποτελέσματα έδειξαν πως η καφεΐνη μείωσε τα επίπεδα TNF-a, cAMP και IL-10 και οι συγκεντρώσεις της καφεΐνης συσχετίζονται άμεσα με το TLR4 ($p<0,001$).

5. Συζήτηση

Στη παρούσα συστηματική ανασκόπηση έγινε προσπάθεια ανάδειξης των επιδράσεων της καφεΐνης στα πρόωρα νεογνά με άπνοια ή αναπνευστική δυσχέρεια καθώς και των ανεπιθύμητων της ενεργειών. Σύμφωνα με τις μελέτες που αναδύθηκαν μέσα από αυτή την ανασκόπηση, η καφεΐνη δρα αποτελεσματικά στην θεραπεία ή μείωση των επεισοδίων άπνοιας, στην μείωση του βαθμού αποτυχίας εξώθησης από τον αναπνευστήρα, δρα προληπτικά στην εμφάνιση ΒΠΔ και στη μείωση εμφάνισης διαφόρων νεογνικών επιπλοκών όπως το ΣΑΔ, του ανοικτού βοτάλιου πόρου και της αμφιβληστροειδοπάθειας κατά την προωρότητα. Αναφορικά με τις ανεπιθύμητες ενέργειες που μπορεί να επιφέρει η καφεΐνη στα πρόωρα νεογνά, φάνηκε ότι μπορεί να προκαλέσει διαταραχή στην νευρολογική ανάπτυξη, το καρδιαγγειακό, σκελετικό και ανοσοποιητικό σύστημα, καθώς επίσης και στα επίπεδα θνησιμότητας των πρόωρων νεογνών.

Η καφεΐνη ανήκει στα φάρμακα που χρησιμοποιούνται ευρέως στην ΜΕΝΝ. Κατά τη διεξαγωγή πολλών μελετών διερευνήθηκε η χρήση των μεθυλξανθινών για την θεραπεία άπνοιας κατά την προωρότητα (Erenberg *et al.*, 2000). Η θεοφυλλίνη ήταν το αρχικό πρότυπο θεραπείας της άπνοιας ωστόσο οι μεθυλξανθινες συμπεριλαμβανομένου της καφεΐνης, αποδείχτηκε πως έχουν καθιερωθεί για την βραχυπρόθεσμή τους αποτελεσματικότητα, να μειώνουν τα απνοϊκά επεισόδια (Henderson-Smart, De Paoli and Haughton, 2010). Μια από τις μεγαλύτερες μελέτες που διεξάχθηκαν για τη σύγκριση της επίδρασης της καφεΐνης σε ομάδα εικονικού φαρμάκου με δείγμα 2006 πρόωρα νεογνά, έδειξαν πως η καφεΐνη συσχετίστηκε με την μείωση της διάρκειας CPAP, του συμπληρωματικού οξυγόνου, του βαθμού ΒΠΔ, αμφιβληστροειδοπάθειας και πρόληψη εγκεφαλικής βλάβης και γνωστικών διαταραχών (Schmidt *et al.*, 2012). Η καφεΐνη θεωρείται πλέον το καταλληλότερο φάρμακο και χρησιμοποιείται τυπικά για τη θεραπεία της άπνοιας κατά την προωρότητα λόγο του ψηλού θεραπευτικού δείκτη, καλύτερης εντερικής απορρόφησης και μεγαλύτερης διάρκειας ημερισιας ζωής σε σχέση με άλλες μεθυλξανθίνες (Ergenekon *et al.*, 2001). Ωστόσο πολλά πρόωρα νεογνά σε ψηλές δόσεις καφεΐνης εμφανίζουν επεισόδια ταχυκαρδίας, ταχυπαλμίας, σπασμών και αύξησης αρτηριακής πίεσης. Ως προς τα επεισόδια αύξησης της αρτηριακής πίεσης τα αποτελέσματα αντιφάσκονται μεταξύ των μελετών. Στη μελέτη των Huvanandana *et al.*, (2019), η ΜΑΠ είχε μειωθεί μετά από χορήγηση καφεΐνης. Μια αναδρομική μελέτη των Pacifici, (2014) η οποία σύγκρινε δύο διαφορετικές δόσεις, έδειξε πως η ψηλή δόση

καφεΐνης συσχετίστηκε σημαντικά με μείωση της αποτυχίας εξώθησης σε μηχανικά αεριζόμενα νεογνά όμως ταυτόχρονα οδηγούσε σε επεισόδια ταχυκαρδίας, ταχύπνοιας και αύξησης της αρτηριακής πίεσης.

Επιπρόσθετα η συσχέτιση της καφεΐνης με την οστεοπενία στα πρόωρα νεογνά αποδεικτικέ θετική στην παρούσα συστηματική ανασκόπηση, ωστόσο έρχεται σε διαφωνία με μια αναδρομική μελέτη (Viswanathan *et al.*, 2014), όπου τα νεογνά με κατάγματα πλευρών δεν παρουσίασαν συσχέτιση της οστεοπενίας κατά την προωρότητα με την καφεΐνη.

Σε όλες τις μελέτες η ηλικία των νεογνών διαδραμάτιζε σημαντικό ρόλο, δηλαδή όσο πιο πρόωρα ήταν τα νεογνά τόσο πιο ευπαθή ήταν στις ανεπιθύμητες ενέργειες από την θεραπεία με καφεΐνη. Ακόμη ένα σημαντικό στοιχείο είναι πως στις δεκαέξι μελέτες η κιτρική καφεΐνη εξετάστηκε μόνο σε πρόωρα νεογνά και δεν συγκρίθηκε με άλλες ηλικιακές ομάδες, εφόσον σύμφωνα με τον Ευρωπαϊκό Οργανισμό Φαρμάκων (2009) η συγκεκριμένη καφεΐνη και οι μεθυλξανθίνες γενικότερα χορηγούνται μόνο σε πρόωρα νεογνά για τη θεραπεία της άπνοιας.

Σύμφωνα με τα πιο πάνω δεδομένα, τονίζεται η σημαντικότητα του νοσηλευτικού ρόλου στην ΜΕΝΝ. Η νοσηλευτική φροντίδα στην ΜΕΝΝ αποτελεί μια συνιστώσα πολλών παραγόντων. Ο νοσηλευτής σε συνδυασμό με τις γνώσεις και δεξιότητες που διαθέτει πρέπει να είναι σε θέση να εκτιμήσει την βαρύτητα του αναπνευστικού προβλήματος από την κλινική εικόνα, ζωτικά σημεία που παρουσιάζει το νεογνό και την φυσική εξέταση, να εντοπίσει τα απνοϊκά επεισόδια και να τα αντιμετωπίσει άμεσα. Έτσι κρίνεται απαραίτητο οι επαγγελματίες υγείας που εργάζονται στις ΜΕΝΝ να είναι εκπαιδευμένοι με τις κατάλληλες γνώσεις και δεξιότητες.

<u>Περιορισμοί των ερευνών που ανασκοπήθηκαν</u>

Η παρούσα συστηματική ανασκόπηση είχε κάποιους περιορισμούς οι οποίοι είναι πιθανόν να επηρεάσουν τα αποτελέσματα. Καταρχάς όλα τα άρθρα που ανευρέθηκαν ήταν γραμμένα στην αγγλική γλώσσα, χωρίς αυτόν τον περιορισμό πιθανόν η ηλεκτρική αναζήτηση να απέδιδε μεγαλύτερο αριθμό μελετών. Ένας εξίσου σημαντικός περιορισμός ήταν ο αριθμός του δείγματος που ήταν πολύ μικρός σε όλες τις μελέτες εκτός από δύο που λάμβαναν μέρος σε ευρεία περιοχή. Βέβαια μιλώντας για πληθυσμό πρόωρων νεογνών όπου είναι δύσκολο να μαζευτεί μεγάλο δείγμα, λόγο επικινδυνότητας της ηλικίας.

6. Συμπεράσματα

Από την ανάλυση των αποτελεσμάτων των μελετών αλλά και στη συνέχεια από τη συζήτηση και σύγκριση των ευρημάτων τους προκύπτει το συμπέρασμα πως η θεραπεία της άπνοιας με καφεΐνη σε πρόωρα νεογνά έχει θετικές επιδράσεις αλλά ταυτόχρονα προκαλεί και ανεπιθύμητες ενέργειες άμεσες ή και μακροπρόθεσμες. Παρόλη την ευρεία ανάλυση του θέματος από το παρελθόν μέχρι και σήμερα οι παρενέργειες εξακολουθούν να υπάρχουν και να παίζουν σημαντικό ρόλο στην υγεία του νεογνού. Οι μελέτης της συγκεκριμένης ανασκόπησης συνιστούν την πραγματοποίηση περαιτέρω τυχαιοποιημένων κλινικών δοκιμών για την αποτελεσματικότητα και ασφάλεια της χορήγησης κιτρικής καφεΐνης σε πρόωρα νεογνά για την θεραπεία της άπνοιας και άλλων αναπνευστικών προβλημάτων.

6.1.Σημασία για την Νοσηλευτική και το σύστημα υγείας

Ένα πρόωρο νεογνό από τη στιγμή που θα γεννηθεί, θα μεταφερθεί στην ΜΕΝΝ, όπου τη φροντίδα του αναλαμβάνει μια πολυθεματική ομάδα επαγγελματιών υγείας που αποτελείται από τους νεογνολόγους, τους νοσηλευτές, φυσιοθεραπευτές, ψυχολόγους κτλ. Λόγο της προωρότητας τα περισσότερα νεογνά λαμβάνουν ενδοφλέβια καφεΐνη ως θεραπεία ή πρόληψη της άπνοιας και άλλων αναπνευστικών προβλημάτων. Την 24ωρη παρακολούθηση, φροντίδα και φαρμακευτική αγωγή παρέχει το νοσηλευτικό προσωπικό. Οι νοσηλευτές είναι οι πρώτοι που θα παρατηρήσουν για τυχόν παρενέργειες της φαρμακευτικής αγωγής ή οποιαδήποτε ανωμαλία παρουσιαστεί στο νεογνό κατά την νοσηλεία του. Έτσι είναι επιτακτική ανάγκη το σύστημα υγείας να εφαρμόσει εκπαιδευτικά προγράμματα ενημέρωσης, πρόληψης και ανίχνευσης περιστατικών που να απευθύνονται στο νοσηλευτικό προσωπικό. Σημαντικό είναι να τονιστεί η συνεχής επιμόρφωση και ενημέρωση των νοσηλευτών στην ΜΕΝΝ σε σχέση με την καφεΐνη, τις επιδράσεις και τις ανεπιθύμητες ενέργειες της με σκοπό την πρόληψη, αντιμετώπιση και μείωση της θνησιμότητας των πρόωρων νεογνών.

6.1 Εισηγήσεις για μελλοντικές έρευνες

Σύμφωνα με τα αποτελέσματα της παρούσας ανασκόπησης, η έρευνα απαιτείται να συνεχιστεί με σκοπό την εξακρίβωση της αποτελεσματικότητας και της ασφάλειας χορήγησης καφεΐνης. Μέσα από διεξοδική μελέτη του θέματος, οι ελλείψεις που ανευρέθηκαν και οι διάφοροι προβληματισμοί των μελετητών που τέθηκαν, έδωσαν τη δυνατότητα για καθορισμό κάποιων εισηγήσεων για μελλοντικές έρευνες.

- Αρχικά ποσοτικές μελέτες θα ήταν χρήσιμές για τον καθορισμό του επιπέδου των γνώσεων των νοσηλευτών σχετικά με την θεραπεία της άπνοιας με κιτρική καφεΐνη. Με τη διερεύνηση των γνώσεων θα φανεί εάν κρίνεται αναγκαία η εφαρμογή προγραμμάτων ενημέρωσης σχετικά με τις επιδράσεις και τις ανεπιθύμητες ενέργειες της καφεΐνης.
- Τυχαιοποιημένες κλινικές δοκιμές για να αποδείξουν ή να απορρίψουν την αποτελεσματικότητα της ψηλής δόσης καφεΐνης για μείωση των επεισοδίων άπνοιας και για διερεύνηση της αποτελεσματικότητας και ασφάλειας της χορήγησης της στα πρόωρα νεογνά.
- Προοπτικές μελέτες για καθορισμό της συνδεσιμότητας της φαρμακοκινιτικής/ φαρμακοδυναμικής για βελτιστοποίηση της δοσολογίας στα πρόωρα νεογνά.

7. Βιβλιογραφία

Abdallah, E. A. A. *et al.* (2016) 'Serial serum alkaline phosphatase as an early biomarker for osteopenia of prematurity', *Medicine (United States)*. Lippincott Williams and Wilkins, 95(37). doi: 10.1097/MD.0000000000004837.

Abdel-Hady, H. (2015) 'Caffeine therapy in preterm infants', *World Journal of Clinical Pediatrics*, 4(4), p. 81. doi: 10.5409/wjcp.v4.i4.81.

Ali, E. *et al.* (2018a) 'Caffeine is a risk factor for osteopenia of prematurity in preterm infants: a cohort study.', *BMC pediatrics*, 18(1), p. 9. doi: 10.1186/s12887-017-0978-6.

Ali, E. *et al.* (2018b) 'Caffeine is a risk factor for osteopenia of prematurity in preterm infants: A cohort study', *BMC Pediatrics*. BMC Pediatrics, 18(1), pp. 1–7. doi: 10.1186/s12887-017-0978-6.

Amaro, C. M. *et al.* (2018) 'Early Caffeine and Weaning from Mechanical Ventilation in Preterm Infants: A Randomized, Placebo-Controlled Trial', *Journal of Pediatrics*. Elsevier Inc., 196, pp. 52–57. doi: 10.1016/j.jpeds.2018.01.010.

Ballard, R. A. *et al.* (2016) 'Randomized Trial of Late Surfactant Treatment in Ventilated Preterm Infants Receiving Inhaled Nitric Oxide', *Journal of Pediatrics*. Mosby Inc., 168, pp. 23-29.e4. doi: 10.1016/j.jpeds.2015.09.031.

Charousová, I. *et al.* (2017) 'The effect of venous caffeine on the prevention of apnea of prematurity in the very preterm infants in the neonatal intensive care unit of Shahid Motahhari Hospital, Urmia, during a year', *Journal of Advanced Pharmaceutical Technology and Research*, 8(2), pp. 46–51. doi: 10.4103/japtr.JAPTR.

Chavez-Valdez, R. *et al.* (2016) 'Mechanisms of modulation of cytokine release by human cord blood monocytes exposed to high concentrations of caffeine', *Pediatric Research*, 80(1), pp. 101–109. doi: 10.1038/pr.2016.50.

Chawanpaiboon, S. *et al.* (2019) 'Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis', *The Lancet Global Health*, 7(1), pp. e37–e46. doi: 10.1016/S2214-109X(18)30451-0.

Cömert, S. *et al.* (2012) 'The cost analysis of preterm infants from a NICU of a state hospital in Istanbul', *Iranian Journal of Pediatrics*, 22(2), pp. 185–190.

Davis, P. G. *et al.* (2010) 'Caffeine for Apnea of Prematurity Trial: Benefits May Vary

in Subgroups', *Journal of Pediatrics*. Mosby Inc., 156(3). doi: 10.1016/j.jpeds.2009.09.069.

Dix, L. M. L. *et al.* (2018) 'Effects of caffeine on the preterm brain: An observational study', *Early Human Development*, 120(March), pp. 17–20. doi: 10.1016/j.earlhumdev.2018.03.008.

Eichenwald, E. C. (2016) 'Apnea of Prematurity', *Pediatrics*, 137(1). doi: 10.1542/peds.2015-3757.

Erenberg, A. *et al.* (2000) 'Caffeine citrate for the treatment of apnea of prematurity: A double- blind, placebo-controlled study', *Pharmacotherapy*. Pharmacotherapy Publications Inc., 20(6 I), pp. 644–652. doi: 10.1592/phco.20.7.644.35167.

Ergenekon, E. *et al.* (2001) 'Caffeine intoxication in a premature neonate', *Paediatric Anaesthesia*, 11(6), pp. 737–739. doi: 10.1046/j.1460-9592.2001.00753.x.

Fakoor, Z. *et al.* (2019) 'The effect of venous caffeine on the prevention of apnea of prematurity in the very preterm infants in the neonatal intensive care unit of Shahid Motahhari Hospital, Urmia, during a year', *Journal of Advanced Pharmaceutical Technology & Research*, 10(1), p. 16. doi: 10.4103/japtr.japtr_334_18.

Faramarzi, F. *et al.* (2018) 'The efficacy and safety of two different doses of caffeine in respiratory function of preterm infants', *Caspian Journal of Internal Medicine*, 9(1), pp. 46–53. doi: 10.22088/cjim.9.1.46.

Fredholm, B. B. (1995) 'Adenosine, Adenosine Receptors and the Actions of Caffeine', *Pharmacology & Toxicology*, 76(2), pp. 93–101. doi: 10.1111/j.1600-0773.1995.tb00111.x.

Henderson-Smart, D. J., De Paoli, A. G. and Haughton, D. (2010) 'Methylxanthine treatment for apnoea in preterm infants', *Cochrane Database of Systematic Reviews*. John Wiley and Sons Ltd. doi: 10.1002/14651858.CD000140.pub2.

Huvanandana, J. *et al.* (2019) 'Cardiovascular impact of intravenous caffeine in preterm infants', *Acta Paediatrica, International Journal of Paediatrics*, 108(3), pp. 423–429. doi: 10.1111/apa.14382.

Julien, C. A., Joseph, V. and Bairam, A. (2010) 'Caffeine reduces apnea frequency and enhances ventilatory long-term facilitation in rat pups raised in chronic intermittent hypoxia', *Pediatric Research*. Lippincott Williams and Wilkins, 68(2), pp. 105–111. doi: 10.1203/PDR.0b013e3181e5bc78.

Kelly, C. E. *et al.* (2018) 'Caffeine for apnea of prematurity and brain development at 11 years of age', *Annals of Clinical and Translational Neurology*, 5(9), pp. 1112–1127. doi:

10.1002/acn3.628.

Kreutzer, K. and Bassler, D. (2014) ‘Caffeine for apnea of prematurity: A neonatal success story’, in *Neonatology*. S. Karger AG, pp. 332–336. doi: 10.1159/000360647.

Lodha, A. *et al.* (2018) ‘Does duration of caffeine therapy in preterm infants born ≤1250 g at birth influence neurodevelopmental (ND) outcomes at 3 years of age?’, *Journal of Perinatology*. Springer US, 38(7), pp. 889–899. doi: 10.1038/s41372-018-0106-y.

Lodha, A. *et al.* (2019) ‘Early caffeine administration and neurodevelopmental outcomes in preterm infants’, *Pediatrics*, 143(1). doi: 10.1542/peds.2018-1348.

Maitre, N. L. *et al.* (2015) ‘Effects of caffeine treatment for apnea of prematurity on cortical speech-sound differentiation in preterm infants’, *Journal of Child Neurology*, 30(3), pp. 307–313. doi: 10.1177/0883073814538500.

Mohammed, S. *et al.* (2015) ‘High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial’, *European Journal of Pediatrics*, 174(7), pp. 949–956. doi: 10.1007/s00431-015-2494-8.

Pacifici, G. M. (2014) ‘Clinical pharmacology of caffeine citrate in preterm infants’, *Medical Express*. GN1 Genesis Network, 1(5), pp. 243–250. doi: 10.5935/medicalexpress.2014.05.06.

Parikka, V. *et al.* (2015) ‘The effect of caffeine citrate on neural breathing pattern in preterm infants’, *Early Human Development*. Elsevier Ireland Ltd, 91(10), pp. 565–568. doi: 10.1016/j.earlhumdev.2015.06.007.

Patel, R. M. *et al.* (2013) ‘Early caffeine therapy and clinical outcomes in extremely preterm infants’, *Journal of Perinatology*. Nature Publishing Group, 33(2), pp. 134–140. doi: 10.1038/jp.2012.52.

Schmidt, B. *et al.* (2012) ‘Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity’, *JAMA - Journal of the American Medical Association*, 307(3), pp. 275–282. doi: 10.1001/jama.2011.2024.

Siu, A. and James, A. (2010) ‘Apnea of prematurity pharmacotherapy’, *U.S. Pharmacist*. Available at: http://stage.uspharmacist.com/article/apnea-of-prematurity-pharmacotherapy (Accessed: 29 March 2020).

Ulanovsky, I. *et al.* (2014) ‘The effects of caffeine on heart rate variability in newborns with apnea of Prematurity’, *Journal of Perinatology*. Nature Publishing Group, 34(8), pp. 620–623. doi: 10.1038/jp.2014.60.

Viswanathan, S. *et al.* (2014) ‘Metabolic bone disease: A continued challenge in extremely low birth weight infants’, *Journal of Parenteral and Enteral Nutrition*, 38(8), pp. 982–990. doi: 10.1177/0148607113499590.

Yiallouros, P. K. *et al.* (2018) ‘Maternal socioeconomic factors and the risk of premature birth and low birth weight in Cyprus: a case–control study’, *Reproductive Health*, 15(1), pp. 1–9. doi: 10.1186/s12978-018-0603-7.

Yu, T. *et al.* (2016) ‘Incorporating pharmacodynamic considerations into caffeine therapeutic drug monitoring in preterm neonates’, *BMC Pharmacology and Toxicology*. BMC Pharmacology and Toxicology, 17(1), pp. 1–8. doi: 10.1186/s40360-016-0065-x.

Στατιστική υπηρεσία, Μ. παρακολούθησης υγειας (2007) *ΕΡΕΥΝΑ ΠΕΡΙΓΕΝΝΗΤΙΚΗΣ ΥΓΕΙΑΣ 2007*.

)2020. (أ. ا, الزاوي *Apnea of prematurity*. Available at: https://www.chiesi.com/en/therapeutic-areas/neonatology/ (Accessed: 1 April 2020).

Yu et al. BMC Pharmacology and Toxicology (2016) 17:22
DOI 10.1186/s40360-016-0065-x

BMC Pharmacology and Toxicology

RESEARCH ARTICLE Open Access

Incorporating pharmacodynamic considerations into caffeine therapeutic drug monitoring in preterm neonates

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Abstract

Background: This study sought to assess the pharmacokinetic and pharmacodynamic relationships of caffeine citrate therapy in preterm neonates who had therapeutic drug monitoring (TDM) in the post-extubation period.

Methods: A retrospective observational study was conducted in preterm neonates who received caffeine citrate therapy for apnea of prematurity and had TDM done in the post-extubation period between January 2006 and October 2011. The relationships between pharmacodynamic effects (heart rate, respiratory rate, episodes of apnea, adverse events) and caffeine serum concentrations were explored.

Results: A total of 177 blood samples were obtained from 115 preterm neonates with a median (range) gestational age of 29 (24 – 33) weeks and birth weight of 1230 (607 – 2304) kg. Caffeine citrate therapy was initiated at a median (interquartile range) postnatal age of 1 (1 – 3) day and TDM was performed at a postnatal age of 15 (10 – 24) days. No direct correlations were found between respiratory rate or apneic episodes and caffeine serum concentrations; however, heart rate and caffeine serum concentrations were significantly correlated ($p < 0.05$). Dosing regimen of 40/5 mg/kg q12h (loading dose/maintenance dose, time interval) led to similar endotracheal re-intubation rate but increased percentage of patients experiencing tachycardia compared to the standard regimen of 20/5 mg/kg q24h (44.7 % vs 10.2 %, $p < 0.001$).

Conclusion: Based on this retrospective study, no correlation between episodes of apnea and caffeine serum concentrations was found in neonates who had TDM of caffeine citrate therapy in the post-extubation period, whereas a significant association between tachycardia and concentrations existed. Notwithstanding the absence of severe adverse reactions, TDM should be considered in critically ill neonates with unexplained adverse effects, such as tachycardia.

Keywords: Caffeine, Neonate, Pharmacodynamics, Therapeutic drug monitoring

Background

Caffeine citrate is the first-line therapy for treatment of apnea of prematurity [1, 2]. The standard dosing regimen, approved by FDA in 1999 [3], is an intravenous loading dose of 20 mg/kg caffeine citrate followed by a maintenance dose of 5 mg/kg daily. Other dosing regimens exist, contingent upon the neonatologist's decision based on the neonate's disease status. The therapeutic range of 5 – 20 mg/L has been used to guide dosing in neonates and has its origin in early works by J. V. Aranda et al., which reported that optimizing ventilatory drive and control of apnea without toxicity were achievable with caffeine serum concentrations within this range [4]. Clinical signs of toxicity have been observed with caffeine serum concentrations above 40 mg/L [5]. However, therapeutic drug monitoring (TDM) is not routinely performed due to its benign safety profile when standard dosing is used [6, 7]. Since TDM usually requires blood sampling by heel prick and can contribute to anemia, it is important to understand if TDM is necessary during caffeine citrate therapy, especially with

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varied dosing regimens other than the FDA approved regimen.

Several studies did not support the practice of routine TDM of caffeine citrate therapy or indicated higher upper bound of therapeutic range (>20 mg/L) in preterm neonates [8–10]. An observational study of 101 preterm neonates revealed that standard maintenance dose led to serum concentrations within the recommended range (5 – 20 mg/L) independent of gestational age (GA), which also held true for patients with concomitant renal or hepatic dysfunction [8]. A prospective study reported that caffeine serum concentrations from standard dosing were in a safe and therapeutic range of 11 – 33 mg/L by 14 postnatal days and were independent of neonatal demographics including GA, postmenstrual age (PMA), and weight, suggesting that routine TDM was not necessary without clinical signs of apnea or toxicity [9]. A population pharmacokinetic (PK) study showed that the inter-occasion (day-to-day) variability of caffeine clearance was twice the inter-individual variability in preterm neonates, which implied that adjusting a maintenance dose based on previous serum concentrations of the individual neonate was not effective due to the marked day-to-day randomness in clearance [10]. Gal suggested that the therapeutic concentrations could range from 10 to 40 mg/L and the likelihood of response and toxicity were specific to each individual [11, 12].

Our study examined cardiovascular/respiratory effects including heart rate, respiratory rate, episodes of apnea, and adverse events as major pharmacodynamic (PD) parameters and delineated their association with caffeine serum concentrations in preterm neonates. Clinical interventions and adverse events were also compared among various dosing regimens to illustrate the aggregated clinical outcomes resulting from different caffeine exposures. The aim of this study was to find the relationship between PD responses and caffeine serum concentrations to inform the use of TDM in neonates. This retrospective study was conducted to serve as a preliminary work for a future prospective study on caffeine citrate dosing regimen optimization in preterm neonates.

