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STUDY PROTOCOL: TREATMENT WITH CAFFEINE OF THE VERY PRETERM INFANT IN THE DELIVERY ROOM

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STUDY PROTOCOL: TREATMENT WITH CAFFEINE OF THE VERY PRETERM INFANT IN THE DELIVERY ROOM

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ABSTRACT

Introduction Early treatment with caffeine in the delivery room has been proposed to decrease the need for MV by limiting crises of apnea and improving respiratory mechanics in preterm infants. Thus, the purpose of this feasibility study is to verify the hypothesis that intravenous or enteral administration of caffeine can be performed in the preterm infant in the delivery room.

Methods and analysis In this multicenter prospective study, infants with 25^{+0}-29^{+6} weeks of gestational age will be enrolled and randomized to receive 20 mg/kg of caffeine citrate intravenously, via the umbilical vein, or enterally, through an orogastric tube, within 10 min of birth. Caffeine plasma level will be measured at 60±15 min after administration and 60±15 min before the next dose (5 mg/kg). The primary endpoint will be evaluation of the success rate of intravenous and enteral administration of caffeine in the delivery room. Secondary endpoints will be the comparison of success rate of intravenous versus oral administration and the evaluation of the need for MV in treated infants. In the absence of previous references, we arbitrarily decided to study 20 infants treated with intravenous caffeine and 20 infants treated with enteral caffeine. Primary endpoint will be evaluated measuring the success rate of intravenous and enteral caffeine administration which will be considered a success when it is followed by the achievement of the caffeine therapeutic level (8-25 µg/mL) 60±15 minutes before administration of the second dose.

Ethics and dissemination The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755) and by Comitato Etico Pediatrico Regione Toscana. The results will be published in peer-reviewed academic journals.

Trial registration: ClinicalTrials.gov Identifier NCT04044976; EudraCT Number 2018-003626-91

Keywords: Caffeine, delivery room, intravenous, enteral, preterm infant.

Strengths and limitations of this study

► This is the first study assessing the possibility of giving intravenous or enteral caffeine to preterm infants in the delivery room.

► Administration will be considered a success when it is followed by the achievement of caffeine blood therapeutic level.

►This study is preliminary to a large randomized controlled trial which will assess whether caffeine administered so early can reduce the risk of mechanical ventilation in very preterm infants.

► This research is being conducted across two sites and may not be representative of other Neonatal Intensive Care Units.

INTRODUCTION

Mechanical ventilation (MV) is one of the most important risk factors for the development of bronchopulmonary dysplasia (BPD) in the preterm infant, due to the early pulmonary inflammation from volume- and baro-trauma, and the high risk of ventilator-associated pneumonia (VAP)[1]. Therefore, in recent years particular attention has been paid to reduce the need for MV and some beneficial interventions, such as early application of nasal continuous positive airway pressure (CPAP) and surfactant treatment, has become widespread [1,2]. These have the common objective of promoting the development and maintenance of alveolar functional residual capacity (FRC), improving pulmonary compliance, reducing the work of breathing, and favoring gas exchanges [1,2]. Unfortunately, it has been found that nasal CPAP in combination or not with surfactant administration fails to prevent MV in about 45-50% of treated infants [3]. In fact, the need for MV often does not depend on the severity of respiratory distress syndrome (RDS), which however remains an important factor, but especially in mild-moderate forms of RDS can be due to the onset of relapsing episodes of apnea. Therefore, it has been proposed to treat very preterm infants with caffeine in the delivery room already in the first minute of life. In a recent pilot study, Katheria et al. randomized 21 infants with gestational age <29 weeks to receive 20 mg/kg of caffeine citrate within 2 h of life or at 12 hours of life [4]. They found that early treatment decreased the need for MV (27 vs. 70%) in comparison to late treatment and allowed an overall hemodynamic improvement of early treated patients [4]. Subsequently, Dekker et al. randomized 23 infants of 24-29 gestational weeks to receive 10 mg/kg of caffeine in the delivery room or immediately after arrival in neonatal intensive care unit (4.4 vs. 48 minutes of life) [5]. They found that early treatment significantly increased tidal volume and decreased the need for oxygen-therapy in comparison to later treatment [5]. Although these results were promising, neither study had sufficient statistical power to assess whether early treatment with caffeine is effective in reducing the need for mechanical ventilation in studied infants.

Study hypothesis

The present feasibility study aims to evaluate the hypothesis that it is operatively possible to administer intravenous or enteral caffeine in the delivery room during infants' postnatal stabilization when resuscitation may be needed. This study is preliminary to the planning of a subsequent large

randomized controlled trial which will assess whether caffeine administered so early can actually reduce the risk of MV in very preterm infants.

Objectives of the study

Primary objective

To evaluate the feasibility of administration of intravenous or enteral caffeine in very preterm infants in the delivery room during assistance for their cardiorespiratory stabilization achieving therapeutic plasma level.

Secondary objectives

To compare the success rate of intravenous versus enteral administration in overall population and to evaluate the need for MV in treated infants.

METHODS AND ANALYSIS

Study setting

This multicenter prospective study will be conducted in two third level Neonatal Intensive Care Units of the Careggi University Hospital of Florence and Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico of Milan, after approval by local ethics committees.

Inclusion criteria

Once the written informed consent of the parents or legal guardians has been obtained, inborn infants of 25^{+0}-29^{+6} weeks of gestational age at high risk of developing RDS, who do not require MV in the delivery room, will be enrolled in the study.

Exclusion criteria

Exclusion criteria will be: maternal consumption of caffeine before giving birth (> 2 cups of coffee in the 6 hours before birth), major congenital malformations, chromosomal syndromes, inherited metabolic disorders, and fetal hydrops.

Interventions

The study design and timeline are summarized in the Figures 1 and 2. Infants will be electronically randomized to receive 20 mg/kg (1 mL=20 mg) of caffeine citrate (Peyona®, Chiesi Farmaceutici

Spa, Parma, Italy) intravenously, via the umbilical vein, or enterally, through an orogastric tube, within 10 minutes of birth.

Intravenous administration will take place via an umbilical venous catheter or a "butterfly" needle inserted into the umbilical vein. The bolus of caffeine will be followed by the administration of a 2 mL "flush" of saline both in the case of administration by venous and enteral route. Completion or failures of administration will be recorded.

The caffeine plasma level will be measured 60±15 min after the administration, to evaluate its peak value, and 60±15 min before administration of the second dose (5 mg/kg/day i.v.) in the neonatal intensive care unit, to evaluate the achievement of therapeutic plasma level (8-25 µg/ml) [6]. The plasma level will be measured using the "dried blood spots" method with spectrometry and "tandem-mass" liquid chromatography [7] in the Laboratory of Clinical Chemistry and Pharmacology of the A. Meyer Pediatric Hospital of Florence. Blood samples will be collected with heel punctures commonly performed to monitor these patients and stored at -80 °C until analysis.