Methods

Study design

This retrospective observational study consisted of preterm neonates who received caffeine citrate for apnea of prematurity at 8 sites of Intermountain Healthcare System in Utah (Utah Valley Hospital, Intermountain Medical Center, McKay-Dee Hospital, Primary Children's Hospital, Dixie Regional Hospital, Latter-day Saints Hospital, American Fork Hospital, Logan Regional Hospital) between January 2006 and October 2011. Neonates who had been previously ventilated at birth, received at least 1 dose of intravenous caffeine citrate within 28 days of postnatal age (PNA), and had at least 1 blood sample taken for caffeine concentration measurement were included for analysis. Patients were excluded if they received caffeine citrate therapy for other indications (neonatal respiratory distress syndrome), apnea due to other causes (confirmed sepsis or pneumonia, diagnosed gastroesophageal reflux), or had no TDM. Preterm neonates with abnormalities in central nervous system were also excluded as the disease may affect the patient response to caffeine. Patient demographics including gender, birth weight, APGAR 1 min score, APGAR 5 min score, GA, PNA at dosing or sampling, PMA at dosing or sampling were recorded in enterprise data warehouse. This study was reviewed, approved, and granted a waiver of informed consent by the University of Utah Institutional Review Board.

Sample collection and measurement

The information on doses, dosing intervals, and TDM sample concentrations were obtained from enterprise data warehouse of Intermountain Healthcare System. In the clinical settings, a loading dose of either 40 mg/kg (20 mg/kg caffeine base equivalent) or 20 mg/kg caffeine citrate (10 mg/kg caffeine base equivalent) was administered by intravenous infusion over 15 min, followed by a maintenance dose of 5 mg/kg caffeine citrate (2.5 mg/kg caffeine base equivalent) every 12 or 24 h through intravenous or orogastric/nasogastric routes. The dosing regimen is denoted as loading dose/maintenance dose, dosing time interval throughout this paper. Decisions regarding caffeine citrate dosing regimen, use of TDM, and timing of blood sample acquisition were made by the clinical staff. The indication for TDM was inadequate responses such as repeated or severe apnea despite the continuation of caffeine therapy or symptoms of adverse events [13, 14]. The timing of sample collection post last dose was random and was at the discretion of the care providers. Total caffeine concentrations in serum were measured by quantitative enzyme multiplied immunoassay (EMIT caffeine assays, Siemens Healthcare, Pennsylvania, USA). The assay was accurate between 1 and 30 mg/L with between-day and within-day imprecision < 10 % across this range [15]. Samples with caffeine concentration > 30 mg/L were diluted in drug-free serum and reanalyzed.

Clinical records identification and analysis

Intermountain HELP2 Clinical Desktop was searched to obtain clinical notes concurrent with sample collections using the patient's enterprise master patient index number. The clinical notes included relevant critical care progress notes or discharge summaries. Vital signs (heart rate and respiratory rate) were recorded in the critical care progress notes on the date of sample collection along with the frequency of apnea and any adverse

effects attributed to caffeine. The normal range of heart rate in neonates is 120 – 160 beats per minute ($b \cdot min^{-1}$) with toxicity associated with > 220 $b \cdot min^{-1}$. Episodes of heart rate > 170 $b \cdot min^{-1}$ were considered as tachycardia according to the clinical notes. The respiratory rate normal range in neonates is 30 – 60 breaths per minute ($br \cdot min^{-1}$) with toxicity defined as tachypnea > 80 $br \cdot min^{-1}$. Information on apnea or adverse events was screened in the notes. Apnea was cessation of breathing lasting > 20 seconds, and/or those that were shorter, but associated with hypoxia (oxygen saturation < 85 %) or bradycardia (heart rate < 100 $b \cdot min^{-1}$). Episodes of apnea (number) or onset of adverse events (yes/no) that happened on the same day of sample collection were recorded. If critical care progress notes concurrent with sample collections were not available, the apnea or adverse event records from the hospital discharge summary were searched to identify any information on apneic episodes or adverse events on the date of sample collection. Records from patients who were not on mechanical ventilators on the days of TDM were used to evaluate the relationships between vital signs/apnea episodes and caffeine serum concentrations. It is to note that vital signs were measured during the physical exam on the same day of TDM as dictated by the attending clinician, thus may not reflect the heart rate in a tachycardia event or respiratory rate in an apneic episode.

Clinical intervention in terms of endotracheal re-intubation was used as a surrogate marker of treatment failure in this study. Patients requiring endotracheal re-intubation during the entire course of caffeine citrate therapy were identified in the clinical notes. The underlying indications for re-intubation were divided into two subgroups, one subgroup was re-intubation secondary to worsening symptoms of apnea of prematurity, the other subgroup was re-intubation secondary to other respiratory failure etiologies, such as significant periodic breathing, increased work of breathing, increased CO_2 levels, significant episodes of bradycardia with desaturations, pleural effusions, pulmonary edema, and suspected infections (no culture confirmation).

Statistics

Differences in caffeine serum concentrations between dosing regimen groups were determined by Mann–Whitney *U* test. Linear regression was used to evaluate the association between PD effects and caffeine serum concentrations. The relationships between treatment efficacy and patient demographics were also evaluated by linear regression. Predicted probabilities for adverse events as a function of caffeine serum concentrations were assessed by logistic regression analysis. The number of patients requiring re-intubation or experiencing adverse events was compared among various dosing regimens via a $\chi 2$ test of independence. Statistics were performed using SAS software (version 9.3) (SAS Inc. North Carolina, USA) and differences were considered significant at $p < 0.05$.

Results

A total of 115 preterm neonates who received caffeine citrate therapy and underwent TDM in the post-extubation period were included in this study. A total of 177 blood samples were taken from these patients with a median (interquartile range) GA of 29 (28 – 30) weeks and birth weight of 1230 (997 – 1485) g (Table 1). Caffeine citrate therapy was started in patients at PNA of 1 (1 – 3) day or PMA of 29.4 (28.1 – 30.7) weeks. Blood samples were taken in patients with PNA of 15 (10 – 24) days or PMA of 31.6 (30.1 – 33.4) weeks (Table 1). Patients had a median of one sample taken for TDM. As shown in Table 2, 47 (40.9 %) patients received 40/5 mg/kg q12h regimen, 49 (42.6 %) patients received 20/5 mg/kg q24h. The dosing regimen of 40/5 mg/kg q12h led to significantly higher concentrations compared with the standard regimen 20/5 mg/kg q24h (median 23 vs 15 mg/L, $p < 0.001$). Patient demographics and clinical statuses were similar among dosing regimen groups (data not shown).

Out of 177 concentrations collected, 149 (84.2 %) concentrations had concurrent clinical notes that provided relevant PD information. Among the 149 concentrations, 125 (83.8 %) concentrations had concurrent heart rate and respiratory rate available in non-ventilated neonates, whereas 89 (59.7 %) concentrations had corresponding definitive number of apneic episodes recorded in non-ventilated neonates. Linear regression analysis on heart rate, respiratory rate, and episodes of apnea as a function of caffeine serum concentrations showed that heart rate was significantly associated with concentration ($p < 0.05$) (Fig. 1a). Although this relationship was statistically significant, the physiological effect was considered small

Table 1 Demographics of preterm neonates included in this study

Characteristics	Median (Interquartile range)	Range
Sex[a]	60 male, 55 female	
GA (week)	29 (28 – 30)	24–33
Birth weight (g)	1230 (997–1485)	607–2304
Apgar score, 1 min	6 (4–8)	1–9
Apgar score, 5 min	8 (7–9)	3–9
PNA at initiation (day)	1 (1–3)	0–25
PMA at initiation (week)	29.4 (28.1–30.7)	24.1–33.6
PNA at sampling (day)	15 (10–24)	3–84
PMA at sampling (week)	31.6 (30.1–33.4)	25.6–40.9

[a]Number

potentially due to the fact that retrospective records were used. The median (range) of heart rates at caffeine serum concentration of 5–10 mg/L and 30–35 mg/L were 160 (130–183) and 168 (151–175) $b \cdot min^{-1}$, respectively. No linear relationships were found for the other PD parameters (Fig. 1b, c). The relations between apnea episodes in the day and patient demographics were assessed. It was found that there was an inverse relationship between number of apnea episodes in the day and GA of neonates ($p < 0.05$) (Fig. 2a). Frequency of apnea episodes decreased significantly as PMA increased ($p < 0.05$) (Fig. 2b).

The most common adverse event during caffeine TDM was tachycardia. Out of 149 concentrations with concurrent medical records documented, there were 34 (22.8 %) concentrations associated with tachycardia, 3 (2.0 %) with tachypnea, and 1 (0.7 %) with mild hypertension, which were considered to be secondary to caffeine citrate therapy. The severity of recorded tachycardia was mostly mild to moderate with heart rate ranging from 170 – 212 $b \cdot min^{-1}$ amid an episode. The frequency of tachycardia or the percentage of samples with tachycardia relative to the concentration was plotted in Fig. 3. Predicted probabilities for tachycardia events as a function of caffeine serum concentrations were also shown in Fig. 4.

Out of 115 patients, a total of 27 patients (23.4 %) were re-intubated onto a mechanical ventilator during the entire course of caffeine citrate therapy, of which 10 patients (8.6 %) were re-intubated secondary to worsening symptoms of apnea. As shown in Table 3, there was no difference in re-intubation rate secondary to apnea of prematurity or other pulmonary etiologies between regimen 40/5 mg/kg q12h and standard 20/5 mg/kg q24h, however, regimen 40/5 mg/kg q12h led to significantly higher percentage of patients experiencing tachycardia than the standard regimen ($p < 0.001$). Patients going through re-intubation tend to be more preterm [mean (range) GA 27 (24–31) weeks] with less birth weight [963 (607 – 1892) g] than average statistics of this study population (Table 1). There was no difference in these patients' demographics among dosing regimens (Additional file 1: Table S1).

Table 2 Caffeine citrate dosing regimens and caffeine serum concentrations during TDM

Dosing regimens	Number of patients	Caffeine serum concentration (mg/L)
40/5 mg/kg		
q12h	47	23 (18–26)***
20/5 mg/kg		
q24h	49	15 (11–17)
q12h	8	17 (13–20)
5/5 mg/kg		
q24h	6	13 (8–17)
q12h	5	22 (21–23)

Data = median (interquartile range)
*** $p < 0.001$, significant differences were observed in caffeine serum concentrations between regimen 40/5 mg/kg q12h and standard 20/5 mg/kg q24h

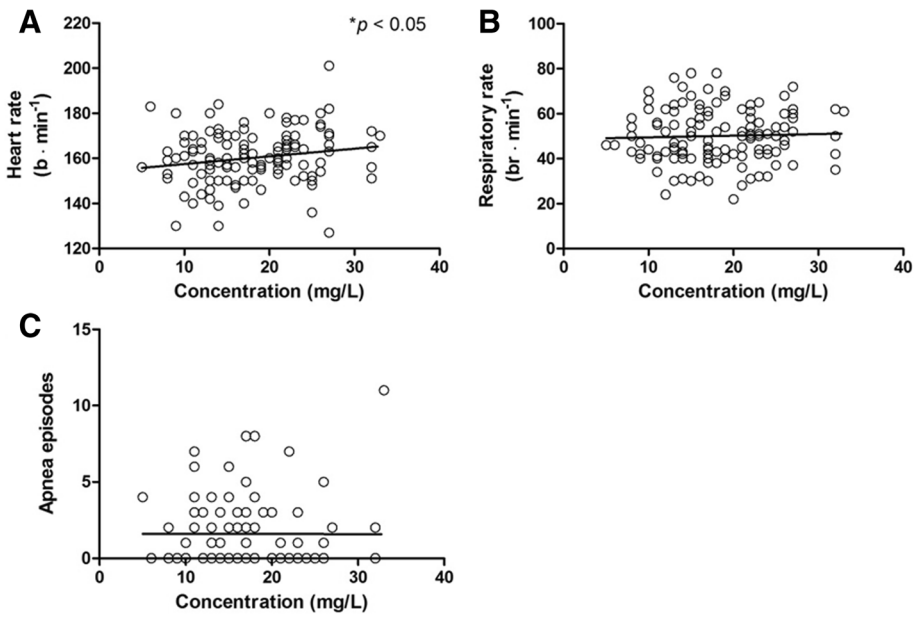

Fig. 1 Relation of **a** heart rate ($r^2 = 0.031$, $p = 0.04$), **b** respiratory rate ($r^2 = 0.001$, $p = 0.68$), **c** episodes of apnea ($r^2 < 0.001$, $p = 0.97$) recorded during the physical exam in the day of TDM as a function of caffeine serum concentration. Note: $b \cdot min^{-1}$, beats per minute; $br \cdot min^{-1}$, breaths per minute

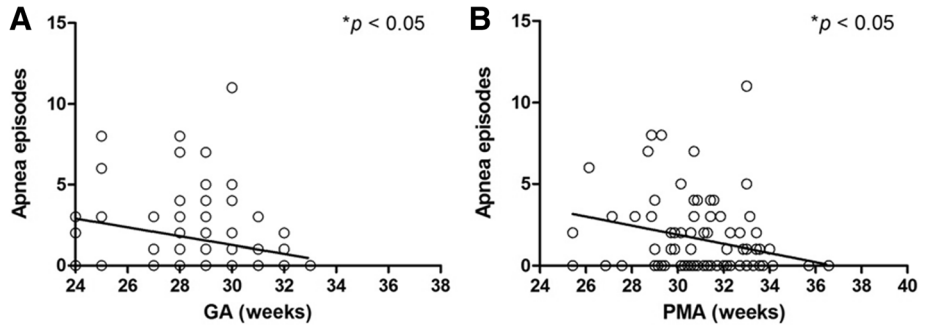

Fig. 2 Number of apnea episodes in the day of TDM as a function of **a** GA ($r^2 = 0.061$, $p = 0.01$), **b** PMA ($r^2 = 0.071$, $p = 0.01$) in preterm neonates

Discussion

The present study revealed that a correlation between number of apneic episodes and caffeine serum concentrations was not established under current dosing regimens. A significant association between heart rate and concentrations was found among the other PD parameters, consistent with the fact that the probability of tachycardia increased as caffeine serum concentration increased. A high dose regimen 40/5 mg/kg q12h led to similar re-intubation rate but significantly higher percentage of patients having tachycardia than standard regimen 20/5 mg/kg q24h, agreeing well with the PK/PD relationships found above. The total re-intubation rate of the standard regimen in our patients (24.5 %) was similar to that reported in the literature (24.0 %) [16].

The lack of correlation between efficacy and caffeine serum concentrations under current dosing regimens was in agreement with the trial that granted caffeine citrate label approval by FDA, which reported no association between success of ≥ 50 % reduction or elimination in apnea events and mean daily caffeine concentrations.[3] Skouroliakou et al.'s study also revealed that methylxanthine concentrations were not significantly associated with number of apneic events per day in neonates with GA < 33 weeks [17]. A previous study comparing 10 mg/kg and 5 mg/kg maintenance doses in neonates with GA < 32 weeks showed similar efficacy in reducing apnea spells despite significantly higher frequency of tachycardia in the 10 mg/kg group [18]. It could be partially due to the underlying multifactorial etiology of apnea, with prematurity being a prerequisite for the indication [19]. Apnea of prematurity is known to have an incidence inversely related to GA and could regress with the maturation of the newborn [19]. This is echoed in our results that the number of apnea episodes reduced significantly as PMA increased as well as in patients with higher GA (Fig. 2).

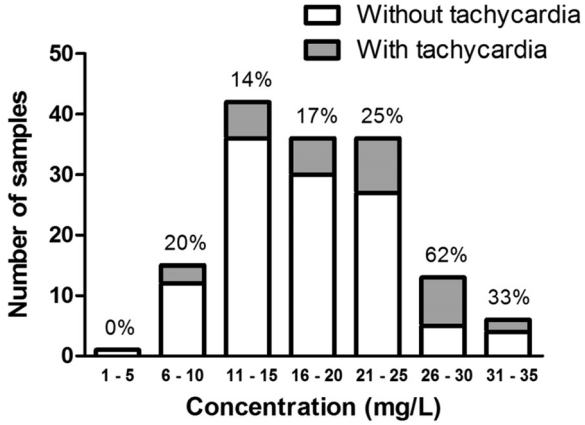

Fig. 3 The frequency of tachycardia or the percentage of samples with tachycardia relative to caffeine serum concentration in preterm neonates

The variable PK/PD response in neonates to caffeine citrate therapy is also likely to be attributed to variability in caffeine metabolism in individuals. Caffeine metabolism by hepatic enzymes is usually limited in neonates. Maturation of metabolic enzymes could lead to the improvement in metabolic function, which is significantly associated with the increase in PNA and varies extensively among individuals (range 1 %–41 %) [20]. N7-demethylation, which produces theophylline, acts as the predominant metabolic pathway in premature neonates (range 1 %–37 %) [20]. Theophylline is the active metabolite that is partially responsible for side effects such as tachycardia [18], the variable caffeine-theophylline conversion rate could lead to PD response variability. Several other factors, including genetic variation in hepatic metabolic enzymes and genetic variations in caffeine receptors may also contribute to the variability in PD responses [21–23]. Due to the variability in the caffeine metabolism and the resulting wide range of half-lives among individuals [10], the measurement of caffeine serum concentrations at a postnatal age of 15 (10–24) days in our study population may not necessarily reflect concentrations at steady state. Thus, caffeine concentrations may vary considerably and make it difficult to find other significant associations between PD responses and concentrations.

The 2-fold higher-than-standard dosing regimen led to similar re-intubation rate but significantly higher

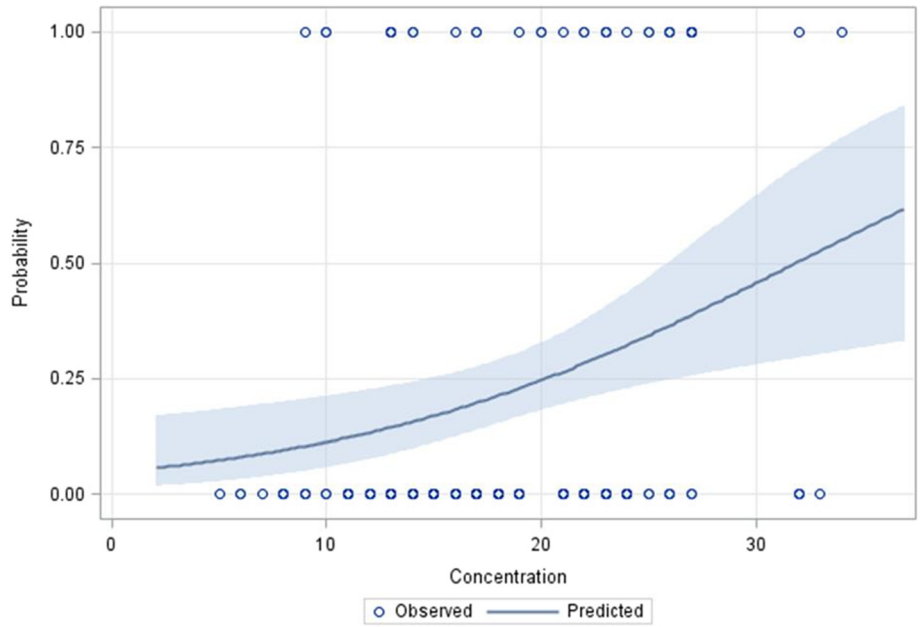

Fig. 4 Predicted probabilities of tachycardia as a function of caffeine serum concentration in preterm neonates. An open circle represents the presence (probability = 1) or absence (probability = 0) of a tachycardia event at the corresponding concentration. The solid line with blue band represents estimated probability and the 95 % confidence limits

percentage of patients having tachycardia than standard regimen. This is similar to Steer et al.'s findings on the use of 3–6 fold higher maintenance doses for a course of 7 days in neonates of similar GA range (<32 weeks) to our study's (<33 weeks) [24]. A significant reduction in re-ventilation was shown when 4-fold higher maintenance doses were used for the duration of averagely 1 month in neonates with GA < 30 weeks [16]. This effect was more evident in the stratified subgroup of neonates with GA < 28 weeks that a significant reduction in the days on mechanical ventilator (average 8 days) was observed [16]. A retrospective study in neonates < 28 weeks GA revealed that patients receiving caffeine citrate > 7.9 mg/kg/day were associated with a decreased need for clinical interventions in terms of dose adjustments compared to those receiving ≤ 7.9 mg/kg/day doses [25]. It suggests that neonates with lower GA, especially extremely low-gestational-age neonates (GA < 28 weeks), could benefit more from high doses of caffeine citrate. Dosing regimens stratified by GA is warranted for more systematic trial evaluation.

Table 3 Summary of clinical interventions/adverse events in terms of re-intubation and tachycardia among dosing regimens

Dosing regimens	Number of patients going through re-intubation (%)		Number of patients having tachycardia (%)
	Secondary to apnea of prematurity	Secondary to other respiratory etiologies	
40/5 mg/kg			
q12h	4 (8.5 %)	7 (14.9 %)	21*** (44.7 %)
20/5 mg/kg			
q24h	4 (8.2 %)	8 (16.3 %)	5 (10.2 %)
q12h	0	1 (12.5 %)	4 (50.0 %)
5/5 mg/kg			
q24h	2 (33.3 %)	0	1 (16.7 %)
q12h	0	1 (20.0 %)	0

***$p < 0.001$, regimen 40/5 mg/kg q12h led to significantly higher percentage of patients experiencing tachycardia secondary to caffeine citrate therapy than standard 20/5 mg/kg q24h

None of the neonates died or had a severe reaction under current dosing regimens, however, TDM may be helpful in suspected toxicity to diagnose caffeine-related adverse events, based on our findings on a significant association between tachycardia and caffeine serum concentrations. The use of high dose caffeine citrate inevitably increases the risk of tachycardia in neonates, this need to be taken into consideration combined with other elements of therapy, such as efficacy and requirement for respiratory support, to determine treatment priority in lieu of medical cost and facility resources available. Caffeine TDM is valuable in the setting of clinically-significant tachycardia to assist differential diagnosis with respect to other potential etiologies.

This study has several limitations associated with its nature of retrospective chart evaluation. First, the TDM was done at the discretion of the medical team and may have patient selection bias towards sicker patients or patients who had adverse events. Second, vital signs were measured during the physical exam in the day of TDM, thus, they

were the approximate rather than the exact values at TDM sampling time. Third, the records were physician notes that were not verified by audits of electronic monitoring, however, they are the critical information used by clinicians for patient management and decision making.

Conclusion

Based on our analysis on the retrospective dataset, little correlation between episodes of apnea and caffeine serum concentrations was observed in neonates who had TDM in the post-extubation period under current dosing regimens, whereas a significant association between tachycardia and concentrations existed. Notwithstanding the absence of severe adverse reactions, TDM should be considered in critically ill neonates with unexplained adverse effects, such as tachycardia. Future prospective study is warranted to establish the linked PK/PD relationship to optimize dosing regimen in preterm neonates.

Availability of supporting data

Supporting data are available in the form of an extended study report to the ethics committee of the University of Utah Institutional Review Board. This report is available upon request, which should be addressed to the corresponding author.

Additional file

Additional file 1: Table S1 Demographics of preterm neonates stratified by major dosing groups (DOCX 14 kb)

Abbreviations

GA: gestational age; PD: pharmacodynamics; PK: pharmacokinetics; PMA: post-menstrual age; PNA: post-natal age; TDM: therapeutic drug monitoring.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CS and RW developed the idea for this study, KK extracted data for this study, TY did the study design, completed the data analysis, and wrote the manuscript, AB assisted with statistical analysis, RW provided clinical consultation on this work. All authors reviewed the manuscript, provided critical feedback, and approved its journal submission.

Acknowledgements

This project was supported in part by a Primary Children's Hospital Foundation Early Career Development Research Grant for Catherine M. T. Sherwin. Authors would like to thank Chris R. Stockmann for assistance with clinical note information.

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Received: 7 November 2015 Accepted: 29 April 2016
Published online: 07 June 2016

References

1. Bhatt-Mehta V, Schumacher RE. Treatment of apnea of prematurity. Paediatr Drugs. 2003;5:195–210.
2. Schoen K, Yu T, Stockmann C, Spigarelli MG, Sherwin CM. Use of methylxanthine therapies for the treatment and prevention of apnea of prematurity. Paediatr Drugs. 2014;16:169–77.
3. Erenberg A, Leff RD, Haack DG, Mosdell KW, Hicks GM, Wynne BA. Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study. Pharmacotherapy. 2000;20:644–52.
4. Aranda JV, Gorman W, Bergsteinsson H, Gunn T. Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. J Pediatr. 1977;90:467–72.
5. Kulkarni PB, Dorand RD. Caffeine toxicity in a neonate. Pediatrics. 1979;64:254–5.
6. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. N Engl J Med. 2006;354:2112–21.
7. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med. 2007;357:1893–902.
8. Natarajan G, Botica ML, Thomas R, Aranda JV. Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? Pediatrics. 2007;119:936–40.
9. Leon AE, Michienzi K, Ma CX, Hutchison AA. Serum caffeine concentrations in preterm neonates. Am J Perinatol. 2007;24:39–47.
10. Charles BG, Townsend SR, Steer PA, Flenady VJ, Gray PH, Shearman A. Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. Ther Drug Monit. 2008;30:709–16.
11. Gal P. Caffeine Therapeutic Drug Monitoring Is Necessary and Cost-effective. J Pediatr Pharmacol Ther. 2007;12:212–5.
12. Gal P. Optimum use of therapeutic drug monitoring and pharmacokinetics-pharmacodynamics in the NICU. J Pediatr Pharmacol Ther. 2009;14:66–74.
13. Ward RM, Lugo RA. Drug therapy in the newborn. In: MacDonald MG, Seshia MMK, Mullett MD, editors. Avery's neonatology: pathophysiology & management of the newborn. 6th ed. Philadelphia PA: Lippincott Williams & Wilkins; 2005. p. 1507–56.
14. Spector R, Park GD, Johnson GF, Vesell ES. Therapeutic drug monitoring. Clin Pharmacol Ther. 1988;43:345–53.
15. Pesce AJ, Rashkin M, Kotagal U. Standards of laboratory practice: theophylline and caffeine monitoring. National Academy of Clinical Biochemistry. Clin Chem. 1998;44:1124–8.
16. Steer P, Flenady V, Shearman A, Charles B, Gray PH, Henderson-Smart D, et al. High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. Arch Dis Child. Fetal Neonatal Ed. 2004;89:499–503.
17. Skouroliakou M, Bacopoulou F, Markantonis SL. Caffeine versus theophylline for apnea of prematurity: a randomised controlled trial. J Paediatr Child Health. 2009;45:587–92.
18. Romagnoli C, De Carolis MP, Muzii U, Zecca E, Tortorolo G, Chiarotti M, et al. Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants. Ther Drug Monit. 1992;14:14–9.
19. Paolillo P, Picone S. Apnea of prematurity. J Pediatr Neonatal Individ Med. 2013;2:1–7.
20. Al-Alaiyan S, Al-Rawithi S, Raines D, Yusuf A, Legayada E, Shoukri MM, et al. Caffeine metabolism in premature infants. J Clin Pharmacol. 2001;41:620–7.
21. Bloch-Salisbury E, Hall MH, Sharma P, Boyd T, Bednarek F, Paydarfar D. Heritability of apnea of prematurity: a retrospective twin study. Pediatrics. 2010;126:779–87.
22. Kumral A, Tuzun F, Yesilirmak DC, Duman N, Ozkan H. Genetic basis of apnoea of prematurity and caffeine treatment response: role of adenosine

receptor polymorphisms: genetic basis of apnoea of prematurity. Acta Paediatr. 2012;101:299–303.
23. Pacifici GM. Clinical pharmacology of caffeine citrate in preterm infants. Med expr. 2014;1:243–50.
24. Steer PA, Flenady VJ, Shearman A, Lee TC, Tudehope DI, Charles BG. Periextubation caffeine in preterm neonates: a randomized dose response trial. J Paediatr Child Health. 2003;39:511–5.
25. Francart SJ, Allen MK, Stegall-Zanation J. Apnea of prematurity: caffeine dose optimization. J Pediatr Pharmacol Ther. 2013;18:45–52.

Ali et al. BMC Pediatrics (2018) 18:9
DOI 10.1186/s12887-017-0978-6

BMC Pediatrics

RESEARCH ARTICLE Open Access

Caffeine is a risk factor for osteopenia of prematurity in preterm infants: a cohort study

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Abstract

Background: Caffeine, the most commonly used medication in Neonatal Intensive Care Units, has calciuric and osteoclastogenic effects.

Methods: To examine the association between the cumulative dose and duration of therapy of caffeine and osteopenia of prematurity, a retrospective cohort study was conducted including premature infants less than 31 weeks and birth weight less than 1500 g. Osteopenia of prematurity was evaluated using chest X-rays on a biweekly basis over 12 weeks of hospitalization.

Results: The cohort included 109 infants. 51% had osteopenia of prematurity and 8% had spontaneous rib fractures. Using the generalized linear mixed model, caffeine dose and duration of caffeine therapy showed a strong association with osteopenia of prematurity. Steroids and vitamin D were also significantly correlated with osteopenia of prematurity while diuretic use did not show a statistically significant effect.

Conclusion: The cumulative dose and duration of therapy of caffeine, as well as steroid are associated with osteopenia of prematurity in this cohort. Future studies are needed to confirm these findings and determine the lowest dose of caffeine needed to treat effectively apnea of prematurity.

Keywords: Premature infants, Osteopenia of prematurity, Metabolic bone disease, Caffeine

Background

Approximately 80% of bone mineralization of the newborn takes place during the third trimester of pregnancy because of the high rate of intrauterine growth [1]. Thus, preterm infants whom deprived of that period, are born with less bone mineral content. In addition, physiological adaptation of bone to extra-uterine life leads to an increase in bone resorption. This process occurs earlier in preterm than in term infants and can be accompanied by high risk of bone fragility and fractures [2]. Bone resorption appears to be more important than decreased bone formation in the pathogenesis of osteopenia of prematurity (OP) [3].

Almost 10% of infants are born prematurely worldwide, representing more than 15 million births every year. The incidence and severity of osteopenia of prematurity increase as the birth weight (BW) and gestational age (GA) decrease [4]. Preterm infants are known to have a lower bone density (BMD) and bone mineral content (BMC) [2] at the corrected age of term, as well as a lower weight and Ponderal index [5]. Moreover, preterm infants have lower bone strength at the distal tibia and radius compared to age and sex-matched controls, when assessed with computerized tomography as young adults [6].

In 1989, the incidence of OP was 55% of infants <1000 g and 23% of infants <1500 g at birth. A notable finding at this time was that OP risk showed an inverse relationship to lower GA and a direct relationship to duration of parenteral nutrition [7]. In 2009, a study

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reported pathological fractures in 30% of preterm infants with osteopenia [8].

Caffeine is the most commonly consumed pharmacologically active compound in the world [9]. In the neonatal intensive care units (NICU), it is one of the most commonly prescribed drugs to treat apnea of prematurity [10]. The half-life in neonates is 72–96 h (range: 40–230 h) and the time to peak serum concentration after oral administration ranges from 30 min to 2 h, whereas 86% of caffeine is excreted unchanged in urine [11]. The liver enzymes responsible for caffeine metabolism mature progressively with increasing GA. Girls were reported to have a higher rate of caffeine metabolism than boys [12]. Clearance of caffeine in infants born prematurely is markedly lower and the volume of distribution is higher than infants at term-equivalent age and beyond. Elimination of caffeine is initially depressed in extremely premature infants and then increases nonlinearly to final assessment at 6 weeks postnatal age [13]. It is well established that caffeine causes calciuria and creates negative calcium balance in preterm rats especially after prolonged use with compensatory increase in PTH to normalize serum calcium at the expense of bone [14–16]. Tolerance to the renal effects of caffeine does not develop with chronic use [17].

In a study in mice, it was found that caffeine effectively enhanced the osteoclastogenesis from bone marrow hematopoietic cells and bone resorption activity as assessed by the pit formation assay [18]. In another study, BMD was significantly lower in growing rats supplemented with 0.2% caffeine in diets for 20 weeks compared with the control group. Additionally, the calcium content in tibiae and femora of caffeine-treated rats was also lower, and the osteoclastogenesis of bone marrow cells isolated from caffeine-treated rats was markedly enhanced as compared with that in the control group. Taken together, these results suggest that caffeine reduces BMD through the enhancement of osteoclastogenesis and its calciuric effect [19].

Based on existing studies we hypothesize that caffeine usage, cumulative dose or duration of usage are associated with OP. and this association exists even when controlled for the effects of other neonatal risk factors.

The primary outcome of this study was to determine the effect of the cumulative dose and the duration of caffeine on OP. Other covariates of interest were included in the analysis, steroids and diuretics cumulative dose vitamin D intake, and maternal parity.

Methods

This retrospective quantitative descriptive pilot cohort study was conducted at Health Sciences Centre in Winnipeg, Manitoba, Canada, from October 2007 to June 2012. Premature infants <31 weeks gestation and birth weight < 1500 g infants were included, all infants had at least 12 weeks of hospital stay. It is difficult to implement case control study having infants with no caffeine intake as all admitted infants less than 33 weeks are on caffeine by hospital guidelines. We excluded infants with congenital anomalies, infants with gut surgery affecting feeding, infants with non-osteopenic fractures, and infants with insufficient data to analyze. The data were collected from the charts in the medical record. The study included 109 infants who met the inclusion criteria. Cases of osteopenia were defined if they have radiological evidence of osteopenia of prematurity.

The data included: GA in weeks, gender, birth weight, average biweekly weight, total parenteral nutrition (TPN) days, and maternal parity level. The later was recorded as categorical data; high if >5, moderate if 3 or 4 and low parity if 1 or 2. Average biweekly vitamin D intake was included as longitudinal data. Serum phosphate measurements were collected on biweekly basis +/−1 week. The phosphate level was recorded as categorical data; high if >2.5 mmol/l, normal if between 1.8 to 2.5 mmol/l, low if between 1.3 to 1.8 mmol/l and very low if <1.3 mmol/l. The radiological data (X rays) were reviewed and interpreted, by a pediatric radiologist and the writer, (the Cohen's kappa was 0.83 and 95% CI 0.82 to 0.084, which indicates very good interrater agreement) [20] both did not know the infants 'clinical status or biochemical data at the time of the interpretation, on a biweekly basis at least for the first 12 weeks of life, using Koo et al. criteria [21]. Table 1.

The descriptive statistics (means and standard deviations) or (median and quartile) were used to summarize the characteristics of the sample. As the grade level of bone of newborn infants was measured fortnightly from birth to 12 weeks old, the binary outcome variables (OP) (0, 1), are longitudinal with up to 7 time points. It was preferable to include grade 1 and 2 of OP together, as the differentiation between the two grades is very subjective. Grade 3 OP was easier to distinguish, as callus formation was indicative of previous underlying spontaneous fracture. Due to the limited sample size, we dichotomized the radiological grading of OP by collapsing grades 1, 2 and 3 together as OP. At the same time, we

Table 1 Koo et al. Criteria for osteopenia of prematurity

Grades	Description
Grade 0:	Normal density of bone cortex along shaft with normal dense white line at metaphysis and normal band of lucency, and thinning of cortex.
Grade 1:	Loss of dense white line at the metaphysis, increased sub-metaphyseal lucency and thinning of cortex.
Grade 2:	Changes in grade 1 plus irregularity and fraying of metaphysis, with splaying and cupping that is indicative of rickets.
Grade 3:	Indications of rickets with evidence of fractures.

considered grade 0 as normal. We assessed the OP status for every two weeks, Therefore, the generalized linear mixed model was used for repeated measures of binary outcome (OP status) [22].

The cumulative dose of caffeine were included in the generalized linear mixed model as covariates. Other covariates added to the generalized linear mixed model included doses of steroids, diuretics, vitamin D intake, and other demographic variables such as GA in weeks and gender. Vitamin D intake, average biweekly weight, and serum phosphate were treated as time-varying covariates. To examine whether the effect of duration of caffeine treatment on OP, a generalized linear mixed model was fitted by including the interaction between caffeine dosage and duration of therapy, and other covariates. The statistical analyses were carried out using SAS 9.3 (SAS Institute, Cary, NC). All p-values are two-sided, and significance was set at a value of 0.05.

Results

The initial cohort included 335 preterm infants, with GA of less than 31 weeks and birth weight less than 1500 g, who were admitted to the NICU between July 2007 and July 2012. Of these 335 infants, 35 infants died, 5 infants were transferred to other facilities and 3 others who had surgical necrotizing enterocolitis with short bowel syndrome were also excluded. Out of the remaining 292 infants, the final study group included 109 infants who had the required 12 weeks of hospital stay, radiological data and laboratory data to analyze.

The raw data were examined for any outliers and influential points before the start of the analysis. The results of GA, birth weight, sex, maternal parity and (TPN) duration are shown in Table 2 as mean ± 2SD, and average biweekly weight and vitamin D intake in Table 3 as mean ± 2SD.

There were 8 infants with bone fractures (8%). The fractures involved the right and left lower ribs and none of them had a spontaneous fracture of the humerus. The prevalence of OP based on Koo et al. in this cohort was 51.3%.

Table 2 The cohort biometric data

Variables	
Gestational Age (weeks) (mean ± 2SD)	27 ± 1.6
Birth Weight (grams) Mean ± 2SD	665 ± 229
Male/Female	54 male/55 female
Maternal Parity	
Low parity < 2	85 (77.9%)
Moderate parity2–4	16 (14.6%)
High parity > 4	8(7.5%
TPN days	
(Median)	21
Quantiles	11, 32

All the infants received caffeine during their hospital stay, starting day one. The mean ± 2SD dose of caffeine was 425.33 ± 235.2 mg as a cumulative dose and the mean ± 2SD duration of caffeine therapy was 60 ± 45.8 days. The mean ± 2SD dose of caffeine was 7.95 ± 2.7 mg per kg per day and the range of caffeine dose was (4.1–15.6 mg/kg/day) including the loading, the maintenance dose and the mini-load doses. The usual starting load was 10 mg/kg followed by maintenance of 5–7 mg/kg/day and the infant received mini-loads of caffeine in-between according to the severity of apnea of prematurity as long as the heart rate was less than 180 beat/min. During the study time, there was no systematic protocol to monitor the serum caffeine level.

There were 79 infants who received diuretics (73%). The median diuretic dose was 5.9 mg with 1st and 3rd quartiles of 1, 25.8 during the hospital stay. The steroids were calculated as dexamethasone dose or equivalent as 100 mg of hydrocortisone are equal to 20 mg of dexamethasone. In this cohort, the median steroid dose was 2 mg and the 1st and 3rd quartiles were 0, 42 mg during the hospital stay.

We first fitted a logistic regression model to examine each individual variable associated with the probability of OP, including gestational age, average biweekly birth weight, maternal parity, TPN duration, vitamin D intake, and serum phosphate level, duration of caffeine treatment and the cumulative doses of caffeine, steroids, and diuretics. The results are presented in Table 4. Table 4 shows that lower gestational age and average biweekly weight are correlated with OP. Similarly, higher caffeine cumulative dose and longer caffeine duration of therapy showed a statistically significant correlation with OP ($p^* < 0.05$). In the univariate model; steroids doses, TPN days and average biweekly intake of vitamin D displayed significant correlation with OP. On the contrary, maternal parity, serum phosphate and diuretics were not associated with OP ($p > 0.05$) in this study. The maternal parity was analyzed as low parity if less than 2 and moderate parity if more than 2. Similarly, serum phosphate was categorized as very low if less than 1.3 mmol/l and low if between 1.3 and 1.8 mmol/l and normal if more than 1.8 mmol/l.

Then we fitted a logistic multivariable generalized linear mixed model with gestational age, average biweekly weight, cumulative dose of caffeine, cumulative steroids dose and vitamin D considering the clinical importance and statistical significance at univariate analysis. The results are showed in Table 5.

Table 5 indicates that higher cumulative dose of caffeine is associated with an increase in the probability of

Table 3 The average biweekly weight and vitamin D intake of the study cohort

	Week1–2	Week3–4	Week5–6	Week7–8	Week9–10	Week11–12
Average weight in grams (mean ± 2SD)	993 ± 23	1108 ± 2	1335 ± 29	1660 ± 4	1984 ± 4	2348 ± 5
Average Vitamin D in units (mean ± 2SD)	392 ± 35	555 ± 37	737 ± 33	834 ± 29	947 ± 29	1034 ± 32

OP. The effect of caffeine was true even when we controlled the effect of other variables (average weight, the gestational age, steroid and vitamin D). The odds of OP is 1.10 times (95%CI: 1.05–1.15) higher for every 5 mg/kg increase in cumulative caffeine dose when other factors are controlled.

The steroid dosage has a statistically significant result in predicting OP with ($p^* < 0.0001$) (estimated Odds ratio = 1.1 and CI: 1.005–1.20).

The results showed that the average biweekly vitamin D intake, both included in the diet and supplemented, had a negative correlation with the OP ($p^* < 0.0001$). The probability of OP is decreased by 0.4% when vitamin D increased from 400 to 800 units.

Figure 1 shows the effect of increasing caffeine dosage on the probability of OP over time in different gestational age (25 weeks GA = 15 infants and 30 weeks GA = 25 infants) based on the above fitted logistic generalized linear mixed model.

To examine whether the effect of duration of caffeine treatment, we fitted another generalized linear mixed model by including the interaction between caffeine dosage and duration of therapy, and other covariates, the results are showed in Table 6. This table shows that, the average caffeine dose, caffeine duration of therapy as well as the interaction between caffeine dose and duration of caffeine treatment has a statistical significant correlation with OP even when controlling for the effects of gestational age, weight and vitamin D ($p < 0.05$).

Based on the model in Table 6, Figs. 2 and 3 show the effect of duration of caffeine usage on the probability of OP based on the logistic model. The probability of OP increased in 25 weeks preterm infants (15 infants), is higher than the 30 weeks preterm infants (25 infants). The figure exhibited that the lower the gestational age the higher the probability of osteopenia over prolonged caffeine use, even when controlling caffeine dose, steroid dose, birth weight, and vitamin D.

Table 4 Factors associated with OP: Results of univariate analysis

Variables	Estimate	Standard Error	*P* value
Gestational age (weeks)	−0.645	0.147	<0.001*
Average biweekly weight (grams)	0.0006	0.0002	0.006*
Caffeine cumulative dose (mg)	0.005	0.001	<0.001*
Caffeine duration (days)	0.051	0.013	<0.001*
Steroids cumulative dose (mg)	0.09	0.046	0.038
TPN duration (days)	0.034	0.012	0.005*
Vitamin D (units)	−1.863	0.36	<0.001*
Diuretics cumulative dose (mg)	0.003	0.002	0.20
Serum phosphate (mmol/l)			
Phosphate <1.3	−0.09	0.16	0.57
Phosphate (1.3–1.8)	0.11	0.33	0.74
Phosphate >1.8 (ref)			
Maternal Parity			
Low parity	−0.016	0.42	0.96
Moderate Parity (ref)			

* Means significant

Discussion

Although the overall survival of extreme low birth weight infants has improved over the past 2 decades, these infants continue to have significant comorbidities. The prevalence of OP in our study is similar to that previously reported in the literature and suggests that OP remains a significant comorbidity in extreme low birth weight infants and puts them at increased risk for spontaneous fractures during the NICU stay. Our results are consistent with this concept, the younger and smaller the babies, the higher the incidence of OP.

The results of this study revealed a strong correlation between caffeine treatment and the presence of OP. Despite caffeine's effect on treating apnea of prematurity with favorable long-term outcomes [23], our study revealed a strong association between cumulative dosage and duration of treatment with caffeine and OP even when controlling for the effect of other risk factors. The results show that the adverse effect of caffeine is more evident in lower gestational age infants, which may be

Table 5 Results from Multivariable generalized linear mixed model

Effect	Estimate (logit)	Standard Error	*P* value
Intercept	5.63	5.59	0.321
Caffeine Cumulative Dose (mg)	0.39	0.05	0.007*
Steroid Cumulative Dose (mg)	0.17	0.05	0.035*
Vitamin D (units)	−1.64	0.47	0.006*
Average Biweekly Weight (grams)	−0.01	0.0001	<0.0001*
Gestational age (weeks)	−0.41	0.19	0.0408*

p^* = significant value

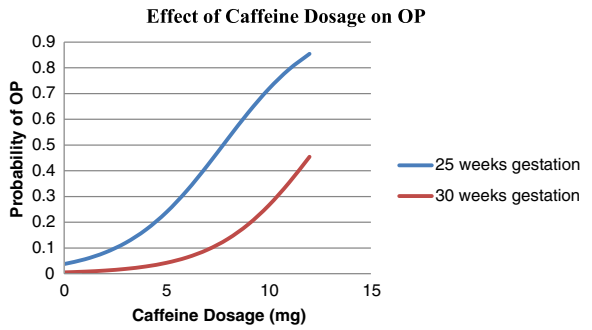

Fig. 1 Probability of OP with increasing caffeine dosage at 25 weeks and at 30 weeks gestational age based on the logistic model

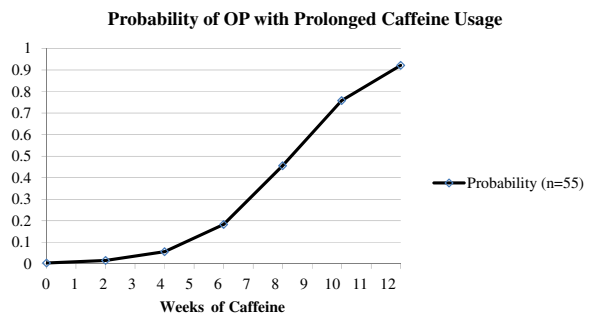

Fig. 2 Probability of OP with prolonged caffeine use based on the logistic model

explained by the prolonged half-life of caffeine in their bodies due to diminished kidney abilities to eliminate the caffeine. Furthermore, extreme preterm infants have immature liver enzymes and are unable to catabolize caffeine leading to a prolonged effect causing calciuria and osteoclastogenesis [14, 19].

In contrast to the current study results, a retrospective study done by Viswanathan et al. (2014), showed that there was no difference in duration of caffeine use between cases of OP and the control group. Viswanathan et al. did not calculate caffeine dose, only caffeine duration was tracked between cases and controls. Additionally, in the Viswanathan et al. (2014) study, infants with spontaneous rib fractures were included in the control group if there was no radiological evidence of OP. In our study, the osteopenic fractures were encompassed in the cohort data and identified as having severe grade osteopenia. The average duration of caffeine treatment in both groups in the Viswanathan et al. study was 40 days, while in our study, the average duration of caffeine treatment was 60 days [24].

Our current study was a retrospective one and there was no accurate documentation of maternal caffeine intake during pregnancy and lactation time. However, it is worth mentioning that in an animal study, maternal caffeine intake negatively affected bone formation and development [25]. Thus our results may still imply an effect of maternal caffeine exposure either in utero or through mother's breast milk and donor breast milk. However, the high doses of caffeine prescribed for apnea of prematurity have paramount contribution to OP.

In this study, there was no difference between male and female infants regarding OP, which is in agreement with another comparable study [26]. But our results do differ from other published studies which found that male infants have higher bone density than females when comparing preterm male and female infants with male and female full term newborns. Such an observation may follow a recognizable trend for testosterone hormone in utero [27, 28].

This study showed significant effect of TPN duration on the development of OP but this effect disappeared when we controlled for other risk factors. This can be explained by considering that other factors contribute more to OP, and that TPN contains the maximum amount of calcium and phosphate according to the

Table 6 Estimates with interaction of caffeine and duration of treatment

Effect	Estimate (logit)	Standard Error	P
Intercept	3.39	5.99	0.57
Average Caffeine dose (mg/kg/d)	0.24	0.09	0.029*
Duration of caffeine treatment (days)	0.64	0.27	0.02*
Caffeine dose* Duration of caffeine treatment (days)	0.07	0.04	0.05*
Steroid cumulative dose (mg)	0.09	0.05	0.07
Vitamin D (units)	−1.86	0.36	0.04*
Average biweekly Birth Weight (grams)	−0.06	0.02	0.001*
Gestational age (weeks)	−0.64	0.15	0.001*

*p** Indicates significant level

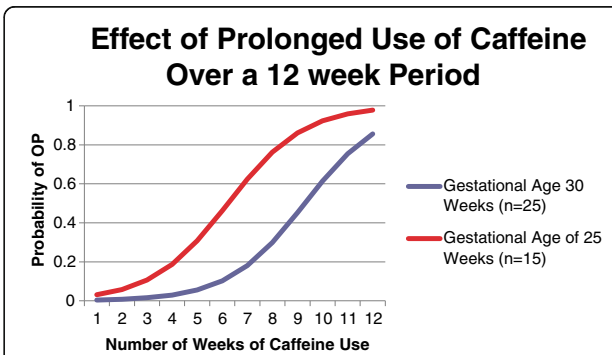

Fig. 3 Probability of OP with same Caffeine dosage at 25 weeks and 30 weeks gestational age over the weeks of treatment based on the logistic model

maximum solubility allowed [29]. In this study, TPN duration count included the null per os days as well as partial feeding days. During the study time, TPN is provided till the infant can tolerate the full enteral feeding.

Although Backström et al. suggested that serum phosphate levels lower than 1.8 mmol/L (5.5 mg/dl) may have a diagnostic sensitivity of 100% and specificity of 70% for OP [30], in our study, serum phosphate on biweekly basis did not show a statistically significant correlation with OP. No other published studies have examined serum phosphate as a longitudinal marker over the hospital stay. Yet, serum phosphate is among the minerals that are regulated tightly, and the average biweekly record may not represent the real situation of serum phosphate in infants on TPN for the first week at least and partial feeding for another week. In agreement with our results, Aly et al., (2005) found that serum phosphate as a single reading at birth was not correlated with OP in preterm infants [27]. In another study serum phosphate and serum alkaline phosphatase were correlated with OP later in infancy, which could be explained by the other confounding factors and medications received that affect premature bone in early life in NICUs [31, 32].

While it is documented that the number of previous pregnancies of a healthy mother correlated negatively with BMD measurements, the effect of previous pregnancies did not show the same effect on infants' bone formation. This supports the fact that an infant acquires the needed minerals and vitamin from the mother's body with active transport against the concentration gradient ignoring the mother's general status [33]. In our study, there was no significant effect of maternal parity on OP. On the other hand, this cohort study with limited sample size did not have enough high parity mothers to detect a correlation, and thus further research is needed that includes high parity mothers.

Our study results show a statistically significant correlation between OP and steroid cumulative dose, while diuretics did show a positive trend in relation to OP. This correlation did not reach statistical significance. This result can be explained by the short duration of diuretics use and the relative small sample size. The use of high dose of caffeine that has a diuretic effect might explain the lower need for the diuretic use.

Conclusions

We conclude that caffeine has a strong association with OP. As limit of viability continues to decrease with 70% survival of infants between 24 and 26 weeks, OP will continue to increase and will results in significant morbidity in childhood and adulthood unless strategies to mitigate risk factors are developed. Our study was limited by the small sample size. The study was conducted at one center, and thus the results may not be generalizable on a wider scale. Further studies are needed to determine effective lower caffeine dosage, different ventilation strategies, adequate vitamin D intake, and passive movement as all these can provide protection against OP.

Abbreviations

BMC: Bone mineral content; BMD: Bone mineral density; BW: Birth weight; GA: Gestational age; NICU: Neonatal intensive care unit; OP: Osteopenia of prematurity; PTH: Parathyroid hormone; TPN: Total parenteral nutrition

Acknowledgements

I acknowledge Mr. Lin Xue and Miss. Aliaa El Tobgy for their help in the data management.

Funding

This study was not funded from any source.

Availability of data and materials

Data will not be shared. The data will be used for other studies.

Authors' contributions

Dr. EA have made the acquisition of data, analysis and interpretation of data and discussion writing. Dr. CRG and MN have been involved in drafting the manuscript and revising it critically for important intellectual content. Dr. MM have made substantial contributions to conception and design ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Dr. MR agreed to be accountable for all aspects of the work related to the radiological data interpretation and drafting the manuscript. Dr. DJ have been involved in all stages of this study and drafting the manuscript and given final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Health Research Ethics Board (HREB) at University of Manitoba number# H2013: 231, and the Health Sciences Center Research Impact Approval from the Health Science Center. Number# RI2013: 088. The included data were retrospective data from medical records and did not include any identifying information. Consent to participate is not applicable for this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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Received: 9 September 2015 Accepted: 28 December 2017
Published online: 22 January 2018

References

1. Specker B. Nutrition influences bone development from infancy through toddler years. J Nutr. 2004;134(3):691S–5S.
2. Bowden LS, Jones CJ, Ryan SW. Bone mineralisation in ex-preterm infants aged 8 years. Eur J Pediatr. 1999;158(8):658–61.