If necessary, resuscitation in the delivery room will be performed following the guidelines of the AAP/ AAH [8]. After admission in the neonatal intensive care unit, infants will be assisted with the following non-invasive respiratory supports: nasal-CPAP, “bi-level” nasal-CPAP (BiPAP), nasal intermittent mandatory ventilation (N-IMV). Surfactant (Curosurf ®, Chiesi, Parma, Italy) will be given (200 mg/kg) according to the InSURE (Intubation-SURfactant-Extubation) or LISA (Less-Invasive-Surfactant-Administration) technique in infants requiring FiO_2 >0.30 to maintain a SpO_2 90-95% and in all infants who will need MV.

Mechanical ventilation will be started if pCO_2 will be >65 mmHg and pH <7.20, or pO_2 <50 mm Hg with FiO_2 >0.50 after surfactant administration or in case of apnea (> 4 episodes in 1 hour or> 2 episodes in 1 hour requiring manual ventilation), and will be continued with the aim of maintaining a pCO_2 of 55-65 mmHg and a SpO_2 of 90-95%, using synchronized MV (patient triggered ventilation: PTV), volume controlled MV, or high frequency ventilation (HFV). Patients treated with MV will receive additional doses of surfactant (100 mg/kg) at the discretion of the attending Neonatologist. Patients will be extubated when a good respiratory autonomy is associated with a FiO_2 <0.30 and a mean airway pressure (MAP) <8 cmH_2O.

Data collection

Following data will be recorded for each infant: gestational age; birth weight; birth weight <10th percentile; gender; type of delivery; Apgar score at 5 min; main disorders of pregnancy (pre-eclampsia, premature rupture of membranes, clinical chorioamnionitis, placental abruption); RDS, diagnosis of which will be based on the occurrence of oxygen-dependence, tachypnea, dyspnea, exclusion of other causes of respiratory failure, and the presence of a typical radiological pattern; treatment with surfactant and nitric oxide; need, type and duration of respiratory assistance (oxygen therapy, NCPAP, BiPAP, N-IMV, PTV, HFV); prenatal and postnatal steroid treatment. In addition, common complications of prematurity will be recorded: patency of the ductus arteriosus (PDA) requiring pharmacological therapy, necrotizing enterocolitis (NEC) <2 grade, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) ≤3 grade, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP) of grade >3 and sepsis. In addition, mortality and the duration of hospitalization will be reported. The adapted classification of Papile et al. will be used to classify the severity of IVH. [9]; the diagnosis of LPV will be made in the presence of cystic areas detected by cerebral ultrasound at 40 post-conceptional weeks [10]; ROP will be graded in accordance with the International Classification of ROP [11]; diagnosis of NEC will be made according to Bell's criteria [12]. Diagnosis of sepsis will be based on clinical and laboratory data (total neutrophil count, C-reactive protein) confirmed by the presence of at least one positive blood or liquor culture.

All collected data will be recorded on a web-based electronic case report form, specifically designed for this study.

Concurrent treatments

Daily treatment of patients enrolled in the study will be performed according to common practice. In particular, infants with RDS will be treated according to the criteria described in the study design. Infants will receive antibiotic prophylaxis after performance of appropriate diagnostic tests. Antibiotic therapy will be stopped after three or four days if these tests are negative. Post-natal treatment with steroids may occur in infants with severe respiratory failure during mechanical ventilation and at high risk of mortality.

The enrolled patients can be treated with the following drugs: surfactant, caffeine, doxapram, ibuprofen, paracetamol, indomethacin, dopamine, dobutamine, milrinone, adrenaline, diuretics, antibiotics, glucocorticoids, immunoglobulins, antiepileptics, nitric oxide, analgesics, sedatives.

Adverse effects

Different adverse effects have been associated to caffeine treatment, although the CAP trial and related studies did not show any significant short or long-term adverse effects of caffeine therapy [15]. We will record the following possible adverse events (AEs): tachycardia, dysrhythmia, gastro-esophageal reflux, seizures. The collection of AEs data will last until discharge.

Statistical methods

In the absence of previous studies to use as a reference and as this is a feasibility study, it was arbitrarily decided to study 40 patients, of whom 20 will be treated with intravenous caffeine and 20 with enteral caffeine.

The clinical characteristics of the two groups will be described by calculating their mean values and standard deviations or rates and percentages.

The primary endpoint will be evaluation of the number of infants for whom administration of caffeine intravenously or enterally occurs successfully in the delivery room within 10 minutes of life. Administration will be considered a success when it is followed by the achievement of caffeine therapeutic level (8-25 µg/mL) 60±15 minutes before the administration of the second dose.

The secondary objectives will be: comparison of the completion rate of intravenous versus oral administration including infants who do not reach caffeine therapeutic level; comparison of caffeine plasma level obtained with intravenous and enteral administration; evaluation of peak caffeine blood levels; assessment of frequency of MV within the first 72 hours of life in studied infants.

The primary endpoint will be assessed calculating the percentage of cases in which caffeine is successfully administered and therapeutic plasma level reached. Comparisons between infants treated with intravenous or enteral caffeine administration will be performed using the Student "t" test for continuous parametric variables, the Wilcoxon rank sum test for non-parametric continuous variables and the χ^2 test for categorical variables. A $p < 0.05$ will be considered as statistically significant.

Patient and public involvement

Patients and the public were not (or will not) be involved in the design, or conduct, or reporting, or dissemination plans of this research because in our study we will only anticipate caffeine treatment that will start in the delivery room rather than few hours later in the neonatal intensive care. However, if we will demonstrate that caffeine administration is feasible in the delivery room, we will involve patients and the public in the design, or conduct, or reporting, or dissemination of a subsequent trial to assess whether this strategy can decrease the need of MV in very preterm infants.

ETHICS AND DISSEMINATION

The study will be carried out in accordance with recognized ethical principles for clinical trials (Helsinki Declaration), with respect for the principles of good clinical practice in the field of clinical investigations on drugs and medical devices and applicable regulations.

The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755, march 31, 2019). Approval was obtained also from Comitato Etico Pediatrico Regione Toscana for the Careggi University Hospital of Florence, while is under submission to Comitato Etico Milano Area B for the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico of Milan. Parents, relatives, and guardians of the enrolled patients will be given all pertinent explanations related to the study and an information sheet about the study will be provided describing the procedure and purpose of the project. Signed parental informed consent is to be obtained by a physician responsible for the study prior to the enrolment.