3. Tsukahara H, Takeuchi M, Fujisawa K, Miura M, Hata K, Yamamoto K, Mayumi M. High-turnover osteopenia in preterm infants: determination of urinary pyridinium cross-links of collagen. Metabolism. 1998;47(3):333–5.
4. Backstrom MC, Kuusela AL, Maki R. Metabolic bone disease of prematurity. Ann Med. 1996;28(4):275–82.
5. Embleton N, Wood CL. Growth, bone health, and later outcomes in infants born preterm. J Pediatr. 2014;90(6):529–32.
6. Backstrom MC, Kuusela AL, Koivisto AM, Sievanen H. Bone structure and volumetric density in young adults born prematurely: a peripheral quantitative computed tomography study. Bone. 2005;36(4):688–93.
7. Koo WW, Sherman R, Succop P, Krug-Wispe S, Tsang RC, Steichen JJ, Crawford AH, Oestreich AE. Fractures and rickets in very low birth weight infants: conservative management and outcome. J Pediatr Orthop. 1989; 9(3):326–30.
8. Vachharajani AJ, Mathur AM, Rao R. Metabolic bone disease of prematurity. NeoReviews. 2009;10(8):e402–11.
9. Heaney RP. Effects of caffeine on bone and the calcium economy. Food Chem Toxicol. 2002;40(9):1263–70.
10. Erenberg A, Leff RD, Haack DG, Mosdell KW, Hicks GM, Wynne BA. Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study. Pharmacotherapy. 2000;20(6):644–52.
11. Natarajan G, Botica ML, Thomas R, Aranda JV. Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? Pediatrics. 2007; 119(5):936–40.
12. Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol Rev. 1999;51(1):83–133.
13. Charles BG, Townsend SR, Steer PA, Flenady VJ, Gray PH, Shearman A. Caffeine citrate treatment for extremely premature infants with apnea: population pharmacokinetics, absolute bioavailability, and implications for therapeutic drug monitoring. Ther Drug Monit. 2008;30(6):709–16.
14. Glajchen N, Ismail F, Epstein S, Jowell P, Fallon M. The effect of chronic caffeine administration on serum markers of bone mineral metabolism and bone histomorphometry in the rat. Calcif Tissue Int. 1988;43(5):277–80.
15. Yeh JK, Aloia JF, Semla HM, Chen SY. Influence of injected caffeine on the metabolism of calcium and the retention and excretion of sodium, potassium, phosphorus, magnesium, zinc and copper in rats. J Nutr. 1986; 116(2):273–80.
16. Zanardo V, Dani C, Trevisanuto D, Meneghetti S, Guglielmi A, Zacchello G, Cantarutti F. Methylxanthines increase renal calcium excretion in preterm infants. Biol Neonate. 1995;68(3):169–74.
17. Bergman EA, Massey LK, Wise KJ, Sherrard DJ. Effects of dietary caffeine on renal handling of minerals in adult women. Life Sci. 1990;47(6):557–64.
18. Harvey NC, Javaid MK, Arden NK, Poole JR, Crozier SR, Robinson SM, Inskip HM, Godfrey KM, Dennison EM, Cooper C. Maternal predictors of neonatal bone size and geometry: the Southampton Women's survey. J Dev Orig Health Dis. 2010;1(1):35–41.
19. Bosley AR, Verrier-Jones ER, Campbell MJ. Aetiological factors in rickets of prematurity. Arch Dis Child. 1980;55(9):683–6.
20. Blackman NJM, Koval JJ. Interval estimation for Cohen's kappa as a measure of agreement. Stat Med. 2000;19(5):723–41.
21. Koo WW, Gupta JM, Nayanar VV, Wilkinson M, Posen S. Skeletal changes in preterm infants. Arch Dis Child. 1982;57(6):447–52.
22. Booth JG, Hobert JP. Maximizing generalized linear mixed model likelihoods with an automated Monte Carlo EM algorithm. *Journal of the Royal Statistical Society Series B*, Statistical Methodology. 1999:265–85.
23. Ofek-Shlomai N, Berger I. Inflammatory injury to the neonatal brain - what can we do? Front Pediatr. 2014;2:30.
24. Viswanathan S, Khasawneh W, McNelis K, Dykstra C, Amstadt R, Super DM, Groh-Wargo S, Kumar D. Metabolic bone disease: a continued challenge in extremely low birth weight infants. JPEN J Parenter Enteral Nutr. 2014;38(8): 982–90.
25. Schneider PE, Miller HI, Nakamoto T. Effects of caffeine intake during gestation and lactation on bones of young growing rats. Res Exp Med (Berl). 1990;190(2):131–6.
26. Littner Y, Mandel D, Mimouni FB, Dollberg S. Bone ultrasound velocity curves of newly born term and preterm infants. J Pediatr Endocrinol Metab. 2003;16(1):43–7.
27. Aly H, Moustafa MF, Amer HA, Hassanein S, Keeves C, Patel K. Gestational age, sex and maternal parity correlate with bone turnover in premature infants. Pediatr Res. 2005;57(5 Pt 1):708–11.
28. Namgung R, Tsang RC. Factors affecting newborn bone mineral content: in utero effects on newborn bone mineralization. Proc Nutr Soc. 2000;59(1):55–63.
29. Pereira-da-Silva L, Costa A, Pereira L, Filipe A, Virella D, Leal E, Moreira A, Rosa M, Mendes L, Serelha M. Early high calcium and phosphorus intake by parenteral nutrition prevents short-term bone strength decline in preterm infants. J Pediatr Gastroenterol Nutr. 2011;52(2):203–9.
30. Backstrom MC, Kouri T, Kuusela AL, Sievanen H, Koivisto AM, Ikonen RS, Maki M. Bone isoenzyme of serum alkaline phosphatase and serum inorganic phosphate in metabolic bone disease of prematurity. Acta paediatrica (Oslo, Norway : 1992). 2000;89(7):867–73.
31. Yesiltepe Mutlu G, Kirmizibekmez H, Ozsu E, Er I, Hatun S. Metabolic bone disease of prematurity: report of four cases. J Clin Res Pediatr Endocrinol. 2014;6(2):111–5.
32. Hellstern G, Poschl J, Linderkamp O. Renal phosphate handling of premature infants of 23-25 weeks gestational age. Pediatr Nephrol. 2003; 18(8):756–8.
33. Ghannam NN, Hammami MM, Bakheet SM, Khan BA. Bone mineral density of the spine and femur in healthy Saudi females: relation to vitamin D status, pregnancy, and lactation. Calcif Tissue Int. 1999;65(1):23–8.

Caspian J Intern Med 2018; 9(1):46-53
DOI: 10.22088/cjim.9.1.46

Original Article

The efficacy and safety of two different doses of caffeine in respiratory function of preterm infants

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Received: 3 Jan 2017
Revised: 5 May 2017
Accepted: 13 May 2017

Abstract

Background: Caffeine is widely used for prevention of apnea and helps successful extubation from mechanical ventilation. It facilitates the transition from invasive to noninvasive support and reduces duration of continuous positive airway pressure (CPAP) in preterm infants. The optimum caffeine dose in preterm infants has not been well-studied in terms of benefits and risks. We compared efficacy and safety of once versus twice-daily caffeine dose in premature infants.

Methods: This study was a randomized clinical trial conducted in Bu-Ali Sina Teaching Hospital, Sari. Patients with gestational age of <37 weeks were included. Both groups received 20 mg/kg loading dose of caffeine intravenously followed by maintenance dose of 5 mg/kg/day in group 1 or 2.5 mg/kg every 12 hours in group 2. Extubation failure, CPAP failure and possibly adverse reactions were evaluated.

Results: The mean of gestational age and birth weight were 32.27±3.23 (weeks) and 1824.5±702.54 (gr), respectively. The rate of extubation and CPAP failure and length of NICU stay were lower in twice-daily-group with no statistically significant difference. The means of O^2 saturations on the first three days of caffeine therapy were higher in twice-daily-group. Caffeine was generally safe and well tolerated.

Conclusions: This study, which assayed short-term effects of caffeine, showed that twice daily caffeine maintenance dose was related to more benefits in facilitating extubation or prevention of CPAP failure in preterm infants. However, there was not statistically significant difference between two groups.

Keywords: Caffeine, Extubation failure, CPAP failure, Preterm infants

Citation:
Faramarzi F, Shiran M, Rafati M, et al. The efficacy and safety of two different doses of caffeine in respiratory function of preterm infants. Caspian J Intern Med 2018; 9(1):46-53.

Respiratory distress syndrome (RDS) is generally seen in preterm infants. RDS in neonates is managed with the intention to supply interventions that enhance survival as well as lessen potential complications, such as the risk of broncopulmonary dysplasia (BPD) (1-3). Many of the patients require mechanical ventilation and may be ventilator dependent for several days or even many weeks. The patients who have apnea and poor respiratory drive need further time of mechanical ventilation. Prolonged mechanical ventilation is associated with several short-term and long-term complications such as barotrauma and the development of chronic lung disease, atelectasis, air leak syndrome, pneumonia, neurodevelopmental impairments and bronchopulmonary dysplasia (4, 5). Methylxanthines (MGs) have been used 25-years ago as the backbone of pharmacologic treatments of respiratory disorders in premature infants. MGs are still widely used to manage apnea and facilitate successful extubation from mechanical ventilation (6-8). The efficiency of caffeine, as a preferred methylxanthine, to stimulate respiration has been well proven.

Caffeine also, has significant favorable impact on neonatal morbidity such as BPD, patent ductus arteriosus ligation and so on. Useful effects, safety, efficacy, and cost-beneficial use caffeine introduced as the 'silver bullet' in neonatology (9). The results of previous studies revealed that caffeine enhances respiratory muscle strength and lung function followed by easier weaning of mechanical ventilation in premature infants (10). Also, a rapid and sustained increase in diaphragmatic activity and tidal volume was reported in preterm infants followed by caffeine administration (11). Previous studies have shown that caffeine citrate was generally well tolerated by premature neonates in clinical trials and declined the incidence of apnea in this population compared with placebo.

It has established treatment and found to be equally effective like theophylline but has an overall superior safety due to a wider therapeutic index (12). Additionally caffeine is related to superior outcomes due to its lower toxicity and it is a preferred drug for apnea in preterm infants with respiratory problems (13).

In a large randomized clinical trial, it has proven that the use of caffeine in very low birth weight infants reduced the incidence of BPD and duration of continuous positive airway pressure (CPAP) with no short-term adverse effects (14). The infants were followed-up until the age of five after caffeine therapy and established its long-term safety (15). Another report in 2006 indicated that infants in the caffeine group had a shorter duration of CPAP and mechanical ventilation than those in the placebo group and have lower incidence of BPD (16).

The assessment of long-term effects of caffeine therapy in neonates showed an improvement in survival rate with no disability in neurodevelopmental status at 18 to 21 months in premature infants (17). Several reviews about caffeine in the treatment of premature infant respiratory disorders confirmed the overall advantages of this drug and explained it as the drug of choice in this condition with some protective effects on the brain and lungs with few side effects (18-23). Additionally, based on the recent multicenter and observational study to assess the clinical use, outcome and safety profile of caffeine in the treatment of apnea of prematurity (AOP), this drug was safe to use and the incidence of adverse drug reactions was low (24). In brief, caffeine has a significant function as a noninvasive respiratory support. It facilitates the transition from invasive to noninvasive support, reduces the duration of positive airway pressure support and decreases the risk of BPD in preterm infants. Nevertheless, the optimum caffeine dose in preterm infants with respiratory distress syndrome has not been well studied as well as heterogeneous reports on the optimal loading and maintenance dose of caffeine in several studies in terms of benefits and risks. Many investigations have been conducted about various dosing regimens in the improvement or prevention of respiratory disorders of premature infants (5, 25-31). These dosage regimens, although, have been associated with varying degrees of success.

The current standard dosing regimen for caffeine citrate is 20 mg/kg (or 10 mg/kg as caffeine base) as a loading dose followed by 5mg/kg/day (or 2.5 mg/kg as caffeine base) as maintenance dose (32, 33). We hypothesized the 12-hour-interval leading to the more stable plasma drug concentrations and improving patient's outcome compared to once-daily dosing. The aim of this study was to compare efficacy and safety of once versus twice-daily caffeine-dose in premature infants with respiratory distress syndrome.

Methods

This study was an open-label randomized clinical trial conducted at a neonatal intensive care unit in Bu-Ali Sina Teaching Hospital, Sari, Iran (between July 2015 and August 2016). Study protocol was approved by the Research Ethics Committee of Mazandaran University of Medical Sciences, Sari, Iran. This trial was registered at IRCT.ir (reference number IRCT201510172342N4). All subjects' parents were informed about the nature and purpose of the study. This included an explanation of aims, methods, objectives, and potential hazards of the study and informed signed consent was obtained from their parents. The investigator explained to the parents that they were under no obligation to take part in the study and could withdraw at any time. Patients were included in the study if they had a gestational age of 26 to 37 weeks, with evidence of respiratory distress syndrome that was diagnosed by a neonatologist and treated by caffeine therapy facilitating earlier weaning process from mechanical ventilation or undergoing CPAP therapy.

The exclusion criteria were asphyxia, hypoglycemia, intracranial ventricular hemorrhage (IVH), major congenital anomaly and previous exposure to methylxanthine therapy. If the patient met the inclusion criteria, he/she was enrolled and randomly assigned to one of the two study groups. Both

groups received a 20 mg/kg loading dose (LD) of caffeine citrate that was administered intravenously over 30 minutes followed by a maintenance dose (MD) of 5 mg/kg every 24 in group 1 or 2.5 mg/kg infused every 12-hour-interval in group 2 over 20 minutes. Demographic characteristics (gestational age, gender, birth weight, type of delivery and Apgar score at 1 and 5 minutes after birth, age at initiation of caffeine, duration of caffeine therapy, length of stay in NICU, ventilator modality, primary RDS score, daily blood gas levels and routine laboratory tests) were recorded. Extubation failure, CPAP failure, duration of the ventilator and CPAP therapy for all patients were also registered as primary outcomes. In addition, an average of heart pulse rate and blood pressure based on the values registered in the daily sheets was recorded for all infants.

The possible adverse drug reaction of caffeine including tachycardia, feeding intolerance, hyperglycemia or hypertension were also investigated in case they happen. Side effects and clinical worsening were used to assess safety and tolerability. The mentioned parameters were assessed since the time of caffeine therapy initiation until the infants treatment. All statistical analyses were conducted using SSPS Version 19 (SPSS Inc., Chicago, IL, USA) and a p-value ≤0.05% was considered statistically significant. Number and percent age are represented the qualitative variables and mean±SD displayed the quantitative variables. Continuous variables of two groups were compared using independent samples t-test, while qualitative variables were analyzed using chi-square test.

Results

1. Demographic and drug dosing data analysis: Forty-seven patients were enrolled in the study protocol and forty of them fulfilled the study criteria. Seven patients were excluded, of these, two patients were due to hypoglycemia, one with IVH, two had congenital anomaly and another two because of death (figure 1). Half of the patients (50%) were girls, the mean of gestational age was 32.3±3.2 weeks weeks, the mean of birth weight was 1824.5±702.54 gr and the type of delivery in majority (92.5%) of patients was cesarean (c/s).

Demographic and clinical characteristics of the neonates in two groups are presented in table 1. There were no significant differences in gender, gestational age, birth weight, type of delivery, Apgar scores at 1 and 5 minutes after birth, RDS score, surfactant therapy (INSURE) and age at the beginning of treatment of the two groups. The average length of stay in NICU was 17.8±18.5 days and duration of caffeine therapy on average was 5.33±2.95 days, however, we considered the first three days of caffeine therapy in our analyses for all the patients.

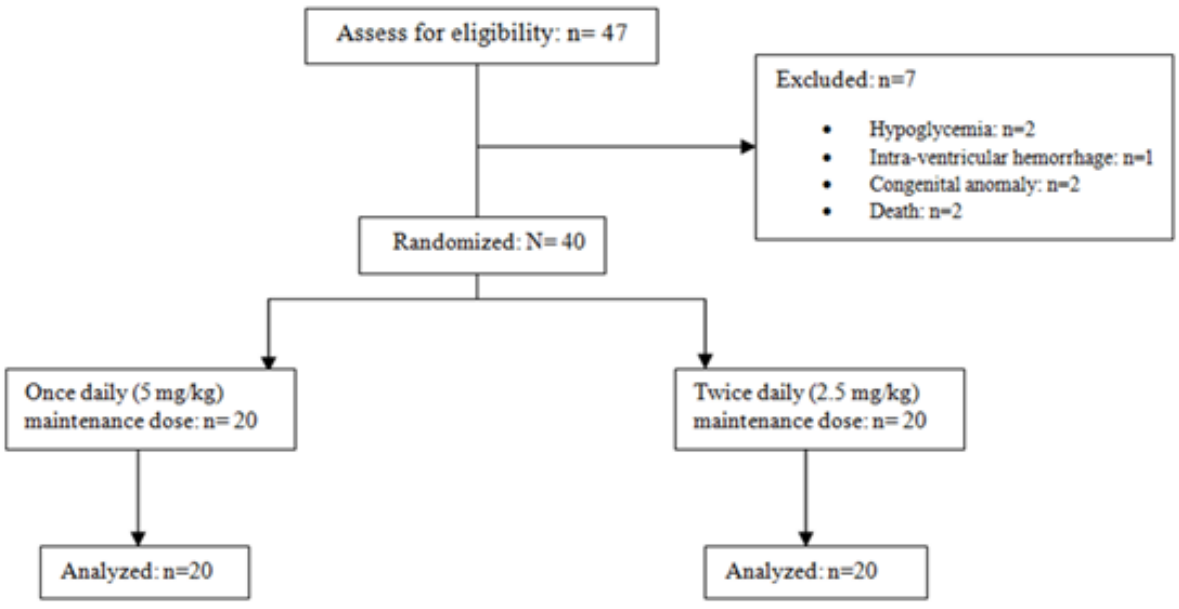

Figure 1. Diagram of the participants

Table1. Demographic and clinical characteristics of the patients in two study groups

Subject	All subjects (n=40)	Group 1 (n=20)	Group 2 (n=20)	P-value
Female/male	20.20	11.9	9.11	0.52
GA at birth (week)	32.27±3.23	32.2±3.06	32.34±3.46	0.89
BW(gr)	1824.5±702.54	1772±675.27	1877±742.5	0.64
Vaginal /Cesarean delivery	3.3	1.19	2.18	0.54
Apgar, 1 min/ Median(IQR)	9 (8-9)	9 (8-9)	9 (9-9)	0.32
Apgar, 5 min/ Median(IQR)	10 (9-10)	10 (9-10)	10 (9.25-10)	0.86
RDS score/ Median(IQR)	6 (4-7)	6 (4.25-7)	5.5 (4-7)	0.49
Surfactant (INSURE)	19 (47.5)	12 (60)	7 (35)	0.11
PNA at initiation of caffeine (day)	8.23±9.2	7.1±7.7	6.7±7.2	0.86

GA:gestational age, BW: birth weight, Apgar1: Apgar score in 1th minutes after birth, Apgar5: Apgar score in 5th minutes after birth, RDS: Respiratory distress syndrome score at the time of admission, PNA: postnatal age. Group1: once daily, group2: two divided dosing per day of caffeine.

2. Effect of caffeine dose on the respiratory status of patients: Twice a day compared to once daily dosing regimen of caffeine resulted in a reduction in failure of extubation and CPAP failure rate and length of NICU stay among preterm infants (14.7 VS 12 days, respectively), although they were not statistically significant. Nonetheless, there were no significant differences in the duration of mechanical ventilation, CPAP therapy and mortality rate between the two groups (table 2).

Table 2. Comparison of neonatal outcomes among preterm infants receiving caffeine either in-group 1 (n=20) (once daily) or group 2 (n=20) (twice daily)

Parameters*	Group 1	Group 2	Pvalue
Extubation failure**	8(40%)	6(30%)	0.50
N-CPAP failure***	5(25%)	4(20%)	0.70
Rate of mortality	4(20%)	4(20%)	1
Duration of mechanical ventilation (days)	12.82±15.12	13.63±11.67	0.90
Duration of CPAP (days)	5.69±4.97	6.36±10.37	0.82
Length of NICU stay (day)	14.7±10.03	12±7.23	0.33

* value are presented in (n(%) or mean±SD)

**Extubation failure: (i) an inability to extubate from mechanical ventilation within 48 h of caffeine loading (ii) the use of reintubation within 7 days of commencing caffeine therapy

***CPAP failure: SpO_2<85%, PO_2<50 mmHg, pH<7.2, PCO_2>60 mmHg.

3. Blood gas levels change during the course of caffeine therapy: Arterial blood gas (ABG) parameters were measured daily for each patient and their mean values are presented in table 3. All pH values were in the normal range except the first day in group 1 that elevated to the normal range on the second day of treatment (from 7.33 to 7.37). In addition, all values of Pco_2 and HCO3 in patients of group 2 were in normal range compared to group1 during the first 3 days of caffeine therapy. At any rate, these differences were not statistically significant. Most of the differences were seen in the values of the O^2 saturation between two groups.

Table 3. Comparison of blood gas values between the two groups in the first 3 days of treatment with caffeine. All values are displayed on (Mean±SD)

Parameters		Group 1	Group 2	Pvalue
pH	Day 1	7.33±0.1	7.37±0.08	0.21
	Day 2	7.37±0.12	7.37±0.06	0.85
	Day 3	7.37±0.16	7.39±0.12	0.68
PCO2 (mmHg)	Day 1	51.9±21.2	43.3±14.3	0.14
	Day 2	46.8±19.2	42.8±11.1	0.42
	Day 3	50.2±31.6	45.5±18.7	0.57
HCO3 (mEq/l)	Day 1	28.4±8.1	25.3±6.5	0.19
	Day 2	28.9±8.3	26.1±4.9	0.18
	Day 3	27.1±5.8	26.2±5.9	0.63
O2 saturation (%)	Day 1	89.9±15.1	93.8±15.5	0.42
	Day 2	89.1±11.2	95.2±7.4	0.049*
	Day 3	89.1±14.6	95.9±5.5	0.056

*There was a significant difference in O2 saturation on day 2 between two groups.

All of O^2 saturation levels in neonates that received caffeine twice a day were higher compared to those with once-daily-dosing even the difference on the 2nd day was significant ($p<0.05$). Furthermore, the value of O^2 saturation on the 3nd day moved towards a meaningful trend ($P<0.05$).

4. Safety and Tolerability: Heart rate, blood pressure, feeding intolerance and blood sugar of all infants were recorded daily based on the infants' laboratory tests or data in the NICU sheets. The mean values over the course of caffeine therapy have been shown in table 4. Hyperglycemia and hypertension episodes were lower in preterm infants that received caffeine twice a day compared to those with once-daily-dose. Hypertension was the most frequently reported adverse effect (AE) that occurred in some cases over the treatment. The mean arterial pressure had the greatest difference between two groups of neonates with the trend toward statistical significance ($p=0.07$).

Totally, intravenous administration of caffeine was generally safe and well tolerated. None of the patients had tachycardia during the study. Most of the AEs were reported as mild in severity, and no serious AEs were recorded. Eight deaths occurred during the study (4 cases in each group) of which they were not caffeine-related.

Table 4. Frequency and type of adverse effects observed following administration of caffeine

Type of AE		Group1	Group2	Pvalue
Feed intolerance		2	1	0.56
Hyperglycemia*		33(61.1%)	21(38.9%)	0.10
Hypertension**	Systolic BP	46(56.8%)	35(43.2%)	0.22
	Diastolic BP	38(52.8%)	34(42.2%)	0.63
	MAP	57(60.6%)	37 (39.4)	0.07

Blood glucose >125 mg/dl, **Systolic blood pressure >75 mmHg, Diastolic blood pressure >45 mmHg, MAP>55 mmHg

Discussion

Caffeine is one of the most currently used medications in the neonatal care units. Despite its widespread use in preterm infants, there has been little information about optimal dose in these patients. This clinical trial was designed to assess the efficacy, safety and short-term effects of two different dosing regimen of caffeine citrate in periextubation management of preterm infants with gestational age <37 weeks. In sum, 40 preterm infants were included in this study and received either caffeine 2.5 mg/kg twice daily or 5 mg/kg once daily. All of them received caffeine 20 mg/kg as a loading dose in the beginning of treatment. The results indicated that caffeine improved the respiratory function of neonates in two study groups. There was a trend to a benefit for patients receiving caffeine 2.5 mg/kg twice daily compared to the 5 mg/kg once daily dosing; yet there was not statistically significant difference. The rate of extubation and CPAP failure and length of NICU stay were lower in the twice-daily-group than once-daily-group, too. In addition, the means of O^2 saturations on the first three days of treatment with caffeine were higher in group 2 compared to group 1. Thus the mean difference of O^2 saturation between two groups was meaningful on the second day ($p<0.05$) and a trend towards significant on the third day ($p<0.05$).

Previous studies indicated the efficacy of caffeine in the improvement of respiratory function in preterm infants with low birth weight. Additionally, there are many reports of caffeine useful effects on the treatment or prevention of apnea in premature infants. Caffeine is an effective respiratory stimulant drug in the premature infants (26). This drug significantly decreases duration of mechanical ventilation and need for it (34). Caffeine led to a significant decrease of apnea in the treatment group as compared with the control group with no adverse effects during the study (35). Besides, this drug improves tidal volume ventilation and mean inspiratory flow mostly by stimulating central respiratory drive (36).

A study has reported that the use of caffeine can lead to prevent apnea episodes that need intervention and also enhances the results of pneumogram (37). A randomized double-blind clinical trial was conducted by Steer et al. that compared three dosing regimens of caffeine (3, 15 or 30 mg/kg) for periextubation control of premature infants. This trial revealed that the infants in higher dose group had lower apnea events through the week after extubation. Likewise, the short term safety of caffeine was endorsed (30). Other trials compared two different doses of caffeine (5 or 20 mg/kg/day) for extubation of preterm infants that was showed short-term effects of higher-dose regimen in the periextubation days. A dose of 20 mg/kg/day was administered in this period eases extubation, declines the time of mechanical ventilation and decreases apnea events after extubation without the increase of short-term side effects (5). The results of a multicentre, randomized and controlled trial that compared two different dosing regimens

of caffeine in preterm infants showed that the high-dose of caffeine as (20 mg/kg/day) reduces the need for respiratory support versus the standard dose (5 mg/kg/day) with no adverse outcomes in two years of age (38).