Every effort will be made to maintain the privacy and confidentiality of patients. To facilitate this, patients' identification data (name, date of birth, medical record number) will be kept in the data set only for the time necessary, therefore the database will be de-identified and an alphanumeric code will be used. After the data has been entered, patient's sensitive data will be anonymised by assigning a numerical identification code that will only allow identification of the patient to be traced back if necessary.

The principal investigator will be responsible for global monitoring of data and the safety of study participants. The principal investigator will be assisted by other members participating in the study.

Data will be the property of the promoter and will be shared with the investigators. Ownership of the study data will belong to the investigators involved. The results of the study will be published and may also be the subject of communications, reports or posters at conferences. We declare that the results of the study will be made available for publication.

Current trial status

Recruitment of participants started in September 2019, and the last participant is expected to reach the primary endpoint in February 2021. Primary data analysis will begin in June 2021.

CONCLUSION

About 80% of infants born with gestational age <27 weeks must be treated with MV [13] for a respiratory distress syndrome (RDS), and in about 65% of cases it starts as early as the first minutes of life in the delivery room [3]. This occurs because current strategies to prevent MV, such as early treatment with nasal CPAP and surfactant, given with INSurE or LISA procedures, have a significant failure rate [1,2]. In fact, these treatments allow lung recruitment and improvement of lung mechanics, but are not always effective, particularly when the need for MV is due to incoming crises of apnea as happens in about the half of cases.

Caffeine is a very effective drug in preterm infants for whom it decreases the frequency of apnea, the risk of BPD, duration of non-invasive respiratory supports, and risk of re-intubation [14], also in patients without previous crises of apnea [15]. In fact, it stimulates spontaneous respiratory activity, improves lung compliance and minute volume ventilation, reduces airway resistance, and increases diaphragm contractility, together with a good safety profile and without significant side effects at current doses [14]. Almost all very preterm infants are treated with caffeine starting from the first days of life but its use in the delivery room has been reported only in one study which, due to its small size, could not demonstrate its effect in decreasing the MV rate due to its small size [5].

Thus, we need results from large studies with adequate statistical power. Therefore, we planned the present study to evaluate the feasibility of both intravenous and enteral caffeine administration in very preterm infants in the delivery room during the first minutes of life when they may frequently need resuscitation. To ascertain the success of administration we decided to measure the caffeine

blood level because this method can objectively demonstrate the achievement of a therapeutic concentration. After obtaining the results of this study, we will be able to plan a well-sized multicenter randomized controlled study to assess the effectiveness of caffeine treatment in the delivery room to decrease the need for MV in very preterm infants.

Contributors All authors made substantive intellectual contributions to the trial design and manuscript. All revised the manuscript critically. CD and FM conceived of the study. AC, GM, and DM will be responsible for the neonatal care to newborns enrolled. GIM will be responsible for the laboratory measurements. LB provided statistical expertise and developed the web-based electronic case report form. All authors contributed to refinement of the study protocol, read and approved the final manuscript.

Funding No external funding was secured for this study.

Competing interests The authors declare that they have no competing interests.

Patient consent for publication Not required.

Ethics approval and consent to participate The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755, march 31, 2019). Approval was obtained also by Comitato Etico Pediatrico Regione Toscana.

Provenance and peer review Not commissioned; externally peer reviewed.

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1	

Figure 1. Flowchart of the study.

Figure 2. Study timeline.

Figure 1.

Inclusion criteria	Exclusion criteria
1. Inborn infants of 25^{+0}-29^{+6} weeks of gestational age at high risk of developing RDS, who do not require MV in the delivery room. 2. Parental informed consent	1. Maternal consumption of caffeine before giving birth (> 2 cups of coffee in the 6 hours before birth); 2. major congenital malformations, chromosomal syndromes, inherited metabolic disorders; 3. fetal hydrops

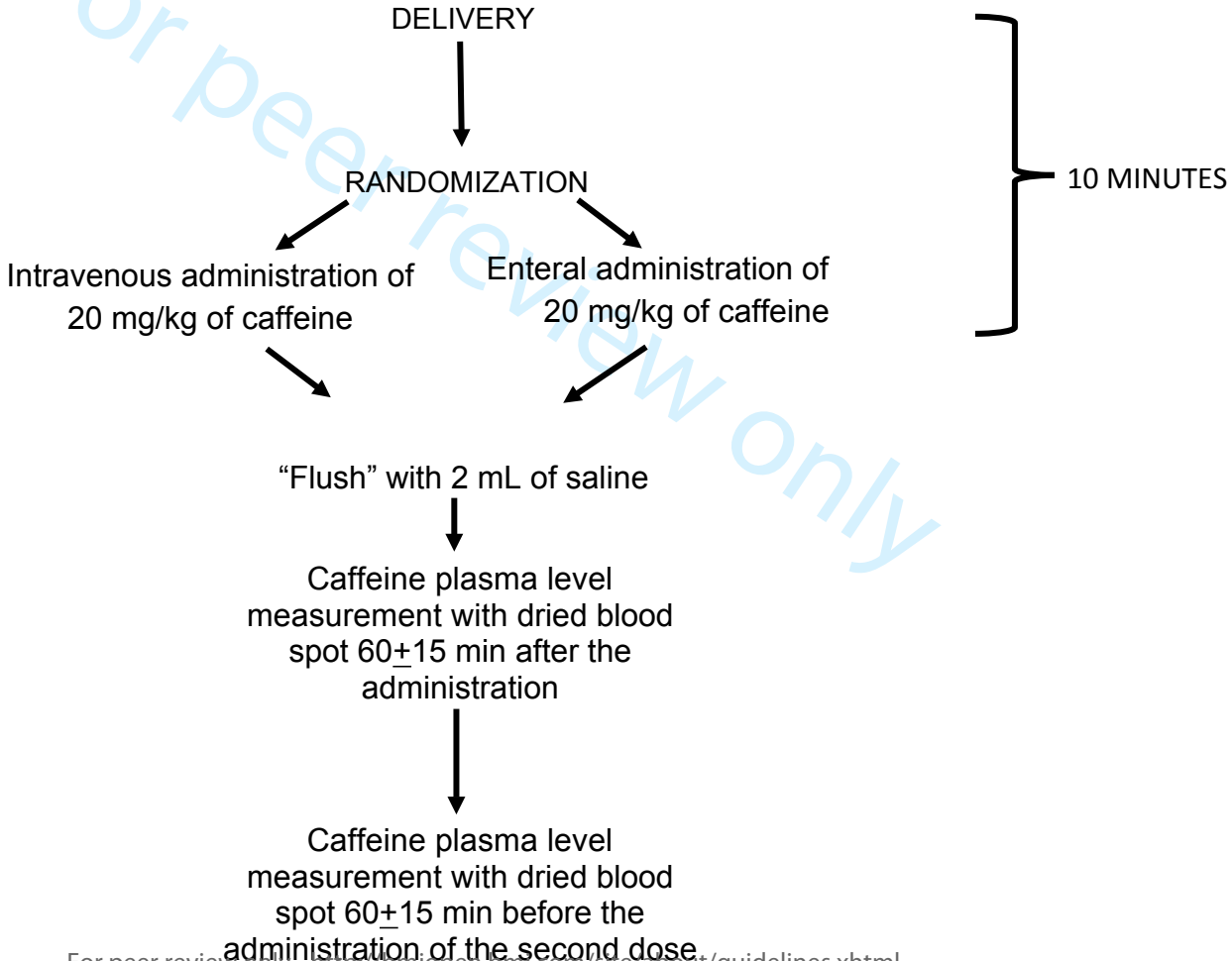

Figure 2.