Extended caffeine therapy causes the lower rate and severity of intermittent hypoxia in premature infants (39). The preventive effect of caffeine on apnea has been proven when it is administered in high-risk premature infants (40). The prophylactic use of caffeine results in the lower rate of mortality or BPD and PDA with no adverse outcomes (41). It has also been shown the favorable effect of caffeine on the treatment of central apnea is via stimulated neural breathing (42). The results of a randomized controlled trial revealed that the administration of high dose caffeine (loading 40 mg/kg then maintenance dose of 20 mg/kg/day) compared with low dose caffeine (loading 20 mg/kg then maintenance dose of 10 mg/kg/day) decreased the rate of extubation failure in ventilated infants and apnea episodes without serious adverse effects (28). Findings of a recent study that have compared two different doses of caffeine in treatment of primary AOP demonstrated that the patients in high caffeine doses (LD: 20 mg/kg and MD: 15 mg/kg/day) had more benefits than the low caffeine doses (LD: 20 mg/kg and MD: 5 mg/kg/day) with no further side effects (31). Besides, caffeine notably improved the early pulmonary function and decreased apnea (43).

In the current study, lower frequency of short-term adverse effects of caffeine was observed in twice-daily-dose group compared to single-daily-dose group. This issue may be due to the stable concentrations and lower plasma peak levels of caffeine following the twice-daily-dose administration. Closely similar to our results, previous studies which compared different dosing regimens of caffeine determined that low dose caffeine was related to fewer side effects. For example after 10 mg/kg loading dose of caffeine, the maintenance dose of 5 or 2.5 mg/kg was administered to groups 1 and 2, respectively. The results indicated that caffeine significantly reduces the apnea episodes in both groups and the rate of adverse effects such as tachycardia and feeding intolerance in group 2 was notably lower than in group 1 (29). A 20 mg/kg followed by 5 mg/kg/day caffeine citrate administered intravenously for 10 days has been shown to be safe and effective for treating apnea in premature infants of gestational age 28–32 weeks (44). The results of this research showed a trend to a partial superiority efficacy for infants receiving a dose of 2.5 mg/kg twice daily compared to 5 mg/kg once daily. Despite more improvements in the clinical outcome of patients in group 2, no significant difference was observed between the two groups. It may result in meaningful outcomes if the drug use in a clinical trial has larger sample size. These beneficial effects in twice-daily maintenance dose group may be due to a more steady state plasma level of caffeine in infants.

This study which assayed the short-term effects of caffeine therapy, concludes that twice versus once-daily caffeine maintenance dose was related to more benefits in facilitating extubation or prevention of CPAP failure in infants of born gestational age less than 37 weeks with no statistically significant difference between two groups.

Acknowledgments

We would like to thank the Research Council of Mazandaran University of Medical Sciences for the financial support and to the NICU nurses and laboratory staff of Bu-Ali Sina Hospital in Sari.

Funding: This study was a part of a PhD thesis of fatemeh Faramarzi and was supported by a grant from Mazandaran University of Medical Sciences.
Conflict of Interest: There is no conflict of interest.

References

1. Edwards MO, Kotecha SJ, Kotecha S. Respiratory distress of the term newborn infant. Paediatr Respir Rev 2013; 14: 29-37.
2. Subiramanian S, Sweet DG. Management of neonatal respiratory distress syndrome. Paediatr Child Health 2012; 22: 518-22.
3. Sweet DG, Carnielli V, Greisen G, et al. European consensus guidelines on the management of respiratory distress syndrome-2016 update. Neonatology 2016; 111: 107-25.
4. Wielenga JM, van den Hoogen A, et al. Protocolized versus non-protocolized weaning for reducing the duration of invasive mechanical ventilation in newborn infants. Cochrane Database Syst Rev 2016; 3: CD011106
5. Steer P, Flenady V, Shearman A, et al. High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2004; 89: F499-503.

6. Baird TM, Martin RJ, Abu-Shaweesh JM. Clinical associations, treatment, and outcome of apnea of prematurity. NeoReviews 2002; 3: e66-70.
7. Bhatia J. Current options in the management of apnea of prematurity. Clin Pediatr 2000; 39: 327-36.
8. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for extubation in preterm infants. Cochrane Database Syst Rev 2003; 1: CD000139.
9. Aranda JV, Beharry K, Valencia GB, Natarajan G, Davis J. Caffeine impact on neonatal morbidities. J Matern Fetal Neonatal Med 2010; 23: 20-3.
10. Kassim Z, Greenough A, Rafferty GF. Effect of caffeine on respiratory muscle strength and lung function in prematurely born, ventilated infants. Eur J Pediatr 2009; 168: 1491-5.
11. Kraaijenga JV, Hutten GJ, de Jongh FH, van Kaam AH. The effect of caffeine on diaphragmatic activity and tidal volume in preterm infants. J Pediatr 2015; 167: 70-5.
12. Comer AM, Perry CM, Figgitt DP. Caffeine citrate. Paediatr Drugs 2001; 3: 61-79.
13. Henderson-Smart DJ, De Paoli AG. Methylxanthine treatment for apnoea in preterm infants. Cochrane Database Syst Rev 2010; 12: CD000140.
14. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006; 354: 2112-21.
15. Schmidt B, Anderson PJ, Doyle LW, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012; 307: 275-82.
16. Bancalari E. Caffeine for apnea of prematurity. N Engl J Med 2006; 354: 2179-81.
17. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007; 357: 1893-902.
18. Mueni E, Opiyo N, English M. Caffeine for the management of apnea in preterm infants. Int Health 2009; 1: 190-5.
19. Johnson P. Caffeine citrate therapy for apnea of prematurity. Neonatal Netw 2011; 30: 408-12.
20. Orozco-Gregorio H, Mota-Rojas D, Villanueva D, et al. Caffeine therapy for apnoea of prematurity: Pharmacological treatment. Afr J Pharm Pharmacol 2011; 5: 564-7.
21. Johnson T. Benefits of caffeine citrate: neurodevelopmental outcomes of ELBW infants. Available at: 2011. http://sophia. stkate. edu/ ma_nursing/44/
22. Pacifici GM. Clinical pharmacology of caffeine citrate in preterm infants. MedicalExpress 2014; 1: 243-50.
23. Abdel-Hady H, Nasef N, Shabaan AE, Nour I. Caffeine therapy in preterm infants. World J Clin Pediatr 2015; 4: 81-93.
24. Lista G, Fabbri L, Polackova R, et al. The real-world routine use of caffeine citrate in preterm infants: a European postauthorization safety study. Neonatology 2016; 109: 221-7.
25. Aranda JV, Cook CE, Gorman W, et al. Pharmacokinetic profile of caffeine in the premature newborn infant with apnea. J Pediatr 1979; 94: 663-8.
26. Aranda JV, Gorman W, Bergsteinsson H, Gunn T. Efficacy of caffeine in treatment of apnea in the low-birth-weight infant. J Pediatr 1977; 90: 467-72.
27. Hoecker C, Nelle M, Beedgen B, et al. Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants. Arch Dis Childhood Fetal Neonatal Ed 2006; 91: F61-4.
28. Mohammed S, Nour I, Shabaan AE, et al. High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial. Eur J Pediatr 2015; 174: 949-56.
29. Romagnoli, C., M. De Carolis, U. Muzii, et al. Effectiveness and side effects of two different doses of caffeine in preventing apnea in premature infants. Ther Drug Monit 1992; 14: 14-19.
30. Steer PA, Flenady VJ, Shearman A, et al. Periextubation caffeine in preterm neonates: a randomized dose response trial. J Paediatr Child Health 2003; 39: 511-15.
31. Zhao Y, Tian X, Liu G. Clinical effectiveness of different doses of caffeine for primary apnea in preterm infants. Zhonghua Er Ke Za Zhi 2016; 54: 33-6.
32. Dobson NR, Hunt CE. Pharmacology review: caffeine use in neonates: indications, pharmacokinetics, clinical effects, outcomes. NeoReviews 2013; 14: e540-e50.
33. Gare S, Lal M, Tin W. Apnoea in premature infants and caffeine therapy. Infant 2013; 9: 9-12.
34. Gunn TR, Metrakos K, Riley P, Willis D, Aranda JV. Sequelae of caffeine treatment in preterm infants with apnea. J Pediatr 1979; 94: 106-9.
35. Murat I, Moriette G, Blin M, et al. The efficacy of caffeine in the treatment of recurrent idiopathic apnea in premature infants. J Pediatr 1981; 99: 984-9.

36. Aranda JV, Turmen T, Davis J, et al. Effect of caffeine on control of breathing in infantile apnea. J Pediatr 1983; 103: 975-9.
37. Anwar M, Mondestin H, Mojica N, et al. Effect of caffeine on pneumogram and apnoea of infancy. Arch Dis Child 1986; 61: 891-5.
38. Gray PH, Flenady VJ, Charles BG, Steer PA; Caffeine Collaborative Study Group. Caffeine citrate for very preterm infants: effects on development, temperament and behaviour. J Paediatr Child Health 2011; 47: 167-72.
39. Rhein LM, Dobson NR, Darnall RA, et al. Effects of caffeine on intermittent hypoxia in infants born prematurely: a randomized clinical trial. JAMA Pediatr 2014; 168: 250-7.
40. Armanian AM, Iranpour R, Faghihian E, Salehimehr N. Caffeine administration to prevent apnea in very premature infants. Pediatr Neonatol 2016; 57: 408-12.
41. Lodha A, Seshia M, McMillan DD, et al. Association of early caffeine administration and neonatal outcomes in very preterm neonates. JAMA Pediatr 2015;169: 33-8.
42. Parikka V, Beck J, Zhai Q, et al. The effect of caffeine citrate on neural breathing pattern in preterm infants. Early Hum Dev 2015; 91: 565-8.
43. Yu M, Huang JH, Zhu R, et al. Effect of caffeine citrate on early pulmonary function in preterm infants with apnea. Zhongguo Dang Dai Er Ke Za Zhi 2016; 18: 206-10.
44. Erenberg A, Leff RD, Haack DG, et al. Caffeine citrate for the treatment of apnea of prematurity: a double-blind, placebo-controlled study. Pharmacotherapy 2000; 20: 644-52.

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RESEARCH ARTICLE

Caffeine for apnea of prematurity and brain development at 11 years of age

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Funding Information
This work was supported by the National Health and Medical Research Council of Australia (Project Grants No. 237117 and No. 108706; Program Grant No. 606789; Centre of Research Excellence No. 1060733; Fellowship No. 1081288 to PJA, No. 1127984 to KJL, No. 1141354 to JLYC and No. 1085754 to DKT). This work was also generously supported by The Royal Children's Hospital Foundation (Grant no. RCH1000) devoted to raising funds for research at The Royal Children's Hospital, as well as the Murdoch Children's Research Institute, the Royal Children's Hospital, Department of Paediatrics at The University of Melbourne and the Victorian Government's Operational Infrastructure Support Program

Received: 8 July 2018; Accepted: 10 July 2018

Annals of Clinical and Translational Neurology **2018; 5(9): 1112–1127**

doi: 10.1002/acn3.628

Abstract

Objective: Caffeine therapy for apnea of prematurity has been reported to improve brain white matter microstructure at term-equivalent age, but its long-term effects are unknown. This study aimed to investigate whether caffeine affects (1) brain structure at 11 years of age, and (2) brain development from term-equivalent age to 11 years of age, compared with placebo. **Methods**: Preterm infants born ≤1250 g were randomly allocated to caffeine or placebo. Magnetic resonance imaging (MRI) was performed on 70 participants (33 caffeine, 37 placebo) at term-equivalent age and 117 participants (63 caffeine, 54 placebo) at 11 years of age. Global and regional brain volumes and white matter microstructure were measured at both time points. **Results**: In general, there was little evidence for differences between treatment groups in brain volumes or white matter microstructure at age 11 years. There was, however, evidence that the caffeine group had a smaller corpus callosum than the placebo group. Volumetric brain development from term-equivalent to 11 years of age was generally similar between treatment groups. However, there was evidence that caffeine was associated with slower growth of the corpus callosum, and slower decreases in axial, radial, and mean diffusivities in the white matter, particularly at the level of the centrum semiovale, over time than placebo. **Interpretation**: This study suggests any benefits of neonatal caffeine therapy on brain structure in preterm infants weaken over time and are not clearly detectable by MRI at age 11 years, although caffeine may have long-term effects on corpus callosum development.

Introduction

Caffeine is used to treat cessation of breathing in infants born preterm (apnea of prematurity).[1] The Caffeine for Apnea of Prematurity (CAP) randomized controlled clinical trial established that caffeine has many benefits, and no harmful effects, on clinically important outcomes in infants born preterm and low birthweight.[1] Benefits included reduced rates of lung injury (bronchopulmonary dysplasia), retinopathy of prematurity and surgery for patent ductus arteriosus, and increased rates of survival free of major neurodevelopmental disabilities at 18–21 months of age.[1,2] The effects of caffeine were attenuated when the children were older, but caffeine was still associated with reduced rates of developmental coordination disorder at 5 years of age,[3] and improved motor outcomes, including manual dexterity and balance, at 5 and 11 years of age.[4,5]

The mechanism by which caffeine improves neurodevelopmental outcomes in preterm infants is not clear.[2] Several animal studies have reported that caffeine has beneficial effects on the brain, but many others warn of adverse effects.[6] In a subgroup of participants from the CAP trial, caffeine was associated with improved white matter (WM) microstructure in preterm infants at approximately term-equivalent age (38–44 weeks' gestational age), which may explain how caffeine improved early neurodevelopmental outcomes.[7] However, it is not known whether this improvement to brain structure persists or weakens in the long-term.

The primary aim of this study was to investigate the relationship between neonatal caffeine treatment and brain structure at 11 years of age in a subgroup of the CAP trial, including the structure of both global brain regions and specific brain regions involved in motor function, given the previously reported benefit of caffeine on long-term motor outcomes in the overall CAP trial.[5] The secondary aim was to investigate the relationship between neonatal caffeine treatment and longitudinal brain development from term-equivalent to 11 years of age.

Materials and Methods

Participants

The CAP trial enrolled 2006 infants with birthweights 500–1250 g, who were randomly allocated to caffeine or placebo.[1,2,4,5,7] Randomization was stratified according to study center. A subgroup ($n = 199$) of the infants enrolled in the CAP trial, who were cared for at the Royal Women's Hospital (RWH), Melbourne, is relevant to this study. Two of the 199 infants were excluded due to congenital abnormalities (craniosynostosis and Klinefelter syndrome). One hundred and seventy-two children (87% of the children recruited at RWH) were followed up at 11 years of age, along with an additional five children who were originally enrolled through other centers. Of these, 118 children had magnetic resonance imaging (MRI). One child was excluded from all subsequent analyses because of dental braces that compromised image quality. This left a maximum of 117 children (63 allocated to caffeine and 54 allocated to placebo) who were included in this study for the primary aim.

Of the 199 infants cared for at the RWH, 70 (33 caffeine, 37 placebo) had MRI at term-equivalent age, including structural MRI, with 28 (15 caffeine, 13 placebo) of those also having diffusion MRI, as previously reported.[7] All of the term-equivalent and 11-year MRI data were included in the secondary aim of the current study.

Ethics approval for recruitment and follow up was granted by the Human Research Ethics Committee at the RWH and written informed parental consent was necessary for participation at each follow up.

Data collection at age 11 years

Children underwent 3 Tesla MRI (Siemens Magnetom Trio-Tim syngo) at 11 years of age at the Royal Children's Hospital, Melbourne. T_1 images were acquired: repetition time (TR)/echo time (TE) 1950/2.24 msec, 0.9 mm isotropic voxels, field of view (FOV) 230 × 221 mm and flip angle 9 degrees. Diffusion images were acquired via two sequences: (1). TR/TE 7500/89 msec, FOV 240 × 240 mm, 2.5 mm isotropic voxels, b-value 1000 sec/mm^2, 25 diffusion-weighted gradient directions, five $b = 0$ sec/mm^2 volumes; (2). TR/TE 8000/112 msec, FOV 240 × 240 mm, 2.5 mm isotropic voxels, b-value = 3000 sec/mm^2, 45 diffusion-weighted gradient directions, six $b = 0$ sec/mm^2 volumes. All children had both of the diffusion sequences, but one child in the caffeine group did not complete the second ($b = 3000$ sec/mm^2) sequence.

Brain volumes

Volumes were generated from the T_1 images. The volumes of the intracranial cavity, total brain tissue and cerebrospinal fluid were calculated using Statistical Parametric Mapping (SPM; version 12).[8] The volume, surface area and thickness of the cortical gray matter (GM), WM volume and brainstem volume were calculated using FreeSurfer (version 5.3).[9–13] Subcortical and deep nuclear GM volumes [thalamus, basal ganglia nuclei, hippocampus and amygdala] were calculated using the Functional MRI of the Brain Software Library's (FSL's) Integrated Registration and Segmentation Tool (FIRST).[14] Cerebellum volume was calculated using SPM's Spatially Unbiased Infra-tentorial template (SUIT; version 3.0).[15,16] Area and thickness of the corpus callosum were calculated using

our previously described software pipeline,[17,18] which divided the corpus callosum into six subregions; genu, rostral body, anterior mid-body, posterior mid-body, isthmus, and splenium.[19] Imaging outputs were visually examined and manually edited as required.

Whole-brain white matter microstructure

Whole brain WM microstructure was analyzed using:

- FSL's (version 5.0.9) Tract-Based Spatial Statistics (TBSS).[20] This involved analyzing the $b = 1000$ sec/mm^2 sequence. Processing steps were: motion and eddy current distortion correction; diffusion tensor fitting to generate fractional anisotropy (FA), and axial (AD), radial (RD), and mean (MD) diffusivity images; alignment of all participants' images to a study-specific template; generation of a tract skeleton. Despite being commonly used, TBSS has methodological limitations, including that the metrics generated can be influenced by factors other than WM microstructure.[21] A complementary analysis using a more sophisticated WM modeling strategy was therefore carried out.
- MRtrix's (version 3) fixel-based analysis.[22] This involved analyzing the $b = 3000$ sec/mm^2 sequence. All recommended steps were followed. Fixel-based analysis enables investigation of the density and cross-section of WM fiber populations across the whole brain, thus providing metrics that are more specific to the WM microstructural environment compared with TBSS.[22]

White matter tractography

We reconstructed the corpus callosum, pyramidal sensorimotor, and cerebellar motor tracts (Fig. 1A). This involved drawing regions of interest on the diffusion images ($b = 3000$ sec/mm^2 sequence) and using a probabilistic fiber orientation distribution-based computer algorithm to reconstruct the tracts (Tournier et al. Improved probabilistic streamlines tractography by second order integration over fiber orientation distributions. *Proceedings of the International Society for Magnetic Resonance in Medicine* 2010;1670). Following tractography reconstructions, we calculated average FA, AD, RD, and MD of each of the tracts for every participant. When tracts were reconstructed using manually drawn regions of interest, we assessed intra-rater reliability using intra-class correlation coefficients, which were all ≥0.88, suggesting high intra-rater reliability.

Data collection for longitudinal analyses

At term-equivalent age, we acquired brain T_1-, T_2- and diffusion images during infants' sleep without sedation using a 1.5 Tesla MRI (General Electric Signa, GE Medical Systems) at the Royal Children's Hospital, Melbourne, as detailed previously.[7]

Based on the T_1 and T_2 images, we generated volumes of the intracranial cavity, cortical GM, WM, deep nuclear GM, cerebellum, brainstem, and hippocampus. We used software specifically designed for neonatal images,[23,24] or manual delineation for the hippocampus.[25] These data were used to analyze brain volumetric development.

Using the neonatal T_1 and diffusion images, we calculated the area of, and diffusion tensor values (FA, AD, RD, and MD) within, the corpus callosum and its six subregions, as previously described.[19] These data were used to analyze corpus callosum development.

In our previous study at term-equivalent age, we calculated diffusion tensor values from within manually drawn regions of interest.[7] Three regions (one in the anterior, one in the central and one in the posterior WM) were placed bilaterally on both an inferior brain slice at the level of the mid-thalamus, and a superior brain slice at the level of the centrum semiovale, that is, a total of 12 regions per participant.[7] To enable a longitudinal analysis, we drew the same regions on the 11-year diffusion images, for the subset of participants with diffusion images at both time points (Fig. 1B). This left us with diffusion values (FA, AD, RD, MD) from 12 regions per participant per time point. Intra-rater reliability for the manually drawn 11-year regions was high (all intra-class correlations ≥0.8, except FA within the right superior central region [0.71] and AD within the right inferior posterior region [0.77]).

Statistical analyses

Cross-sectional analysis at age 11 years (primary aim)

For the whole-brain analyses, we compared cortical GM surface area, thickness, and volume between treatment groups using FreeSurfer's Query, Design, Estimate and Contrast (QDEC).[26] We compared WM diffusion tensor values (derived from TBSS) between treatment groups using FSL's randomize, with 5000 permutations and threshold-free cluster enhancement.[27] We compared fiber density and cross-section (derived from the fixel-based analysis) between treatment groups using connectivity-based fixel enhancement.[28] These analyses were adjusted for age and sex, and corrected for multiple comparisons using the false discovery rate method (for QDEC) or the family-wise error rate method (for TBSS and fixel-based analyses).

Global and regional volume and WM microstructure measures were compared between treatment groups using

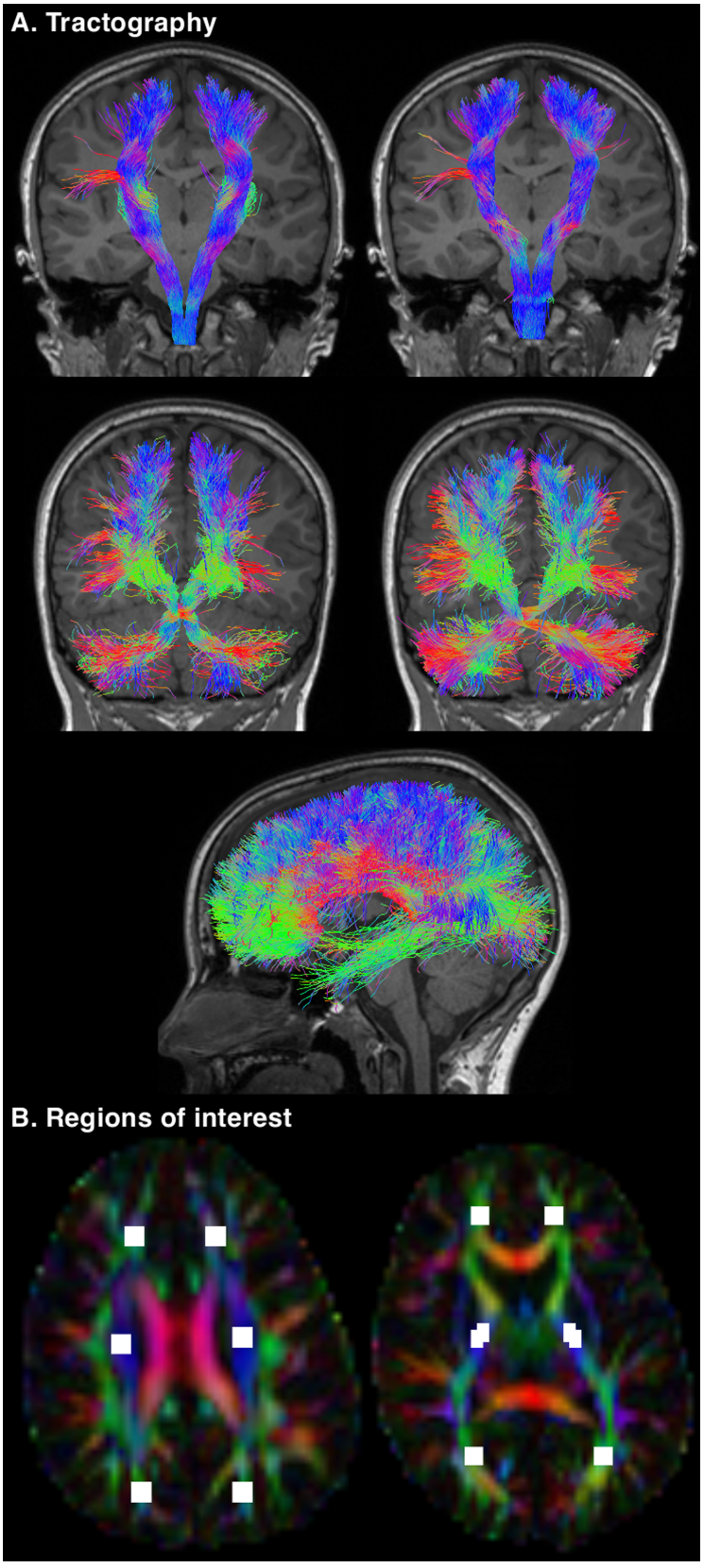


Figure 1. Illustration of some of the data generated for this study. (A) Tractography performed using the 11-year diffusion images. *Top row:* the pyramidal sensorimotor tracts. The corticospinal tract (left) was reconstructed using seed regions in the pons and inclusion regions in the posterior limb of the internal capsule. The somatosensory tract (right) was reconstructed using seed regions in the medial lemniscus, inclusion regions in the thalamus and the combined pericentral cortices (precentral, paracentral, and postcentral cortices), and exclusion regions in the corticospinal tract portion of the pons. *Middle row:* the cerebellar motor tracts. The cerebellar-thalamo-cortical tract (left) was reconstructed using seed regions in the dentate nucleus and inclusion regions in the decussation of the superior cerebellar peduncle, and the contralateral red nucleus, thalamus, and prefrontal cortex. The cortico-ponto-cerebellar tract (right) was reconstructed using seed regions in the middle cerebellar peduncle, inclusion regions in the contralateral cerebral peduncle, anterior limb of the internal capsule and prefrontal cortex, and exclusion regions in the decussation of the superior cerebellar peduncle and medial lemniscus. *Bottom row:* the corpus callosum tracts, reconstructed using automatically generated[17,18] seed regions in the corpus callosum, with the addition of exclusion regions at the brainstem, cerebral peduncle and thalamus. (B) Regions of interest drawn on the 11-year diffusion images. Six regions were placed on a single superior brain slice at the level of the centrum semiovale (left) and six regions were placed on a single inferior brain slice at the level of the mid-thalamus (right). These regions of interest were intended to reproduce the regions of interest drawn on the neonatal diffusion images, to enable a comparison of white matter microstructure between the time points. The neonatal regions of interest are shown in Figure 1 of our previous publication.[7]

separate linear regression models, with adjustment for age and sex (Stata version 14). Models were fitted using generalized estimating equations to account for correlations between data from multiple births, which represent a large proportion of our sample (Table 1). Some outcomes were measured in both brain hemispheres, in which case we included data from both hemispheres in a single model, and instead of allowing for correlations between data from multiple births, we allowed for correlations between data from individuals, which we expected to be more important. There was little evidence for any interactions between group and hemisphere, so the interaction terms were removed and results are reported combined across hemispheres.