	Before randomization	Randomization	60±15 min after caffeine administration	1 h before next caffeine administration	Within 72 h of life	Within 7d of life	Discharge or death
Informed consent	X						
Inclusion and exclusion criteria	X						
Clinical characteristics	X						
Maternal data	X						
Pregnancy diseases	X						
Antenatal steroids	X						
Type of delivery	X						
Apgar score	X						
Caffeine administration		X					
Caffeine plasma level			X	X			
Adverse events			X	X	X	X	X
Surfactant treatment			X	X	X		
Type and duration of respiratory assistance			X	X	X	X	X
Sepsis, PDA, IVH, LPV, NEC, BPD, ROP			X	X	X	X	X

PDA: Patent ductus arteriosus; IVH: intraventricular hemorrhage; PVL: periventricular hemorrhage; NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	Page 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	PAGE 8/9

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 3,4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 4,5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 6,7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7,8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 4-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 4,5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 4,5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	--
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 8,9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 8,9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-N/A

BMJ Open

STUDY PROTOCOL: TREATMENT WITH CAFFEINE OF THE VERY PRETERM INFANT IN THE DELIVERY ROOM

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STUDY PROTOCOL: TREATMENT WITH CAFFEINE OF THE VERY PRETERM INFANT IN THE DELIVERY ROOM

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ABSTRACT

Introduction Early treatment with caffeine in the delivery room has been proposed to decrease the need for MV by limiting episodes of apnea and improving respiratory mechanics in preterm infants. Thus, the purpose of this feasibility study is to verify the hypothesis that intravenous or enteral administration of caffeine can be performed in the preterm infant in the delivery room.

Methods and analysis In this multicenter prospective study, infants with 25^{+0}-29^{+6} weeks of gestational age will be enrolled and randomized to receive 20 mg/kg of caffeine citrate intravenously, via the umbilical vein, or enterally, through an orogastric tube, within 10 min of birth. Caffeine plasma level will be measured at 60±15 min after administration and 60±15 min before the next dose (5 mg/kg). The primary endpoint will be evaluation of the success rate of intravenous and enteral administration of caffeine in the delivery room. Secondary endpoints will be the comparison of success rate of intravenous versus oral administration and the evaluation of the need for MV in treated infants. In the absence of previous references, we arbitrarily decided to study 20 infants treated with intravenous caffeine and 20 infants treated with enteral caffeine. Primary endpoint will be evaluated measuring the success rate of intravenous and enteral caffeine administration which will be considered a success when it is followed by the achievement of the caffeine therapeutic level (8-25 µg/mL) 60±15 minutes before administration of the second dose.

Ethics and dissemination The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755) and by Comitato Etico Pediatrico Regione Toscana. The results will be published in peer-reviewed academic journals.

Trial registration: ClinicalTrials.gov Identifier NCT04044976; EudraCT Number 2018-003626-91

Keywords: Caffeine, delivery room, intravenous, enteral, preterm infant.

Strengths and limitations of this study

► This is the first study assessing the possibility of giving intravenous or enteral caffeine to preterm infants in the delivery room.

► Administration will be considered a success when it is followed by the achievement of caffeine blood therapeutic level.

►This study is preliminary to a large randomized controlled trial which will assess whether caffeine administered so early can reduce the risk of mechanical ventilation in very preterm infants.

► This research is being conducted across two sites and may not be representative of other Neonatal Intensive Care Units.

INTRODUCTION

Mechanical ventilation (MV) is one of the most important risk factors for the development of bronchopulmonary dysplasia (BPD) in the preterm infant, due to the early pulmonary inflammation from volume- and baro-trauma, and the high risk of ventilator-associated pneumonia (VAP)[1]. Therefore, in recent years particular attention has been paid to reduce the need for MV and some beneficial interventions, such as early application of nasal continuous positive airway pressure (CPAP) and surfactant treatment, has become widespread [1,2]. These have the common objective of promoting the development and maintenance of alveolar functional residual capacity (FRC), improving pulmonary compliance, reducing the work of breathing, and favoring gas exchanges [1,2]. Unfortunately, it has been found that nasal CPAP in combination or not with surfactant administration fails to prevent MV in about 45-50% of treated infants [3]. In fact, the need for MV often does not depend on the severity of respiratory distress syndrome (RDS), which however remains an important factor, but especially in mild-moderate forms of RDS can be due to the onset of relapsing episodes of apnea. Therefore, it has been proposed to treat very preterm infants with caffeine in the delivery room already in the first minute of life. In a recent pilot study, Katheria et al. randomized 21 infants with gestational age <29 weeks to receive 20 mg/kg of caffeine citrate within 2 h of life or at 12 hours of life [4]. They found that early treatment decreased the need for MV (27 vs. 70%) in comparison to late treatment and allowed an overall hemodynamic improvement of early treated patients [4]. Subsequently, Dekker et al. randomized 23 infants of 24-29 gestational weeks to receive 10 mg/kg of caffeine in the delivery room or immediately after arrival in neonatal intensive care unit (4.4 vs. 48 minutes of life) [5]. They found that early treatment significantly increased tidal volume and decreased the need for oxygen-therapy in comparison to later treatment [5]. Although these results were promising, neither study had sufficient statistical power to assess whether early treatment with caffeine is effective in reducing the need for mechanical ventilation in studied infants.

Study hypothesis

The present feasibility study aims to evaluate the hypothesis that it is operatively possible to administer intravenous or enteral caffeine in the delivery room during infants' postnatal stabilization when resuscitation may be needed. This study is preliminary to the planning of a subsequent large randomized controlled trial which will assess whether caffeine administered so early can actually reduce the risk of MV in very preterm infants.

Objectives of the study

Primary objective

To evaluate the feasibility of administration of intravenous or enteral caffeine in very preterm infants in the delivery room during assistance for their cardiorespiratory stabilization achieving therapeutic plasma level.

Secondary objectives

To compare the success rate of intravenous versus enteral administration in overall population and to evaluate the need for MV in treated infants.

METHODS AND ANALYSIS

Study setting

This multicenter prospective study will be conducted in two level three Neonatal Intensive Care Units of the Careggi University Hospital of Florence and Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico of Milan, after approval by local ethics committees.

Inclusion criteria

Once the written informed consent of the parents or legal guardians has been obtained, inborn infants of 25^{+0}-29^{+6} weeks of gestational age at high risk of developing RDS, who do not require MV in the delivery room, will be enrolled in the study.

Exclusion criteria

Exclusion criteria will be: maternal consumption of caffeine before giving birth (> 2 cups of coffee in the 6 hours before birth), major congenital malformations, chromosomal syndromes, inherited metabolic disorders, and fetal hydrops.

Interventions

The study design and timeline are summarized in the Figures 1 and 2. Infants will be electronically randomized to receive 20 mg/kg (1 mL=20 mg) of caffeine citrate (Peyona®, Chiesi Farmaceutici Spa, Parma, Italy) intravenously, via the umbilical vein, or enterally, through an orogastric tube, within 10 minutes of birth. The randomization sequence will be generated from the e-clintrials platform (https: // www. eclintrials.org/ect/O) whose manager is L.B..

Intravenous administration will take place via an umbilical venous catheter or a "butterfly" needle inserted into the umbilical vein. The bolus of caffeine will be followed by the administration of a 2 mL "flush" of saline both in the case of administration by venous and enteral route. Completion or failures of administration will be recorded.

The caffeine plasma level will be measured 60±15 min after the administration, to evaluate its peak value, and 60±15 min before administration of the second dose (5 mg/kg/day i.v.) in the neonatal intensive care unit, to evaluate the achievement of therapeutic plasma level (8-25 µg/ml) [6]. The plasma level will be measured using the "dried blood spots" method with spectrometry and "tandem-mass" liquid chromatography [7] in the Laboratory of Clinical Chemistry and Pharmacology of the A. Meyer Pediatric Hospital of Florence. Blood samples will be collected with heel punctures commonly performed to monitor these patients and stored at -80 °C until analysis.

If necessary, resuscitation in the delivery room will be performed following the guidelines of the AAP/ AAH [8]. After admission in the neonatal intensive care unit, infants will be assisted with the following non-invasive respiratory supports: nasal-CPAP, “bi-level” nasal-CPAP (BiPAP), nasal intermittent mandatory ventilation (N-IMV). Surfactant (Curosurf ®, Chiesi,

Parma, Italy) will be given (200 mg/kg) according to the InSURE (Intubation-SURfactant-Extubation) or LISA (Less-Invasive-Surfactant-Administration) technique in infants requiring FiO_2 >0.30 to maintain a SpO_2 90-95% and in all infants who will need MV.

Mechanical ventilation will be started if pCO_2 will be >65 mmHg and pH <7.20, or pO_2 <50 mm Hg with FiO_2 >0.50 after surfactant administration or in case of apnea (> 4 episodes in 1 hour or > 2 episodes in 1 hour requiring manual ventilation [9]), and will be continued with the aim of maintaining a pCO_2 of 55-65 mmHg and a SpO_2 of 90-95%, using synchronized MV (patient triggered ventilation: PTV), volume controlled MV, or high frequency ventilation (HFV). Patients treated with MV will receive additional doses of surfactant (100 mg/kg) at the discretion of the attending Neonatologist. Patients will be extubated when a good respiratory autonomy is associated with a FiO_2 <0.30 and a mean airway pressure (MAP) <8 cmH_2O.

Data collection

Following data will be recorded for each infant: gestational age; birth weight; birth weight <10th percentile; sex; type of delivery; Apgar score at 5 min; main disorders of pregnancy (pre-eclampsia, premature rupture of membranes, clinical chorioamnionitis, placental abruption); RDS, diagnosis of which will be based on the occurrence of oxygen-dependence, tachypnea, dyspnea, exclusion of other causes of respiratory failure, and the presence of a typical radiological pattern; treatment with surfactant and nitric oxide; need, type and duration of respiratory assistance (oxygen therapy, NCPAP, BiPAP, N-IMV, PTV, HFV); prenatal and postnatal steroid treatment. In addition, common complications of prematurity will be recorded: patency of the ductus arteriosus (PDA) requiring pharmacological therapy, necrotizing enterocolitis (NEC) <2 grade, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) ≤3 grade, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP) of grade >3 and sepsis. In addition, mortality and the duration of hospitalization will be reported. The adapted classification of Papile et al. will be used to

classify the severity of IVH. [10]; the diagnosis of PVL will be made in the presence of cystic areas detected by cerebral ultrasound at 40 post-conceptional weeks [11]; ROP will be graded in accordance with the International Classification of ROP [12]; diagnosis of NEC will be made according to Bell's criteria [13]. Diagnosis of sepsis will be based on clinical and laboratory data (total neutrophil count, C-reactive protein) confirmed by the presence of at least one positive blood or cerebrospinal fluid (CSF) culture.

All collected data will be recorded on a web-based electronic case report form, specifically designed for this study.

Concurrent treatments

Daily treatment of patients enrolled in the study will be performed according to common practice. In particular, infants with RDS will be treated according to the criteria described in the study design. Infants will receive antibiotic prophylaxis after performance of appropriate diagnostic tests. Antibiotic therapy will be stopped after three or four days if these tests are negative. Post-natal treatment with steroids may occur in infants with severe respiratory failure during mechanical ventilation and at high risk of mortality.

The enrolled patients can be treated with the following drugs: surfactant, caffeine, doxapram, ibuprofen, paracetamol, indomethacin, dopamine, dobutamine, milrinone, adrenaline, diuretics, antibiotics, glucocorticoids, immunoglobulins, antiepileptics, nitric oxide, analgesics, sedatives.

Adverse effects

Different adverse effects have been associated to caffeine treatment, although the CAP trial and related studies did not show any significant short or long-term adverse effects of caffeine therapy [14]. We will record the following possible adverse events (AEs): tachycardia, dysrhythmia, gastro-esophageal reflux, and seizures. Diagnosis of gastro-esophageal reflux will be made on the basis of clinical signs, such as persistent crying, irritability, back-arching, feeding, and frequent awakening [15].

The collection of AEs data will last until discharge.

Statistical methods

In the absence of previous studies to use as a reference and as this is a feasibility study, it was arbitrarily decided to study 40 patients, of whom 20 will be treated with intravenous caffeine and 20 with enteral caffeine.