Longitudinal analysis (secondary aim)

We compared the rate of change in the global and regional volume and WM microstructural measures from term-equivalent to 11 years of age between the caffeine and placebo groups using separate mixed effects models (Stata version 14). Models included a fixed effect of age and group, a random effect to allow for the repeated observations within individuals, and adjustment for sex. Age-by-group interactions were included. The diffusion values from regions of interest were measured in both brain hemispheres at both time points, and values from both hemispheres were analyzed using a single model that included a fixed effect of hemisphere. There was little evidence of any interactions between group, age and hemisphere, so these interaction terms were removed and results are reported combined across hemispheres.

For both aims, all the results were very similar before and after adjustment for total intracranial volume, so unadjusted results have been reported. Given the influence that bronchopulmonary dysplasia,[29] major neonatal brain injuries[30] and socioeconomic status[31] can have on brain development in preterm-born children, we also conducted three separate sensitivity analyses: (1) adjusting for bronchopulmonary dysplasia; (2) excluding the two children in our sample who had major neonatal brain injury (one had intraventricular hemorrhage (IVH) grade 3 and one had both IVH grade 3 and cystic periventricular leukomalacia (PVL)); (3) adjusting for maternal education level at birth.

Given the large number of comparisons performed, the analyses with global and regional volumes and WM microstructure measures were interpreted based on the overall patterns and magnitudes of findings, rather than specific *P*-values.

Results

Participants

Baseline characteristics were similar between participants in this study in the caffeine ($n = 63$) and placebo ($n = 54$) groups, except fewer participants in the caffeine group had bronchopulmonary dysplasia and treatment for a patent ductus arteriosus than in the placebo group (Table 1). This is consistent with the findings of the overall CAP trial.[1]

There was little evidence that cognitive and motor outcomes at 11 years of age differed between the caffeine ($n = 63$) and placebo ($n = 54$) participants in this study (Table 1). This is in contrast to the results of the overall CAP trial (total 920 participants), which found that the caffeine group had better motor outcomes at 11 years of age than the placebo group.[5] However, the magnitudes of the differences observed in motor scores in our subset (Table 1) were similar to those reported for the CAP trial overall,[5] suggesting that this difference in study results is most likely due to a lack of power in our substudy rather than systematic differences in the substudy population.

Of the seven children included in this study who had cerebral palsy at age 11 years (Table 1), none had cystic PVL or IVH grade 3 or 4 in the neonatal period.

Table 1. Summary of the perinatal and 11-year characteristics by treatment group.

Characteristic	Caffeine $n = 63$	Placebo $n = 54$	Mean difference (95% CI)	*P*-value
Around birth[1]				
Birth weight in grams	960 (188)	935 (184)	26 (−43, 94)	0.46
Gestational age at birth in weeks	27.7 (1.7)	27.4 (1.7)	0.3 (−0.3, 0.9)	0.36
Male sex, *n* (%)	28 (44.4)	30 (55.6)	OR 0.6, 95% CI 0.3, 1.3	0.23
Multiple births, *n* (%)	21 (33.3)	16 (29.6)	OR 1.2, 95% CI 0.5, 2.6	0.67
Cystic periventricular leukomalacia, *n* (%)	0 (0.0)	1 (1.9)	NA	NA
Intraventricular hemorrhage grade 3/4, *n* (%)	0 (0.0)	2 (3.7)	NA	NA
Bronchopulmonary dysplasia, *n* (%)	18 (28.6)	33 (61.1)	OR 0.3, 95% CI 0.1, 0.6	0.001
Patent ductus arteriosus, *n* (%)	12 (19.1)	22 (40.7)	OR 0.3, 95% CI 0.1, 0.8	0.01
Corrected postmenstrual age at MRI in weeks	40.7 (1.1)[3]	40.9 (1.4)[4]	−0.1 (−0.9, 0.6)	0.71
Mother completed post-secondary school education, *n* (%)	25 (41.0)[7]	18 (33.3)	OR 1.4, 95% CI 0.6, 3.0	0.40
At 11 years[2]				
Corrected age at MRI in years	11.3 (0.4)	11.3 (0.4)	0.03 (−0.1, 0.2)	0.69
Corrected age at neurodevelopmental assessment in years	11.3 (0.4)	11.3 (0.4)	0.03 (−0.1, 0.2)	0.69
IQ				
Full scale	95.2 (12.4)	96.9 (13.4)[5]	−1.6 (−6.4, 3.1)	0.50
Verbal comprehension index	97.3 (11.5)	97.5 (13.7)[5]	−0.2 (−4.9, 4.4)	0.93
Perceptual reasoning index	94.5 (15.5)	96.8 (15.7)	−2.3 (−8.0, 3.4)	0.43
Wide range achievement test				
Word reading standard score	98.5 (15.2)	97.1 (13.1)	1.5 (−3.8, 6.7)	0.58
Sentence comprehension standard score	100.0 (13.9)	100.2 (15.9)	−0.2 (−5.7, 5.2)	0.94
Spelling standard score	96.9 (13.4)	95.5 (14.9)	1.4 (−3.8, 6.6)	0.59
Math computation standard score	86.4 (14.1)	89.1 (15.4)	−2.8 (−8.2, 2.6)	0.31
Digit span				
Forwards	7.3 (2.7)[5]	7.8 (2.8)	−0.5 (−1.5, 0.6)	0.38
Backwards	8.4 (2.5)[5]	8.4 (2.2)	0.1 (−0.8, 0.9)	0.88
Beery VMI				
Visual perception standard score	95.9 (11.6)	94.1 (13.9)	1.8 (−2.9, 6.4)	0.45
Motor coordination standard score	92.1 (12.6)	90.4 (15.5)	1.7 (−3.4, 6.8)	0.51
Movement ABC				
Total standard score	9.2 (3.2)[6]	8.7 (2.9)[5]	0.5 (−0.6, 1.7)	0.37
Manual dexterity standard score	8.1 (3.1)[7]	8.1 (2.9)[5]	0.03 (−1.1, 1.2)	0.95
Aiming/catching standard score	10.3 (3.8)[5]	9.6 (0.5)[5]	0.7 (−0.7, 2.0)	0.33
Balance standard score	10.1 (3.4)[7]	9.6 (2.6)[5]	0.6 (−0.6, 1.7)	0.33
Cerebral palsy, *n* (%)	5 (7.9)	2 (3.7)	OR 2.2, 95% CI 0.4, 12.1	0.35
Blindness, *n* (%)	0 (0.0)	0 (0.0)	NA	NA
Deafness, *n* (%)	1 (4.8)[3]	2 (9.5)[3]	OR 0.5, 95% CI 0.04, 5.7	0.56

Data are mean (SD), unless otherwise stated.

ABC, Assessment battery for children; CI, confidence interval; OR, odds ratio; MRI, magnetic resonance imaging; NA, not applicable; VMI, visual motor integration test.

[1]Perinatal data were collected by chart review. Intraventricular hemorrhage was defined as described previously.[40] Bronchopulmonary dysplasia was defined as requirement for supplemental oxygen at 36 weeks' postmenstrual age. Patent ductus arteriosus was defined as any case requiring medical or surgical treatment. We did not have data on retinopathy of prematurity.

[2]Data on functional outcomes at 11 years of age (cognitive, academic, motor and behavioral outcomes) were collected as detailed previously.[5] We did not collect any data on pubertal development.

[3]$n = 21$.

[4]$n = 22$.

[5]$n = 1$ with missing data.

[6]$n = 3$ with missing data.

[7]$n = 2$ with missing data.

Radiologists reviewed the MRI of these seven children at age 11 years, and reported that none of these children had features on their MRI that warranted clinical follow up.

Perinatal characteristics were similar between the $n = 117$ participants included in this study and the remaining $n = 85$ participants from the RWH who were excluded from this study (Table S1). Perinatal characteristics of our subset ($n = 117$) were also similar to those previously reported for the overall CAP cohort ($n = 920$).[5]

Cross-sectional analysis at age 11 years

Whole brain

Using FreeSurfer's QDEC, there was little evidence that cortical GM area, thickness and volume differed between treatment groups. Using TBSS, there was little evidence that FA, AD, RD, and MD differed between treatment groups (that is, there were no vertices for QDEC and no voxels for TBSS that differed between groups at $P < 0.05$, multiple comparison corrected, hence no data can be shown). Using the fixel-based analysis, there was evidence that fiber cross-section was lower in the caffeine group compared with the placebo group in 450 fixels (0.2% of the total 210998 fixels), located predominantly in the

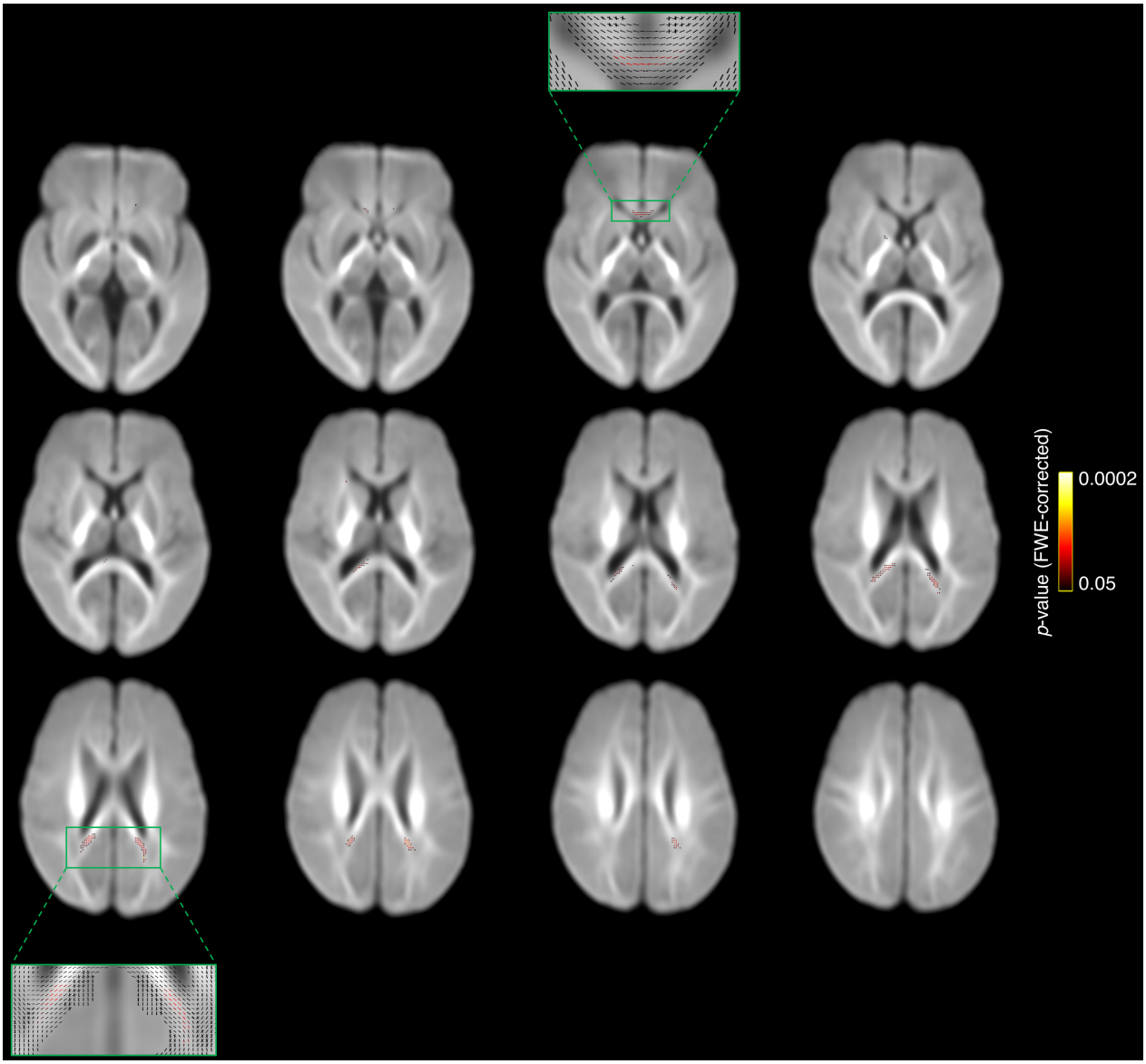


Figure 2. Results of the whole brain white matter microstructure analysis (fixel-based analysis) at 11 years of age. The fiber populations that had a lower fiber cross-section in the caffeine group compared with the placebo group at $P < 0.05$, family-wise error rate (FWE) corrected, are shown in red-yellow and overlaid on the study-specific fiber-orientation distribution template. These fibers were located mostly in the isthmus or splenium of the corpus callosum, as well as the genu of the corpus callosum, and a very small number were in the left anterior limb of the internal capsule. We have presented every second axial slice (in the range of the significant results). We have zoomed in on representative slices to show the fiber orientation distribution in these slices, which shows that the significant results were located in single fiber regions. These results are based on an analysis with $n = 116$ children (62 caffeine, 54 placebo), that is, one less than the total $n = 117$. One child was excluded from this analysis as they did not complete the $b = 3000$ sec/mm^2 diffusion sequence.

corpus callosum isthmus or splenium subregions, and to a lesser extent the genu, and a very small number were located in the right anterior limb of the internal capsule (Fig. 2). Only 6 fixels (0.0003% of the total fixels) in the left anterior limb of the internal capsule had lower values of the combined measure of fiber density and cross-section in the caffeine group compared with the placebo group (data not shown). There was little evidence that fiber density differed between treatment groups. Results were very similar in the three sensitivity analyses, but the number of fixels increased slightly in each sensitivity analysis compared with the original analysis (Table S2).

Global and regional volumes and white matter microstructure

Overall, there was little evidence that global brain volumes (Fig. 3A), cortical, subcortical and deep nuclear GM volumes and cerebellar volumes (Fig. 3B), and microstructure and volume of primary sensorimotor and cerebellar tracts (Fig. 3C) differed between treatment groups. However, there was some evidence that volume of the cerebellar tracts was lower in the caffeine group compared with the placebo group (Fig. 3C). All these results were very similar in the three sensitivity analyses (data not shown).

There was some evidence that the corpus callosum was thinner along much of its length in the caffeine group compared with the placebo group (Fig. 4A), and this difference was strongest in the rostral body and isthmus subregions (Fig. 4A and B). There was also evidence that corpus callosum area was smaller in the caffeine group compared with the placebo group, particularly in the genu, rostral body, and isthmus (Fig. 4B). Microstructure and volume of corpus callosum tracts were generally similar between treatment groups, although there was some evidence that RD and MD in all subregions, and particularly the genu, were higher in the caffeine group compared with the placebo group (Fig. 4B). These differences in the corpus callosum were generally very similar in the three sensitivity analyses; if anything, the strength and magnitude of the differences generally increased slightly after adjusting for bronchopulmonary dysplasia (data not shown).

Longitudinal analysis

There was little evidence that the rate of change in brain volumes varied between the caffeine and placebo groups (Fig. 5).

There was some evidence that the area of the corpus callosum increased more slowly in the caffeine group compared with the placebo group, particularly in the genu, rostral body, and isthmus (Fig. 6). There was also evidence that AD, RD, and MD in the corpus callosum tracts, particularly the genu, rostral body, and splenium, decreased more slowly in the caffeine group compared with the placebo group.

There was evidence that AD, RD, and MD (but not FA) within the regions of interest decreased more slowly in the caffeine group compared with the placebo group, and the evidence was stronger for the superior regions than the inferior regions (Fig. 7).

The results of the longitudinal analyses were very similar in the three sensitivity analyses (data not shown).

Discussion

Short-term neonatal caffeine treatment had little effect on the volume or microstructure of most of the brain 11 years later, except for the corpus callosum, which was smaller in the caffeine group. Additionally, caffeine was weakly associated with brain volumetric development from term-equivalent to 11 years of age, but caffeine was associated with slower growth of the corpus callosum over time, and slower decreases in WM diffusivities over time.

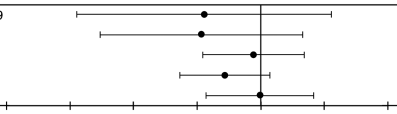
In our previous study, caffeine had little effect on brain volumes, but benefitted WM microstructure by reducing AD, RD, and MD in superior WM regions at the level of the centrum semiovale compared with placebo, at term-equivalent age.[7] In the current study, we showed that WM diffusivities decreased more slowly from term-equivalent to 11 years of age in the caffeine group compared with the placebo group, such that they generally did not differ between treatment groups at age 11 years. If we accept from previous studies that decreases in diffusivities, particularly RD and MD, are expected and beneficial during childhood development,[32,33] the slower

Figure 3. Global and regional brain volumes and white matter microstructure, contrasted between treatment groups at 11 years of age. Mean differences and *P*-values are from separate linear regression models for each MRI outcome, adjusted for age and sex of the child. The plots are visual representations of the mean differences and 95% confidence intervals (CI). For bilateral outcomes, data from the left and right hemispheres were analyzed in a single regression model, and results are presented as a single estimate for the difference for the two hemispheres, as there was little evidence of group by hemisphere interactions. Units are cm^3 for volumes and $\times 10^{-3}$ mm^2/sec for diffusivities. SD = standard deviation. The analyses are based on the total $n = 117$ (63 caffeine, 54 placebo) children, although some children are missing from some analyses because their images had artifact which affected that particular analysis: [a]$n = 3$ missing; [b]$n = 2$ missing; [c]$n = 1$ missing; [d]$n = 5$ missing; [e]$n = 4$ missing. The total numbers are lower for the tractography analyses ($n = 116$; 62 caffeine, 54 placebo) because one child in the caffeine group did not have $b = 3000$ sec/mm^2 diffusion images acquired and hence had to be excluded from the tractography analyses.

A. Global brain volumes

Brain region/tissue type	Caffeine, *n*=63 Mean	SD	Placebo, *n*=54 Mean	SD	Mean difference	95% CI Lower	95% CI Upper	*p*-value
Intracranial volume	1399	131	1429	109	-17.8	-57.9	22.2	0.38
Total brain tissue volume	1194	105	1222	89	-18.7	-50.5	13.2	0.25
Total cortical gray matter volume	545[a]	50	55[b]	43	-2.3	-18.2	13.7	0.78
Total white matter volume	399[a]	46	415[b]	44	-11.3	-25.5	2.9	0.12
Total cerebrospinal fluid volume	205	44	207	53	-0.3	-17.2	16.7	0.97

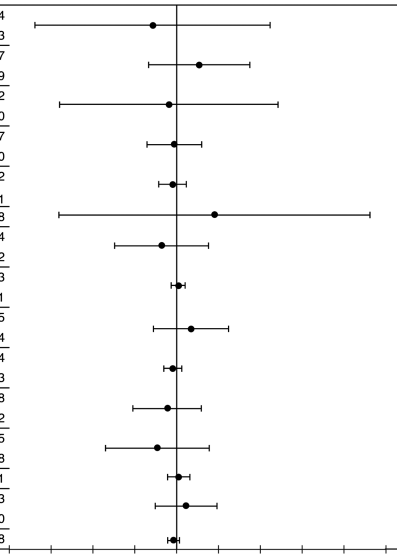
Plots of mean differences and 95% CI



B. Regional brain volumes

Brain region/tissue type	Sub-region	Caffeine, *n*=63 Mean	SD	Placebo, *n*=54 Mean	SD	Mean difference	95% CI Lower	95% CI Upper	*p*-value
Cortical gray matter (primary motor)	Precentral- left	14.88[a]	1.69	15.06[b]	1.84	-0.12	-0.68	0.45	0.69
	Precentral- right	14.52[a]	1.77	14.81[b]	1.73				
	Paracentral- left	4.44[a]	0.75	4.31[b]	0.77	0.11	-0.13	0.35	0.38
	Paracentral- right	4.87[a]	0.79	4.84[b]	0.69				
	Postcentral- left	11.03[a]	1.62	10.93[b]	1.42	-0.04	-0.56	0.48	0.89
	Postcentral- right	10.18[a]	1.59	10.52[b]	1.60				
Subcortical gray matter	Hippocampus- left	3.42	0.38	3.44	0.47	-0.01	-0.14	0.12	0.87
	Hippocampus- right	3.40	0.38	3.43	0.40				
	Amygdala- left	1.34	0.19	1.37	0.22	-0.02	-0.09	0.05	0.55
	Amygdala- right	1.27	0.20	1.28	0.21				
	Brainstem	19.12[a]	2.11	19.05[b]	2.28	0.18	-0.56	0.92	0.63
Deep nuclear gray matter	Thalamus- left	7.73	0.61	7.87	0.74	-0.07	-0.30	0.15	0.53
	Thalamus- right	7.54	0.59	7.61	0.72				
	Accumbens- left	0.49	0.10	0.48	0.13	0.01	-0.03	0.04	0.69
	Accumbens- right	0.43	0.07	0.43	0.11				
	Caudate- left	3.62	0.48	3.54	0.55	0.07	-0.11	0.25	0.46
	Caudate- right	3.64	0.53	3.61	0.54				
	Pallidum- left	1.59	0.14	1.62	0.14	-0.02	-0.06	0.02	0.39
	Pallidum- right	1.60	0.13	1.62	0.13				
	Putamen- left	4.80	0.48	4.85	0.58	-0.05	-0.21	0.12	0.58
	Putamen- right	4.71	0.46	4.82	0.52				
Cerebellar gray matter	Hemispheres- left	58.88	0.73	58.92	0.55	-0.09	-0.34	0.16	0.47
	Hemispheres- right	60.46	0.93	60.56	0.58				
	Vermis	6.07	0.15	6.07	0.11	0.01	-0.04	0.06	0.72
Cerebellar white matter	Hemispheres- left	4.10	0.44	4.08	0.33	0.04	-0.10	0.19	0.55
	Hemispheres- right	3.84	0.50	3.80	0.40				
	Vermis	0.25	0.09	0.27	0.08	-0.01	-0.04	0.01	0.30

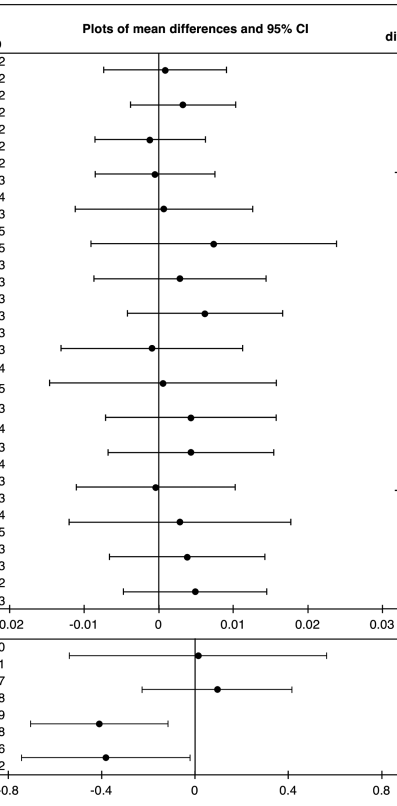
Plots of mean differences and 95% CI



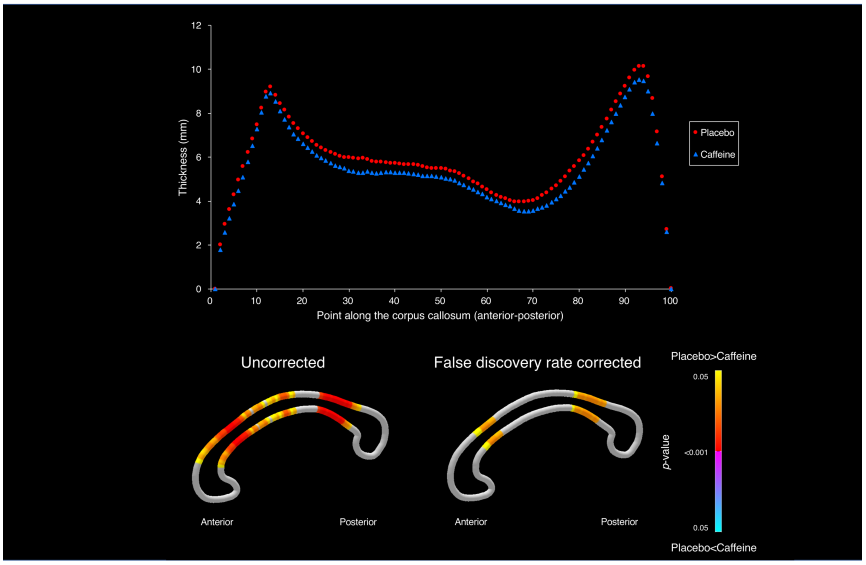
C. White matter tracts

Tract measure	Tract	Caffeine, *n*=62 Mean	SD	Placebo, *n*=54 Mean	SD	Mean difference	95% CI Lower	95% CI Upper	*p*-value
Fractional anisotropy	Corticospinal- left	0.46	0.03	0.45	0.02	0.001	-0.007	0.009	0.84
	Corticospinal- right	0.45	0.03	0.45	0.02				
	Somatosensory- left	0.42[c]	0.02	0.42	0.02	0.003	-0.004	0.010	0.36
	Somatosensory- right	0.42[c]	0.02	0.41	0.02				
	Cerebellar-thalamo-cortical - left	0.40[a]	0.02	0.40[c]	0.02	-0.001	-0.009	0.006	0.76
	Cerebellar-thalamo-cortical - right	0.40[a]	0.03	0.41[c]	0.02				
	Cortico-ponto-cerebellar- left	0.37[d]	0.02	0.38[e]	0.02	-0.0005	-0.009	0.008	0.90
	Cortico-ponto-cerebellar- right	0.37[d]	0.03	0.37[e]	0.03				
Axial diffusivity	Corticospinal- left	1.25	0.03	1.25	0.04	0.001	-0.011	0.013	0.91
	Corticospinal- right	1.26	0.04	1.26	0.03				
	Somatosensory- left	1.27[c]	0.05	1.26	0.05	0.007	-0.009	0.024	0.38
	Somatosensory- right	1.28[c]	0.05	1.27	0.05				
	Cerebellar-thalamo-cortical - left	1.20[a]	0.03	1.19[c]	0.03	0.003	-0.009	0.014	0.63
	Cerebellar-thalamo-cortical - right	1.19[a]	0.04	1.19[c]	0.03				
	Cortico-ponto-cerebellar- left	1.14[d]	0.03	1.14[e]	0.03	0.006	-0.004	0.017	0.24
	Cortico-ponto-cerebellar- right	1.15[d]	0.03	1.14[e]	0.03				
Radial diffusivity	Corticospinal- left	0.60	0.04	0.60	0.03	-0.001	-0.013	0.011	0.88
	Corticospinal- right	0.61	0.04	0.61	0.03				
	Somatosensory- left	0.66[c]	0.04	0.66	0.04	0.001	-0.015	0.016	0.94
	Somatosensory- right	0.66[c]	0.04	0.66	0.05				
	Cerebellar-thalamo-cortical - left	0.64[a]	0.03	0.63[c]	0.03	0.004	-0.007	0.016	0.46
	Cerebellar-thalamo-cortical - right	0.63[a]	0.04	0.63[c]	0.04				
	Cortico-ponto-cerebellar- left	0.64[d]	0.03	0.63[e]	0.03	0.004	-0.007	0.015	0.45
	Cortico-ponto-cerebellar- right	0.65[d]	0.04	0.64[e]	0.04				
Mean diffusivity	Corticospinal- left	0.81	0.03	0.82	0.03	-0.0004	-0.011	0.010	0.94
	Corticospinal- right	0.83	0.03	0.82	0.03				
	Somatosensory- left	0.86[c]	0.04	0.86	0.04	0.003	-0.012	0.018	0.71
	Somatosensory- right	0.87[c]	0.04	0.87	0.05				
	Cerebellar-thalamo-cortical - left	0.82[a]	0.03	0.82[c]	0.03	0.004	-0.007	0.014	0.47
	Cerebellar-thalamo-cortical - right	0.82[a]	0.03	0.81[c]	0.03				
	Cortico-ponto-cerebellar- left	0.81[d]	0.03	0.80[e]	0.02	0.005	-0.005	0.014	0.32
	Cortico-ponto-cerebellar- right	0.81[d]	0.03	0.81[e]	0.03				
Volume	Corticospinal- left	16.92	1.79	17.02	1.60	0.01	-0.54	0.56	0.97
	Corticospinal- right	17.28	1.72	17.24	1.61				
	Somatosensory- left	11.94[c]	0.92	11.72	0.97	0.09	-0.23	0.41	0.57
	Somatosensory- right	11.69[c]	1.06	11.80	1.18				
	Cerebellar-thalamo-cortical - left	13.16[a]	1.00	13.57[c]	0.99	-0.41	-0.70	-0.12	0.01
	Cerebellar-thalamo-cortical - right	12.85[a]	1.01	13.34[c]	1.08				
	Cortico-ponto-cerebellar- left	14.64[d]	1.12	15.15[e]	1.06	-0.38	-0.74	-0.02	0.04
	Cortico-ponto-cerebellar- right	14.43[d]	1.40	14.70[e]	1.22				