The clinical characteristics of the two groups will be described by calculating their mean values and standard deviations or rates and percentages.

The primary endpoint will be evaluation of the number of infants for whom administration of caffeine intravenously or enterally occurs successfully in the delivery room within 10 minutes of life. Administration will be considered a success when it is followed by the achievement of caffeine therapeutic level (8-25 µg/mL [16]) 60±15 minutes before the administration of the second dose. We decided to measure caffeine level to have objective evidence that caffeine administration has occurred successfully and that intravenous and enteral administration is equivalent or not.

The secondary objectives will be: comparison of the completion rate of intravenous versus oral administration including infants who do not reach caffeine therapeutic level; comparison of caffeine plasma level obtained with intravenous and enteral administration; evaluation of peak caffeine blood levels; assessment of frequency of MV within the first 72 hours of life in studied infants.

The primary endpoint will be assessed calculating the percentage of cases in which caffeine is successfully administered and therapeutic plasma level reached. Comparisons between infants treated with intravenous or enteral caffeine administration will be performed using the Student "t" test for continuous parametric variables, the Wilcoxon rank sum test for non-parametric continuous variables and the χ^2 test for categorical variables. A $p < 0.05$ will be considered as statistically significant.

Patient and public involvement

Patients and the public were not (or will not) be involved in the design, or conduct, or reporting, or dissemination plans of this research because in our study we will only anticipate caffeine treatment that will start in the delivery room rather than few hours later in the neonatal intensive care. However, if we will demonstrate that caffeine administration is feasible in the delivery room, we will involve patients and the public in the design, or conduct, or reporting, or dissemination of a subsequent trial to assess whether this strategy can decrease the need of MV in very preterm infants.

ETHICS AND DISSEMINATION

The study will be carried out in accordance with recognized ethical principles for clinical trials (Helsinki Declaration), with respect for the principles of good clinical practice in the field of clinical investigations on drugs and medical devices and applicable regulations.

The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755, march 31, 2019). Approval was obtained also from Comitato Etico Pediatrico Regione Toscana for the Careggi University Hospital of Florence, while is under submission to Comitato Etico Milano Area B for the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico of Milan. Parents, relatives, and guardians of the enrolled patients will be given all pertinent explanations related to the study and an information sheet about the study will be provided describing the procedure and purpose of the project. Signed parental informed consent is to be obtained by a physician responsible for the study prior to the enrolment. All consents will be obtained before the delivery, possibly at the time of admission of pregnant women at risk of preterm birth.

Every effort will be made to maintain the privacy and confidentiality of patients. To facilitate this, patients' identification data (name, date of birth, medical record number) will be kept in the data set only for the time necessary, therefore the database will be de-identified and an alphanumeric code will be used. After the data has been entered, patient's sensitive data

will be anonymised by assigning a numerical identification code that will only allow identification of the patient to be traced back if necessary.

The principal investigator will be responsible for global monitoring of data and the safety of study participants. The principal investigator will be assisted by other members participating in the study.

Data will be the property of the promoter and will be shared with the investigators. Ownership of the study data will belong to the investigators involved. The results of the study will be published and may also be the subject of communications, reports or posters at conferences. We declare that the results of the study will be made available for publication.

Current trial status

Recruitment of participants started in September 2019, and the last participant is expected to reach the primary endpoint in February 2021. Primary data analysis will begin in June 2021.

CONCLUSION

About 80% of infants born with gestational age <27 weeks must be treated with MV [14] for a respiratory distress syndrome (RDS), and in about 65% of cases it starts as early as the first minutes of life in the delivery room [3]. This occurs because current strategies to prevent MV, such as early treatment with nasal CPAP and surfactant, given with INSurE or LISA procedures, have a significant failure rate [1,2]. In fact, these treatments allow lung recruitment and improvement of lung mechanics, but are not always effective, particularly when the need for MV is due to incoming crises of apnea as happens in about the half of cases.

Caffeine is a very effective drug in preterm infants for whom it decreases the frequency of apnea, the risk of BPD, duration of non-invasive respiratory supports, and risk of re-intubation [17], also in patients without previous episodes of apnea [18]. In fact, it stimulates spontaneous respiratory activity, improves lung compliance and minute volume ventilation,

reduces airway resistance, and increases diaphragm contractility, together with a good safety profile and without significant side effects at current doses [17]. Almost all very preterm infants are treated with caffeine starting from the first days of life but its use in the delivery room has been reported only in one study which, due to its small size, could not demonstrate its effect in decreasing the MV rate due to its small size [5].

Thus, we need results from large studies with adequate statistical power. Therefore, we planned the present study to evaluate the feasibility of both intravenous and enteral caffeine administration in very preterm infants in the delivery room during the first minutes of life when they may frequently need resuscitation. To ascertain the success of administration we decided to measure the caffeine blood level because this method can objectively demonstrate the achievement of a therapeutic concentration. After obtaining the results of this study, we will be able to plan a well-sized multicenter randomized controlled study to assess the effectiveness of caffeine treatment in the delivery room to decrease the need for MV in very preterm infants.

Contributors All authors made substantive intellectual contributions to the trial design and manuscript. All revised the manuscript critically. CD and FM conceived of the study. AC, GM, and DM will be responsible for the neonatal care to newborns enrolled. GIM will be responsible for the laboratory measurements. LB provided statistical expertise and developed the web-based electronic case report form. All authors contributed to refinement of the study protocol, read and approved the final manuscript.

Funding No external funding was secured for this study.

Competing interests The authors declare that they have no competing interests.

Patient consent for publication Not required.

Ethics approval and consent to participate The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755, march 31, 2019). Approval was obtained also by Comitato Etico Pediatrico Regione Toscana.

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure 1. Flowchart of the study.

Figure 2. Study timeline.

Figure 1.