Plots of mean differences and 95% CI



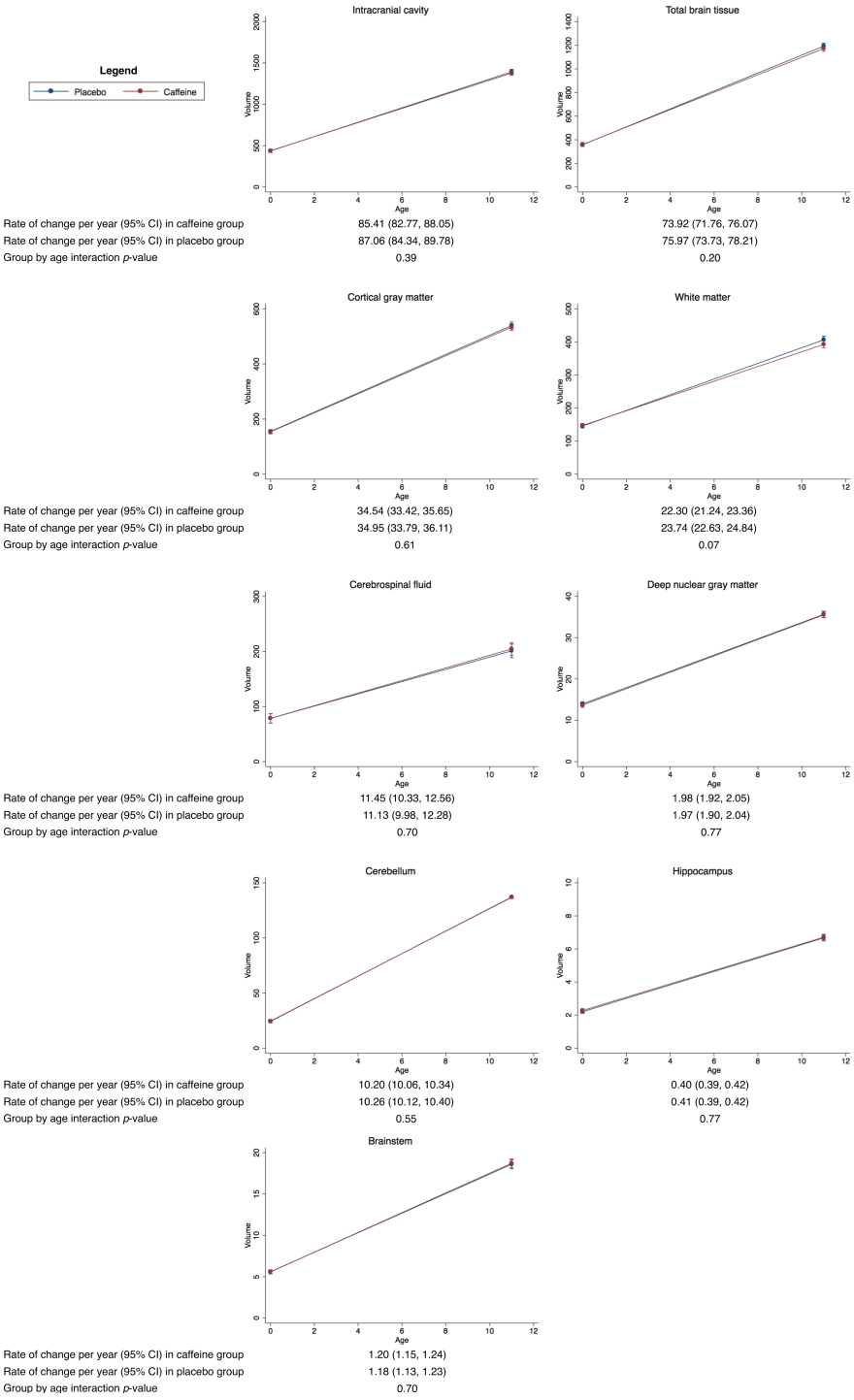
A. Corpus callosum thickness profile



B. Structure of the total corpus callosum and sub-regions

Corpus callosum measure	Sub-region	Caffeine, *n*=62 Mean	Caffeine, *n*=62 SD	Placebo, *n*=54 Mean	Placebo, *n*=54 SD	Plots of mean differences and 95% CI	Mean difference	95% CI lower	95% CI upper	*p*-value
Area	Total	4.91	1.03	5.43	0.84		-0.486	-0.812	-0.161	0.003
	Genu	1.35	0.31	1.52	0.28		-0.156	-0.261	-0.052	0.004
	Rostral body	0.69	0.16	0.77	0.14		-0.068	-0.118	-0.018	0.007
	Anterior mid body	0.60	0.14	0.65	0.11		-0.041	-0.085	0.003	0.067
	Posterior mid body	0.50	0.11	0.55	0.11		-0.042	-0.081	-0.003	0.033
	Isthmus	0.41	0.12	0.48	0.12		-0.065	-0.106	-0.023	0.002
	Splenium	1.34	0.33	1.46	0.31		-0.113	-0.231	0.005	0.061
Thickness	Total	0.51	0.08	0.55	0.08		-0.044	-0.072	-0.016	0.002
	Genu	0.49	0.08	0.53	0.07		-0.035	-0.060	-0.009	0.007
	Rostral body	0.55	0.10	0.61	0.11		-0.051	-0.085	-0.018	0.002
	Anterior mid body	0.52	0.10	0.55	0.09		-0.030	-0.064	0.005	0.090
	Posterior mid body	0.42	0.08	0.45	0.09		-0.028	-0.059	0.002	0.069
	Isthmus	0.41	0.11	0.47	0.12		-0.067	-0.107	-0.026	0.001
	Splenium	0.65	0.13	0.71	0.13		-0.054	-0.101	-0.008	0.023
FA	Total	0.49[a]	0.03	0.50[b]	0.02		-0.011	-0.022	-0.0003	0.043
	Genu	0.52[a]	0.05	0.54[b]	0.04		-0.017	-0.038	0.003	0.092
	Rostral body	0.44[a]	0.04	0.45[b]	0.04		-0.011	-0.026	0.004	0.143
	Anterior mid body	0.45[a]	0.04	0.47[b]	0.03		-0.010	-0.023	0.003	0.132
	Posterior mid body	0.47[a]	0.03	0.48[b]	0.02		-0.005	-0.016	0.006	0.377
	Isthmus	0.45[a]	0.04	0.46[b]	0.03		-0.007	-0.020	0.006	0.270
	Splenium	0.58[a]	0.06	0.60[b]	0.04		-0.018	-0.036	0.001	0.060
AD	Total	1.48[a]	0.07	1.48[b]	0.05		0.004	-0.020	0.028	0.767
	Genu	1.49[a]	0.09	1.49[b]	0.07		0.006	-0.023	0.036	0.675
	Rostral body	1.36[a]	0.08	1.37[b]	0.08		-0.005	-0.036	0.026	0.757
	Anterior mid body	1.37[a]	0.06	1.39[b]	0.07		-0.017	-0.043	0.009	0.202
	Posterior mid body	1.43[a]	0.07	1.42[a]	0.06		0.012	-0.014	0.037	0.372
	Isthmus	1.49[a]	0.10	1.49[b]	0.09		0.004	-0.032	0.041	0.823
	Splenium	1.73[a]	0.15	1.71[b]	0.12		0.019	-0.030	0.068	0.444
RD	Total	0.66[a]	0.06	0.64[b]	0.05		0.020	-0.002	0.042	0.070
	Genu	0.61[a]	0.07	0.58[b]	0.05		0.026	0.004	0.048	0.022
	Rostral body	0.66[a]	0.07	0.64[b]	0.06		0.015	-0.008	0.039	0.210
	Anterior mid body	0.65[a]	0.06	0.64[b]	0.06		0.010	-0.012	0.031	0.386
	Posterior mid body	0.67[a]	0.07	0.65[b]	0.06		0.016	-0.008	0.040	0.179
	Isthmus	0.73[a]	0.09	0.72[b]	0.08		0.019	-0.013	0.052	0.240
	Splenium	0.65[a]	0.14	0.62[b]	0.10		0.035	-0.012	0.082	0.146
MD	Total	0.93[a]	0.06	0.92[b]	0.05		0.015	-0.007	0.036	0.176
	Genu	0.90[a]	0.06	0.88[b]	0.04		0.023	0.004	0.043	0.018
	Rostral body	0.89[a]	0.07	0.88[b]	0.06		0.008	-0.016	0.031	0.531
	Anterior mid body	0.89[a]	0.05	0.89[b]	0.06		0.0002	-0.021	0.021	0.983
	Posterior mid body	0.92[a]	0.07	0.91[b]	0.06		0.015	-0.008	0.038	0.212
	Isthmus	0.99[a]	0.09	0.97[b]	0.07		0.014	-0.017	0.046	0.373
	Splenium	1.01[a]	0.14	0.98[b]	0.10		0.030	-0.016	0.075	0.199
Tract volume	Total	41.68[a]	3.46	42.03[b]	3.69		-0.274	-1.588	1.039	0.682
	Genu	6.25[a]	0.81	6.10[b]	1.03		0.150	-0.187	0.487	0.379
	Rostral body	6.16[a]	0.76	6.31[b]	0.67		-0.142	-0.410	0.126	0.300
	Anterior mid body	6.40[a]	0.71	6.42[b]	0.75		-0.019	-0.290	0.253	0.894
	Posterior mid body	7.20[a]	0.93	7.43[b]	0.84		-0.213	-0.558	0.133	0.228
	Isthmus	7.71[a]	1.01	7.64[b]	1.03		0.066	-0.315	0.447	0.736
	Splenium	7.94[a]	0.82	8.13[b]	0.88		-0.166	-0.486	0.154	0.310

Figure 4. Structure of the corpus callosum, contrasted between treatment groups at 11 years of age, based on the corpus callosum segmentation. (A) Top: Mean thickness at each of 100 points along the corpus callosum; bottom: results of *t*-tests comparing thickness at each point between treatment groups, with colors indicating *P*-values. (B) Data from the total corpus callosum and six sub-regions. Mean differences are from separate linear regression models for each outcome, adjusted for age and sex of the child. The plots are visual representations of the mean differences and 95% confidence intervals (CI). Units are cm^2 for area, cm for thickness and $\times 10^{-3}$ mm^2/sec for diffusivities. SD = standard deviation. The analyses are based on a total n = 116 (62 caffeine, 54 placebo) children, that is, one less than the total n = 117 children. One child from the caffeine group was excluded from all the corpus callosum analyses because they had artefact on their structural image and because they did not have b = 3000 sec/mm^2 diffusion images acquired. Additional children were excluded from the corpus callosum tractography analysis, because their diffusion images had artefact or structural abnormalities which affected that particular analysis: [a]n = 2 missing; [b]n = 5 missing.



Rate of change per year (95% CI) in caffeine group	85.41 (82.77, 88.05)	73.92 (71.76, 76.07)
Rate of change per year (95% CI) in placebo group	87.06 (84.34, 89.78)	75.97 (73.73, 78.21)
Group by age interaction *p*-value	0.39	0.20
Rate of change per year (95% CI) in caffeine group	34.54 (33.42, 35.65)	22.30 (21.24, 23.36)
Rate of change per year (95% CI) in placebo group	34.95 (33.79, 36.11)	23.74 (22.63, 24.84)
Group by age interaction *p*-value	0.61	0.07
Rate of change per year (95% CI) in caffeine group	11.45 (10.33, 12.56)	1.98 (1.92, 2.05)
Rate of change per year (95% CI) in placebo group	11.13 (9.98, 12.28)	1.97 (1.90, 2.04)
Group by age interaction *p*-value	0.70	0.77
Rate of change per year (95% CI) in caffeine group	10.20 (10.06, 10.34)	0.40 (0.39, 0.42)
Rate of change per year (95% CI) in placebo group	10.26 (10.12, 10.40)	0.41 (0.39, 0.42)
Group by age interaction *p*-value	0.55	0.77
Rate of change per year (95% CI) in caffeine group	1.20 (1.15, 1.24)	
Rate of change per year (95% CI) in placebo group	1.18 (1.13, 1.23)	
Group by age interaction *p*-value	0.70	

Figure 5. Rates of change in brain volumes from term-equivalent age to 11 years of age, contrasted between treatment groups. Results are from separate mixed effects models for each brain region, adjusted for sex of the child. The plots show the estimated means and 95% confidence intervals (CI) per group for each time point and the rate of change between time points from the mixed models. The y-axes show the volumes and the x-axes show age. Units are cm^3 for volumes and years for age. The results are based on the total number of children who had usable MRI data at either term-equivalent age or 11 years of age; for the intracranial cavity, total brain tissue, cerebrospinal fluid, deep nuclear gray matter and cerebellum, n = 187 (n = 70 with term-equivalent data plus n = 117 with 11-year data); for the cortical gray matter, white matter and brainstem, n = 182 (n = 70 with term-equivalent data plus n = 112 with 11-year data); for the hippocampus, n = 179 (n = 62 with term-equivalent data plus n = 117 with 11-year data).

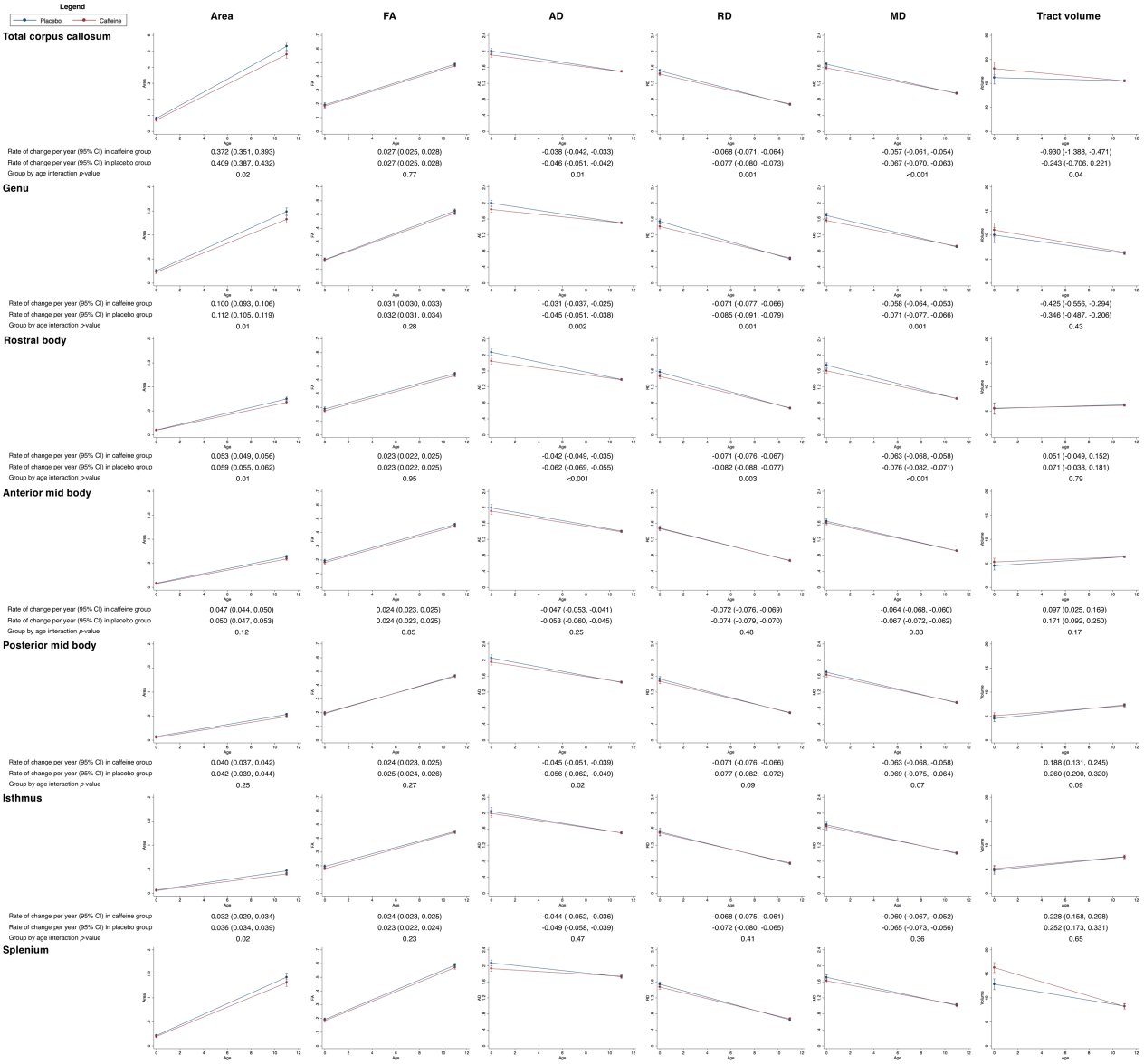


Figure 6. Rates of change in the structure of the total corpus callosum and sub-regions from term-equivalent age to 11 years of age, contrasted between treatment groups. Results are from separate mixed effects models for each corpus callosum region and parameter (area, thickness, diffusion value or tract volume), adjusted for sex of the child. The plots show the estimated means and 95% confidence intervals (CI) per group for each time point and the rate of change between time points from the mixed models. The y-axes show the parameters (area, thickness, diffusion value or tract volume) and the x-axes show age. Units are cm for thickness, cm^2 for area, cm^3 for volumes, $\times 10^{-3}$ mm^2/sec for diffusivities and years for age. The results are based on the total number of children who had usable MRI data at either term-equivalent age or 11 years of age; for the area measures, n = 144 (28 with term-equivalent data plus 116 with 11-year data); for the total tract diffusion and volume measures, n = 129 (20 plus 109); for the genu diffusion and volume measures, n = 137 (28 plus 109); for the rostral body diffusion and volume measures, n = 135 (26 plus 109); for the anterior mid body diffusion and volume measures, n = 133 (24 plus 109); for the posterior mid body diffusion and volume measures, n = 134 (25 plus 109); for the isthmus diffusion and volume measures, n = 134 (25 plus 109); for the splenium diffusion and volume measures, n = 137 (28 plus 109). FA, fractional anisotropy; AD, axial diffusivity; RD, radial diffusivity; MD, mean diffusivity.

decreases in diffusivities over time in the caffeine group may suggest that any early benefits of caffeine treatment on WM microstructure weaken over time.

However, caffeine appeared to influence corpus callosum size, and microstructure to a lesser extent, at age 11 years. The smaller fiber cross-section, thickness and

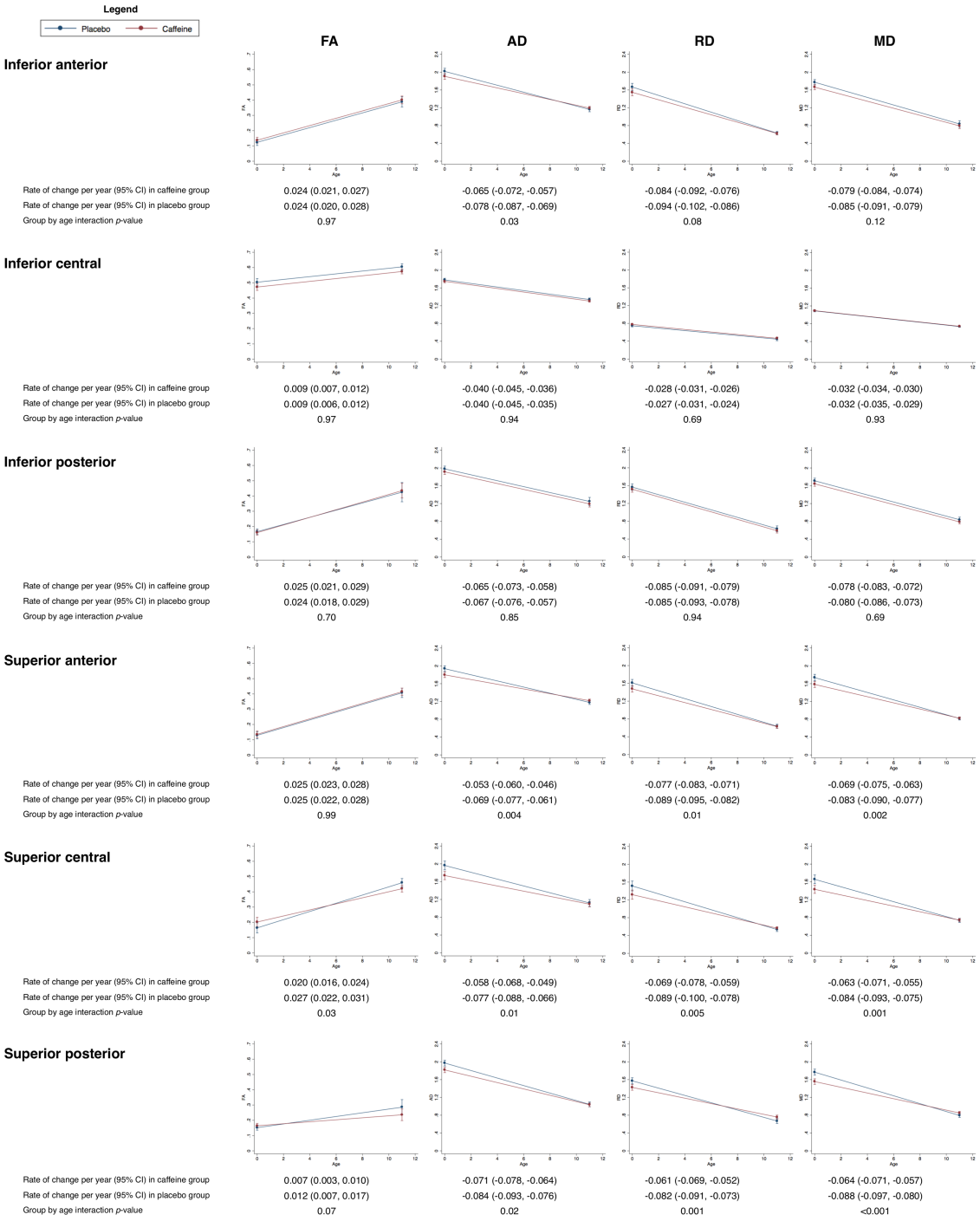


Figure 7. Rates of change in diffusion values in regions of interest from term-equivalent age to 11 years of age, contrasted between treatment groups. Results are from separate mixed effects models for each region and parameter (FA, AD, RD, and MD), adjusted for sex of the child. The plots show the estimated means and 95% confidence intervals (CI) per group for each time point and the rate of change between time points from the mixed models. The y-axes show the parameters (FA, AD, RD, MD) and the x-axes show age. Results are combined across brain hemispheres as there was negligible evidence that results differed by hemisphere. Units are $\times 10^{-3}$ mm^2/sec for diffusivities and years for age. The regions of interest were drawn on diffusion images from 28 infants at term-equivalent age.[7] Of those 28 infants, 19 had MRI at 11 years of age, and matching regions of interest were drawn on the 11-year diffusion images of these 19 children. These longitudinal analysis results are based on the 28 infants with usable term-equivalent data and the 19 children with usable 11-year data. FA, fractional anisotropy; AD, axial diffusivity, RD, radial diffusivity; MD, mean diffusivity.

area in the caffeine group compared with the placebo group found with both the fixel-based analysis and specific corpus callosum segmentation suggests the caffeine group's corpus callosum fibers are taking up less space. The magnitude of the area difference (~half a square centimeter) did not appear to be marginal, rather it is similar to the magnitude of the difference in corpus callosum area between very preterm and term-born children reported previously.[34] This finding could reflect axon loss in the caffeine group, with the concurrent lack of differences in the fiber density measure from the fixel-based analysis suggesting the remaining axons are still densely packed.[22] The finding could also reflect differences in myelin between caffeine and placebo groups, but we cannot be certain of this, because none of the techniques we used specifically measure myelin. Future analyses using MRI acquisitions and analysis techniques more sensitive to myelin would be beneficial.[35,36] Another possibility is that the finding reflects more coherent alignment of axons in the caffeine group. Because the precise cellular interpretation is unclear, it is not possible for us to conclude whether this difference would affect the ability of the corpus callosum to transfer information and in turn affect the cognitive or motor functioning of children treated with caffeine. Our finding may line up with some studies using animal models that reported adverse effects of caffeine on the developing brain.[6] Regardless, the clinical impact of this finding is likely to be negligible, given the overall CAP trial clearly indicated that caffeine is associated with benefits, and no harm, to short- and long-term health and neurodevelopmental outcomes for infants born low birthweight.[1–5]

The mechanisms for caffeine's beneficial neurological effects have never been clear.[2] Given that caffeine had no clear benefits on brain structure at age 11 years, our results do not support that brain structure at age 11 years provides a link between caffeine and improved neurodevelopmental outcomes, although brain-behavior relationships require direct investigation in future. The early improvements to WM microstructure in our previous study[7] may be more important than later brain development for determining neurodevelopmental outcomes. It is also possible that, rather than acting directly on the brain, caffeine may act indirectly by reducing comorbidities such as bronchopulmonary dysplasia and retinopathy of prematurity,[1,2] which themselves are strongly associated with neurodevelopmental disabilities.[37,38]

The major strength of our study is that it is part of a large randomized controlled trial, which is unlikely to be replicated due to the clear clinical benefits of caffeine. However, our study is limited in that only a small sample of children from the CAP trial had MRI, reducing our power to make inferences about the effects of caffeine on the brain. MRI is also inherently limited in that it does not directly measure brain structure and has too low resolution to identify alterations induced by caffeine at a cellular level. Additional follow-up of the CAP children would be beneficial, because until brain development has plateaued in late adolescence or adulthood, any differences between treatment groups may not reflect benefits or risks of caffeine, but may simply reflect normal variations during a period of rapid brain development. There are many factors known to influence brain development, which could confound our findings, including perinatal medical factors, environmental and sociodemographic factors, and pubertal factors.[30,31,39] Our results were independent of three important factors that influence brain development in preterm-born children: bronchopulmonary dysplasia, major neonatal brain injuries and maternal education level, which may relate to socioeconomic status.