Inclusion criteria	**Exclusion criteria**
1. Inborn infants of 25^{+0}-29^{+6} weeks of gestational age at high risk of developing RDS, who do not require MV in the delivery room. 2. Parental informed consent	1. Maternal consumption of caffeine before giving birth (> 2 cups of coffee in the 6 hours before birth); 2. major congenital malformations, chromosomal syndromes, inherited metabolic disorders; 3. fetal hydrops

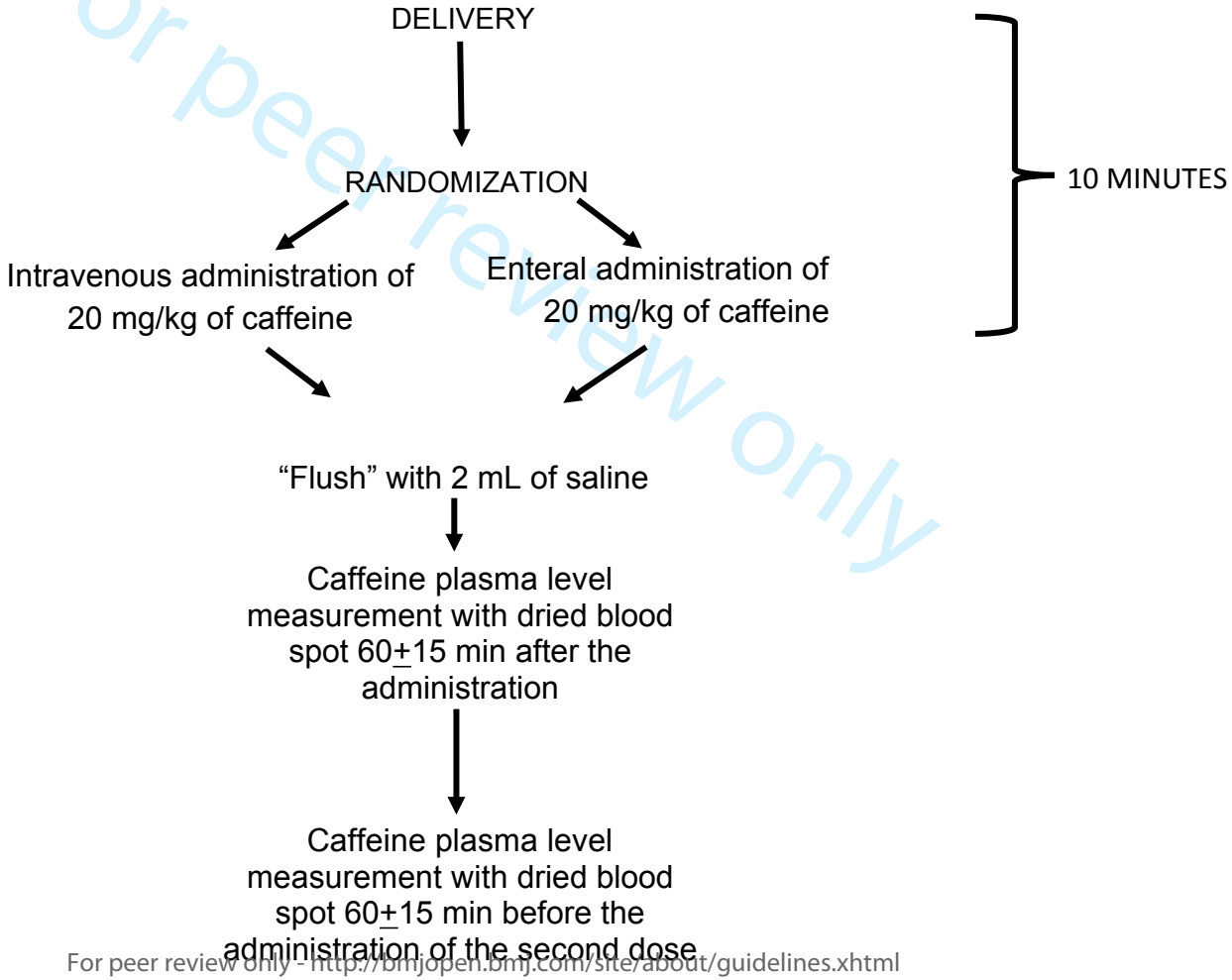

Figure 2.

	Before randomization	Randomization	60±15 min after caffeine administration	1 h before next caffeine administration	Within 72 h of life	Within 7d of life	Discharge or death
Informed consent	X						
Inclusion and exclusion criteria	X						
Clinical characteristics	X						
Maternal data	X						
Pregnancy diseases	X						
Antenatal steroids	X						
Type of delivery	X						
Apgar score	X						
Caffeine administration		X					
Caffeine plasma level			X	X			
Adverse events			X	X	X	X	X
Surfactant treatment			X	X	X		
Type and duration of respiratory assistance			X	X	X	X	X
Sepsis, PDA, IVH, LPV, NEC, BPD, ROP			X	X	X	X	X

PDA: Patent ductus arteriosus; IVH: intraventricular hemorrhage; PVL: periventricular hemorrhage; NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	Page 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	PAGE 8/9

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 3,4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 4,5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 6,7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7,8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 4-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 4,5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 4,5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	--
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 8,9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 8,9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-N/A

BMJ Open

STUDY PROTOCOL: TREATMENT WITH CAFFEINE OF THE VERY PRETERM INFANT IN THE DELIVERY ROOM: A FEASIBILITY STUDY

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Primary Subject Heading:	Paediatrics
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STUDY PROTOCOL: TREATMENT WITH CAFFEINE OF THE VERY PRETERM INFANT IN THE DELIVERY ROOM: A FEASIBILITY STUDY

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ABSTRACT

Introduction Early treatment with caffeine in the delivery room has been proposed to decrease the need for mechanical ventilation (MV) by limiting episodes of apnea and improving respiratory mechanics in preterm infants. Thus, the purpose of this feasibility study is to verify the hypothesis that intravenous or enteral administration of caffeine can be performed in the preterm infant in the delivery room.

Methods and analysis In this multicenter prospective study, infants with 25^{+0}-29^{+6} weeks of gestational age will be enrolled and randomized to receive 20 mg/kg of caffeine citrate intravenously, via the umbilical vein, or enterally, through an orogastric tube, within 10 min of birth. Caffeine plasma level will be measured at 60±15 min after administration and 60±15 min before the next dose (5 mg/kg). The primary endpoint will be evaluation of the success rate of intravenous and enteral administration of caffeine in the delivery room. Secondary endpoints will be the comparison of success rate of intravenous versus oral administration and the evaluation of the need for MV in treated infants. In the absence of previous references, we arbitrarily decided to study 20 infants treated with intravenous caffeine and 20 infants treated with enteral caffeine. Primary endpoint will be evaluated measuring the success rate of intravenous and enteral caffeine administration which will be considered a success when it is followed by the achievement of the caffeine therapeutic level (8-25 µg/mL) 60±15 minutes before administration of the second dose.

Ethics and dissemination The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755) and by Comitato Etico Pediatrico Regione Toscana. The results will be published in peer-reviewed academic journals.

Trial registration: ClinicalTrials.gov Identifier NCT04044976; EudraCT Number 2018-003626-91

Keywords: Caffeine, delivery room, intravenous, enteral, preterm infant.