In conclusion, our study suggests there are no clear benefits of caffeine on brain structure and development at age 11 years that are detectable by MRI, although caffeine may affect long-term corpus callosum development.

Acknowledgments

This research was conducted within the Developmental Imaging research group, Murdoch Children's Research Institute and the Children's MRI Centre, Royal Children's Hospital, Melbourne, Australia. We thank the Royal Children's Hospital Medical Imaging staff for their assistance and expertise in the collection of the MRI data included in this study. We thank the CAP Steering Committee, chaired by Barbara Schmidt, for permitting the release of the CAP study randomization sequence for the children who are included in this report. This work was supported by the National Health and Medical Research Council of Australia (Project Grants No. 237117 and No. 108706; Program Grant No. 606789; Centre of Research Excellence No. 1060733; Fellowship No. 1081288 to PJA, No. 1127984 to KJL, No. 1141354 to JLYC and No. 1085754 to DKT). This work was also generously supported by The Royal Children's Hospital Foundation (Grant no. RCH1000) devoted to raising funds for research at The Royal Children's Hospital, as well as the Murdoch Children's Research Institute, the Royal Children's Hospital, Department of Paediatrics at The University of Melbourne and the Victorian Government's Operational Infrastructure Support Program.

Role of the funding sources: The funding sources had no role in the design, implementation, analysis, interpretation, or writing of the results of this study, or in the decision to submit.

Author Contributions

Conception and design of the study: LWD, PJA, JLYC, DKT. Acquisition and analysis of data: all authors. Drafting a significant portion of the manuscript or figures (i.e., a substantial contribution beyond copy editing and approval of the final draft, which is expected of all authors): CEK.

Conflict of Interest

Nothing to report.

References

1. Schmidt B, Roberts RS, Davis P, et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006;354:2112–2121.
2. Schmidt B, Roberts RS, Davis P, et al. Long-term effects of caffeine therapy for apnea of prematurity. N Engl J Med 2007;357:1893–1902.
3. Doyle LW, Schmidt B, Anderson PJ, et al. Reduction in developmental coordination disorder with neonatal caffeine therapy. J Pediatr 2014;165(356–359):e352.
4. Schmidt B, Anderson PJ, Doyle LW, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012;307:275–282.
5. Schmidt B, Roberts RS, Anderson PJ, et al. Academic performance, motor function, and behavior 11 years after neonatal caffeine citrate therapy for apnea of prematurity: an 11-year follow-up of the CAP randomized clinical trial. JAMA Pediatr 2017;171:564–572.
6. Atik A, Harding R, De Matteo R, et al. Caffeine for apnea of prematurity: effects on the developing brain. Neurotoxicology 2017;58:94–102.
7. Doyle LW, Cheong J, Hunt RW, et al. Caffeine and brain development in very preterm infants. Ann Neurol 2010;68:734–742.
8. Ashburner J, Friston KJ. Unified segmentation. NeuroImage 2005;26:839–851.
9. Fischl B. FreeSurfer. NeuroImage 2012;62:774–781.
10. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis I. Segmentation and surface reconstruction. NeuroImage 1999;9:179–194.
11. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. NeuroImage 1999;9:195–207.
12. Fischl B, Salat DH, Busa E, et al. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341–355.
13. Desikan RS, Segonne F, Fischl B, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. NeuroImage 2006;31:968–980.
14. Patenaude B, Smith SM, Kennedy DN, et al. A Bayesian model of shape and appearance for subcortical brain segmentation. NeuroImage 2011;56:907–922.
15. Diedrichsen J. A spatially unbiased atlas template of the human cerebellum. NeuroImage 2006;33:127–138.
16. Diedrichsen J, Balsters JH, Flavell J, et al. A probabilistic MR atlas of the human cerebellum. NeuroImage 2009;46:39–46.
17. Adamson C, Beare R, Walterfang M, et al. Software pipeline for midsagittal corpus callosum thickness profile processing : automated segmentation, manual editor, thickness profile generator, group-wise statistical comparison and results display. Neuroinformatics 2014;12:595–614.
18. Adamson CL, Wood AG, Chen J, et al. Thickness profile generation for the corpus callosum using Laplace's equation. Hum Brain Mapp 2011;32:2131–2140.
19. Thompson DK, Inder TE, Faggian N, et al. Characterization of the corpus callosum in very preterm and full-term infants utilizing MRI. NeuroImage 2011;55:479–490.
20. Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage 2006;31:1487–1505.
21. Bach M, Laun FB, Leemans A, et al. Methodological considerations on tract-based spatial statistics (TBSS). NeuroImage 2014. https://doi.org/10.1016/j.neuroimage.2014.06.021.
22. Raffelt DA, Tournier JD, Smith RE, et al. Investigating white matter fibre density and morphology using fixel-based analysis. NeuroImage 2017;144:58–73.
23. Beare RJ, Chen J, Kelly CE, et al. Neonatal brain tissue classification with morphological adaptation and unified segmentation. Front Neuroinform 2016;. https://doi.org/10.3389/fninf.2016.0001212.
24. Loh WY, Connelly A, Cheong JL, et al. A New MRI-Based Pediatric Subcortical Segmentation Technique (PSST). Neuroinformatics 2016;14:69–81.
25. Thompson DK, Wood SJ, Doyle LW, et al. Neonate hippocampal volumes: prematurity, perinatal predictors, and 2-year outcome. Ann Neurol 2008;63:642–651.
26. Greve DN, Van der Haegen L, Cai Q, et al. A surface-based analysis of language lateralization and cortical asymmetry. J Cogn Neurosci 2013;25:1477–1492.
27. Winkler AM, Ridgway GR, Webster MA, et al. Permutation inference for the general linear model. NeuroImage 2014;. https://doi.org/10.1016/j.neuroimage.2014.01.060.
28. Raffelt DA, Smith RE, Ridgway GR, et al. Connectivity-based fixel enhancement: whole-brain statistical analysis of diffusion MRI measures in the presence of crossing fibres. NeuroImage 2015;117:40–55.
29. Alexandrou G, Martensson G, Skiold B, et al. White matter microstructure is influenced by extremely preterm

birth and neonatal respiratory factors. Acta Paediatr 2014;103:48–56.
30. Inder TE, Warfield SK, Wang H, et al. Abnormal cerebral structure is present at term in premature infants. Pediatrics 2005;115:286–294.
31. Hackman DA, Farah MJ, Meaney MJ. Socioeconomic status and the brain: mechanistic insights from human and animal research. Nat Rev Neurosci 2010;11:651–659.
32. Lebel C, Beaulieu C. Longitudinal development of human brain wiring continues from childhood into adulthood. J Neurosci 2011;31:10937–10947.
33. Thompson DK, Lee KJ, Egan GF, et al. Regional white matter microstructure in very preterm infants: predictors and 7 year outcomes. Cortex 2014;. https://doi.org/10.1016/j.cortex.2013.11.010.
34. Thompson DK, Lee KJ, van Bijnen L, et al. Accelerated corpus callosum development in prematurity predicts improved outcome. Hum Brain Mapp 2015;36:3733–3748.
35. Deoni SC, Rutt BK, Arun T, et al. Gleaning multicomponent T1 and T2 information from steady-state imaging data. Magn Reson Med 2008;60:1372–1387.
36. Glasser MF, Van Essen DC. Mapping human cortical areas in vivo based on myelin content as revealed by T1- and T2-weighted MRI. J Neurosci 2011;31:11597–11616.
37. Anderson PJ, Doyle LW. Neurodevelopmental outcome of bronchopulmonary dysplasia. Semin Perinatol 2006;30:227–232.
38. Schmidt B, Asztalos EV, Roberts RS, et al. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA 2003;289:1124–1129.
39. Lebel C, Deoni S. The development of brain white matter microstructure. NeuroImage 2018. https://doi.org/10.1016/j.neuroimage.2017.12.097.
40. Papile LA, Burstein J, Burstein R, et al. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529–534.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Perinatal characteristics contrasted between included participants and excluded participants from the Royal Women's Hospital, Melbourne.
Table S2. Results of the fixel-based analysis, before and after adjusting for possible confounding factors.

Original article

The effect of venous caffeine on the prevention of apnea of prematurity in the very preterm infants in the neonatal intensive care unit of Shahid Motahhari Hospital, Urmia, during a year

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J. Adv. Pharm. Technol. Res.

Abstract

Due to the importance of prevention of apnea of prematurity in the very preterm infants and the side effects of using methylxanthines in preterm infants, the present study was conducted and aimed at investigating the effects of prophylactic caffeine on the incident of apnea (short-term consequence). This is a clinical–experimental trial, in which the infants were included after receiving written consent from their parents. The infants were randomly divided into two groups, namely, Group A (receive caffeine) and Group B (did not receive caffeine). After sampling of the collected data, the two groups were analyzed using statistical tests using SPSS software 23. Among the 50 infants in the caffeine group and 50 infants in the control group, 1 (2%) and 2 (4%) infants required long-term oxygen, respectively. Three (6%) infants from the caffeine group and 2 (4%) infants from the control group had an intraventricular hemorrhage. Two (4%) infants from the caffeine group and 1 (2%) infant from the control group had a positive patent ductus arteriosus and needed treatment. Among the 50 infants in the caffeine group and 50 infants in the control group, 7 (14%) and 9 (18%) infants had apnea, respectively. According to the Fisher's exact test, there was no significant difference between the incident of apnea in the two groups (P = 0.58). Ten (20%) infants from the caffeine group and 7 (14%) infants from the control group died. The prescription of prophylactic caffeine had no effect on the incident of apnea in the infants. Hence, the use of that should be limited to the preterm infants lower than 1250 g in the prophylactic form.

Key words: Apnea, methylxanthines, very-low-birthweight infants

INTRODUCTION

In general, mortality of the preterm infants, especially the low-weight infants, is more than the normal infants, and these infants are prone to different kinds of short- and long-term diseases after birth.[1] Apnea of prematurity is one of the problems with which the very preterm infants face.[2] Experts have not still achieved a joint conclusion about the prevention and treatment of apnea; there are many uncertainties up to the present time.[3] Methylxanthines such as caffeine, theophylline, and aminophylline are considered as the major treatments of apnea through nasal continuous positive

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Access this article online	
Quick Response Code:	Website:

www.japtr.org

DOI:
10.4103/japtr.JAPTR_334_18

How to cite this article: Fakoor Z, Makooie AA, Joudi Z, Asl RG. The effect of venous caffeine on the prevention of apnea of prematurity in the very preterm infants in the neonatal intensive care unit of Shahid Motahhari Hospital, Urmia, during a year. J Adv Pharm Technol Res 2019;10:16-9.

airway pressure (CPAP); however, dose, usage period, and the long-term complications of using these strategies have not been still exactly specified.[4] Treatment with methylxanthines is used for the prevention of the following attacks of apnea in the preterm infants with apnea.[5] Methylxanthines improve the lung mechanics by increasing minute ventilation, reducing the respiratory depression caused by hypoxia, increasing the brainstorm sensitivity to the density of the blood carbon dioxide, improving the contraction and activity of diaphragm and bronchodilation, and reducing the periodic breathing.[2,6] Hydrophobic properties of caffeine let it easily pass through all biological membranes such as the blood– brain barrier and enter central nervous system (CNS).[4] The ability of methylxanthines regarding the competitiveness of the adenosine receptors in CNS is a mechanism that stimulates respiratory rhythm by these factors. A secondary mechanism may also occur by the effects of methylxanthines on gamma-aminobutyric acid receptors, phosphodiesterase inhibition, and calcium release (Ca^{2+}).[7] The objective of the present study was to determine the effect of the venous caffeine on the prevention of apnea of prematurity.

MATERIALS AND METHODS

This study is a clinical–experimental trial that was conducted on the very preterm infants with a gestational age ≤32 weeks and a birthweight ≤1500 g in the Neonatal Intensive Care Unit (NICU) Department of Shahid Motahhari Hospital, Urmia. The infants were included in the study after receiving written consent from their parents. They were randomly divided into two groups, namely, Group A and Group B. 20 mg/kg of venous caffeine was injected to Group A in the 2nd day of birth (24–48 h). Then, a maintenance dose was injected 24 h after the first injection with the daily dose of 5 mg/kg. Group B did not receive caffeine. The infants were taken under cardiovascular-pulmonary monitoring, control of the number of heartbeats and number of breaths, and the control of arterial oxygen saturation. Due to the effectiveness of the birthweight on the study consequences, the patients were divided into three groups (<1000 g, 1000–1249 g, and 1250–1500 g) regarding the birthweight. After sampling of the collected data, the two groups were analyzed by the statistical tests using SPSS 23, IBM SPSS Statistics for Windows (IBM SPSS, Armonk, NY, USA).

RESULTS

In this study, 100 very preterm infants hospitalized in the NICU Department of Shahid Motahhari Hospital, Urmia, were included in the study with a weight of 1228.80 ± 22.26 g (with a minimum of 600 and maximum of 1500 and the weight median of 600 g). They were divided into two groups: caffeine and control groups (50 infants in each group). The average gestational age was 29.21 ± 0.11 weeks, and the average Apgar score was 6.23 ± 0.11 weeks. Among 100 infants of the study, 52 (52%) were female and 48 (48%) were male. Twenty-seven (27%) and 73 (73%) infants were born through natural delivery and cesarean, respectively. Among the infants of the caffeine group, 11 (22%) infants weighed <1000 g, 15 (30%) weighed between 1000 and 1249 g, and 24 (48%) weighed between 1250 and 1500 g. Among the infants of the control group, 4 (8%) infants weighed <1000 g, 17 (34%) weighed between 1000 and 1249 g, and 29 (58%) weighed between 1250 and 1500 g. According to the Chi-square test, there was no significant difference between the weight of the infants in the two groups ($P = 0.14$). The average weights in the caffeine and control groups were 1192.0 ± 249.61 g and 1265.50 ± 187.32 g, respectively. According to the *t*-test, there was no significant difference between the average weight in the two groups ($P = 0.09$). The average gestational ages in the caffeine and control groups were 29.04 ± 1.30 and 29.38 ± 1.0 weeks, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the gestational age ($P = 0.14$). The average Apgar score in the caffeine and control groups were 6.14 ± 1041 and 6.32 ± 0.81, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the Apgar score (P =

0.45). Among 50 infants of the caffeine group, 27 (54%) were female and 23 (46%) were male. Among 50 infants of the control group, 25 (50%) were female and 25 (50%) were male. According to the Chi-square test, there was no significant relationship between the two groups in terms of the patients' gender ($P = 0.68$). Among 50 infants in the caffeine group, 14 (28%) and 36 (72%) were born through natural delivery and cesarean, respectively. Among 50 infants in the control group, 13 (26%) and 37 (74%) were born through natural delivery and cesarean, respectively. According to the Chi-square test, there was no significant difference between the two groups in terms of the infants' type of birth ($P = 0.77$). The average respiratory distress syndrome (RDS) score in the caffeine and control groups were 5.58 ± 0.97 and 5.34 ± 1.13, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of RDS score ($P = 0.25$). Among 100 infants of the study, 55 (55%) received surfactant and 45 (45%) did not receive it. Among 50 infants in the caffeine group, 31 (62%) received surfactant and 19 (38%) did not receive surfactant. Among 50 infants in the control group, 24 (48%) received surfactant and 26 (52%) did not receive surfactant. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the use of surfactant ($P = 0.14$). In the caffeine and control groups, 7 (14%) and 9 (18%) infants had apnea, respectively. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the incident of apnea ($P = 0.58$). In the caffeine (50 infants) and control (50 infants) groups, 9 (18%) and 9 (18%) infants had bradycardia (the heart rate <100 beats per minute), respectively. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the incident of bradycardia ($P = 1$).

In the caffeine (50 infants) and control (50 infants) groups, 10 (20%) (<85%) and 10 (20%) infants had saturation decline. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the incident of saturation decline ($P = 0.1$). Among 50 infants of the caffeine group, 19 (38%) needed environmental oxygen and 31 (62%) did not need environmental oxygen. Among 50 infants of the control group, 11 (22%) needed environmental oxygen and 39 (78%) did not need environmental oxygen. According to the Fisher's exact test, there was no significant difference between the two groups in terms of the need for environmental oxygen ($P = 0.08$). Among 50 infants of the caffeine group, 38 (76%) needed a headbox and 12 (24%) did not need an oxygen headbox. Among 50 infants of the control group, 42 (84%) infants needed a headbox and 8 (16%) infants did not need an oxygen headbox. According to the Chi-square test, there was no significant difference between the two groups in terms of the need for the oxygen head ($P = 0.31$). In the caffeine (50 infants) and control (50 infants) groups, 43 (86%) and 37 (74%) infants needed NCPAP, respectively. According to the Chi-square test, there was no significant difference between the two groups in terms of the need for NCPAP ($P = 0.13$). In the caffeine (50 infants) and control (50 infants) groups, 7 (14%) and 4 (8%) infants needed a medical ventilator, respectively. According to the Chi-square test, there was no significant difference between the two groups in terms of the need for a medical ventilator ($P = 0.33$). The average days of the need for environmental oxygen in the caffeine and control groups were 7.13 ± 3.12 and 6.77 ± 3.32, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the need for environmental oxygen ($P = 0.64$). The average days of the need for a headbox in the caffeine and control groups were 3.79 ± 2.62 and 3.28 ± 2.78, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the need for a headbox ($P = 0.4$). The average days of the need for NCPAP in the caffeine and control groups were 3.81 ± 2.34 and 3.43 ± 2.56, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the need for NCPAP ($P = 0.48$). The average need for mechanical ventilation in the caffeine and control groups was 4 ± 3 and 4.50 ± 5.06 days, respectively. According to the *t*-test, there was no significant difference between the two groups in terms of the duration of mechanical ventilation ($P = 0.83$). The average hospitalization period in the caffeine and control groups was 13.88 ± 6.74 and 15.72 ± 10.23, respectively. According to the *t*-test, there was a significant difference between the two groups in terms of the hospitalization period ($P = 0.02$) [Table 1].

In the caffeine (50 infants) and control (50 infants) groups, 3 (6%) and 2 (4%) infants had positive intraventricular hemorrhage (IVH), respectively. According to the Chi-square test, there was no significant relationship between the two groups in terms of IVH ($P = 0.81$). In the caffeine (50 infants)

Table 1: Comparison of the mean and standard deviation of the need for environmental oxygen, headbox, nasal continuous positive airway pressure, mechanical ventilation, and the hospitalization period in the two groups

Variable	Caffeine group	Control group	*P*
Need for environmental oxygen	7.13±3.12	6.77±3.32	0.64
Need for headbox	3.79±2.62	3.28±2.78	0.4
Need for NCPAP	3.81±2.34	3.43±2.56	0.48
Need for mechanical ventilation	4±3	4.50±5.06	0.83
Hospitalization period	13.88±6.74	15.72±10.23	0.02

NCPAP: Nasal continuous positive airway pressure

and control (50 infants) groups, 2 (4%) and 1 (2%) infant had positive patent ductus arteriosus (PDA) and needed treatment, respectively. According to the Chi-square test, there was no significant relationship between the two groups in terms of PDA (P = 0.55). In the caffeine (50 infants) and control (50 infants) groups, 1 (2%) and 2 (4%) infants needed to receive long-term oxygen, respectively. According to the Chi-square test, there was no significant relationship between the two groups in terms of the need to receive long-term oxygen (P = 0.55). Ten (20%) and 7 (14%) infants in the caffeine and control groups died, respectively. According to the Chi-square test, there was no significant relationship between the two groups in terms of the infants' consequence (P = 0.42).

DISCUSSION

Caffeine is extensively used for the treatment of apnea; it stimulates the respiratory system and improves the function of the respiratory muscles.[8] The present study was a randomized control trial research in a health center that was conducted on the very preterm infants with a weight <1500 g and the gestational age of <32 weeks. The results of the study did not indicate a significant difference in the two groups of control and intervention (caffeine citrate injection) during hospitalization in terms of the incident rate of apnea, hypoxia, and bradycardia. The results of the studies of Schmidt *et al*.[9] showed that prophylactic caffeine significantly reduced apnea and the chronic lung disease (CLD). They mentioned the reason for the reduction as the reduced time of the need for oxygen, CPAP, and mechanical ventilation in the infants receiving prophylactic caffeine. In the present study, there was no difference between the two groups in terms of the time needed for complementary oxygen, NCPAP, and mechanical ventilation; as such, there was not also any difference between the two groups in terms of CLD. In the caffeine group, an infant was affected by a severe CLD, hospitalized for approximately 2 months, and discharged after recovery. Maybe, the difference between the present study and that of Schmidt *et al*. known as CAP Trial is the small sample size of the first and the very large sample size as well as the multicentric study of the latter. Moreover, the infants of the present study were <1500 g and they were heavier than the infants in the study of Schmidt *et al*.[9] Furthermore, this study recommends not using methylxanthines in the prophylactic way for the infants in the weight range of 1250–1500 g; the use of prophylactic should be limited to the infants who are <1250 g. In the present study, there was no difference in terms of the need for environmental oxygen, NCPAP, mechanical ventilation, and the usage period. Besides, there was no difference in terms of the incident of complications such as CLD, PDA, and IVH. Zhao *et al*.[10] conducted a study and showed that there is no difference between the two groups who received high- and low-dose caffeine in terms of the incident of the complications due to caffeine such as tachycardia, irritability, problem in feeding, hyperglycemia, high blood pressure, digestive disorders, and electrolyte disorders. Lodha *et al*.[11] conducted a study and the results indicated that, in the infants who received caffeine in the first 3 days of their life, their CLD and PDA significantly decreased compared to the group that received caffeine after 72 h. There was a difference between the two groups in terms of the hospitalization period. The infants who received caffeine had a lower hospitalization period; this may be because caffeine is a stimulating drug and makes the infants more conscious and results in better feeding. However, the study of Schmidt *et al*. showed that the caffeine group had a lower weight in the first 3 weeks compared to the placebo group.[10]

CONCLUSION

The prescription of prophylactic caffeine had no effect on the incident of apnea in the infants. Regarding the fact that the drug may cause some side effects and influence the infant weight, the use of that should be limited to the preterm infants with lower weights in the prophylactic form; it can be therapeutically used for the infants with higher weights in the case of apnea.

Financial support and sponsorship
Nil.

Conflicts of interest There are no conflicts of interest.

REFERENCES

1. Upadhyay K, Pourcyrous M, Dhanireddy R, Talati AJ. Outcomes of neonates with birth weight ≤500 g: A 20-year experience. J Perinatol 2015;35:768-72.
2. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, *et al.* Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol 2007;196:147.e1-8.
3. Eichenwald EC, Zupancic JA, Mao WY, Richardson DK, McCormick MC, Escobar GJ, *et al.* Variation in diagnosis of apnea in moderately preterm infants predicts length of stay. Pediatrics 2011;127:e53-8.
4. Atik A, Harding R, De Matteo R, Kondos-Devcic D, Cheong J, Doyle LW, *et al.* Caffeine for apnea of prematurity: Effects on the developing brain. Neurotoxicology 2017;58:94-102.
5. Henderson-Smart DJ, Subramaniam P, Davis PG. Continuous positive airway pressure versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev 2001;(4):CD001072.

6. Goldsmith JP, Karotkin EH. Assisted ventilation of the neonate. Philadelphia, W.B. Saunders, 1981. p. 31-2.
7. Fisone G, Borgkvist A, Usiello A. Caffeine as a psychomotor stimulant: Mechanism of action. Cell Mol Life Sci 2004;61:857-72.
8. Vliegenthart R, Miedema M, Hutten GJ, van Kaam AH, Onland W. High versus standard dose caffeine for apnoea: A systematic review. Arch Dis Child Fetal Neonatal Ed 2018;103:F523-9.
9. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, *et al.* Caffeine therapy for apnea of prematurity. N Engl J Med 2006;354:2112-21.
10. Zhao Y, Tian X, Liu G. Clinical effectiveness of different doses of caffeine for primary apnea in preterm infants. Zhonghua Er Ke Za Zhi 2016;54:33-6.
11. Lodha A, Seshia M, McMillan DD, Barrington K, Yang J, Lee SK, *et al.* Association of early caffeine administration and neonatal outcomes in very preterm neonates. JAMA Pediatr 2015;169:33-8.