Strengths and limitations of this study

- This is the first study assessing the possibility of giving intravenous or enteral caffeine to preterm infants in the delivery room.
- Administration will be considered a success when it is followed by the achievement of caffeine blood therapeutic level.
- The caffeine plasma level will be measured using the "dried blood spots".
- This study is preliminary to a large randomized controlled trial which will assess whether caffeine administered so early can reduce the risk of mechanical ventilation in very preterm infants.
- This research is being conducted across two sites and may not be representative of other Neonatal Intensive Care Units.

INTRODUCTION

Mechanical ventilation (MV) is one of the most important risk factors for the development of bronchopulmonary dysplasia (BPD) in the preterm infant, due to the early pulmonary inflammation from volume- and baro-trauma, and the high risk of ventilator-associated pneumonia (VAP)[1]. Therefore, in recent years particular attention has been paid to reduce the need for MV and some beneficial interventions, such as early application of nasal continuous positive airway pressure (CPAP) and surfactant treatment, has become widespread [1,2]. These have the common objective of promoting the development and maintenance of alveolar functional residual capacity (FRC), improving pulmonary compliance, reducing the work of breathing, and favoring gas exchanges [1,2]. Unfortunately, it has been found that nasal CPAP in combination or not with surfactant administration fails to prevent MV in about 45-50% of treated infants [3]. In fact, the need for MV often does not depend on the severity of respiratory distress syndrome (RDS), which however remains an important factor, but especially in mild-moderate forms of RDS can be due to the onset of relapsing episodes of apnea. Therefore, it has been proposed to treat very preterm infants with caffeine in the delivery room already in the first minute of life. In a recent pilot study, Katheria et al. randomized 21 infants with gestational age <29 weeks to receive 20 mg/kg of caffeine citrate within 2 h of life or at 12 hours of life [4]. They found that early treatment decreased the need for MV (27 vs. 70%) in comparison to late treatment and allowed an overall hemodynamic improvement of early treated patients [4]. Subsequently, Dekker et al. randomized 23 infants of 24-29 gestational weeks to receive 10 mg/kg of caffeine in the delivery room or immediately after arrival in neonatal intensive care unit (4.4 vs. 48 minutes of life) [5]. They found that early treatment significantly increased tidal volume and decreased the need for oxygen-therapy in comparison to later treatment [5]. Although these results were promising, neither study had sufficient statistical power to assess whether early treatment with caffeine is effective in reducing the need for mechanical ventilation in studied infants.

Study hypothesis

The present feasibility study aims to evaluate the hypothesis that it is operatively possible to administer intravenous or enteral caffeine in the delivery room during infants' postnatal stabilization when resuscitation may be needed. This study is preliminary to the planning of a subsequent large randomized controlled trial which will assess whether caffeine administered so early can actually reduce the risk of MV in very preterm infants.

Objectives of the study

Primary objective

To evaluate the feasibility of administration of intravenous or enteral caffeine in very preterm infants in the delivery room during assistance for their cardiorespiratory stabilization achieving therapeutic plasma level.

Secondary objectives

To compare the success rate of intravenous versus enteral administration in overall population and to evaluate the need for MV in treated infants.

METHODS AND ANALYSIS

Study setting

This multicenter prospective study will be conducted in two level three Neonatal Intensive Care Units of the Careggi University Hospital of Florence and Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico of Milan, after approval by local ethics committees.

Inclusion criteria

Once the written informed consent of the parents or legal guardians has been obtained (see supplementary file), inborn infants of 25^{+0}-29^{+6} weeks of gestational age at high risk of developing RDS, who do not require MV in the delivery room, will be enrolled in the study.

Exclusion criteria

Exclusion criteria will be: maternal consumption of caffeine before giving birth (> 2 cups of coffee in the 6 hours before birth), major congenital malformations, chromosomal syndromes, inherited metabolic disorders, and fetal hydrops.

Interventions

The study design and timeline are summarized in the Figures 1 and 2. Infants will be electronically randomized to receive 20 mg/kg (1 mL=20 mg) of caffeine citrate (Peyona®, Chiesi Farmaceutici Spa, Parma, Italy) intravenously, via the umbilical vein, or enterally, through an orogastric tube, within 10 minutes of birth. The randomization sequence will be generated from the e-clintrials platform (https: // www. eclintrials.org/ect/O) whose manager is L.B..

Intravenous administration will take place via an umbilical venous catheter or a "butterfly" needle inserted into the umbilical vein. The bolus of caffeine will be followed by the administration of a 2 mL "flush" of saline both in the case of administration by venous and enteral route. Completion or failures of administration will be recorded.

The caffeine plasma level will be measured 60±15 min after the administration, to evaluate its peak value, and 60±15 min before administration of the second dose (5 mg/kg/day i.v.) in the neonatal intensive care unit, to evaluate the achievement of therapeutic plasma level (8-25 µg/ml) [6]. The plasma level will be measured using the "dried blood spots" method with spectrometry and "tandem-mass" liquid chromatography [7] in the Laboratory of Clinical Chemistry and Pharmacology of the A. Meyer Pediatric Hospital of Florence. Blood samples will be collected with heel punctures commonly performed to monitor these patients and stored at -80 °C until analysis.

If necessary, resuscitation in the delivery room will be performed following the guidelines of the AAP/ AAH [8]. After admission in the neonatal intensive care unit, infants will be assisted with the following non-invasive respiratory supports: nasal-CPAP, “bi-level” nasal-CPAP (BiPAP), nasal intermittent mandatory ventilation (N-IMV). Surfactant (Curosurf ®, Chiesi,

Parma, Italy) will be given (200 mg/kg) according to the InSURE (Intubation-SURfactant-Extubation) or LISA (Less-Invasive-Surfactant-Administration) technique in infants requiring FiO_2 >0.30 to maintain a SpO_2 90-95% and in all infants who will need MV.

Mechanical ventilation will be started if pCO_2 will be >65 mmHg and pH <7.20, or pO_2 <50 mm Hg with FiO_2 >0.50 after surfactant administration or in case of apnea (> 4 episodes in 1 hour or > 2 episodes in 1 hour requiring manual ventilation [9]), and will be continued with the aim of maintaining a pCO_2 of 55-65 mmHg and a SpO_2 of 90-95%, using synchronized MV (patient triggered ventilation: PTV), volume controlled MV, or high frequency ventilation (HFV). Patients treated with MV will receive additional doses of surfactant (100 mg/kg) at the discretion of the attending Neonatologist. Patients will be extubated when a good respiratory autonomy is associated with a FiO_2 <0.30 and a mean airway pressure (MAP) <8 cmH_2O.

Data collection

Following data will be recorded for each infant: gestational age; birth weight; birth weight <10th percentile; sex; type of delivery; Apgar score at 5 min; main disorders of pregnancy (pre-eclampsia, premature rupture of membranes, clinical chorioamnionitis, placental abruption); RDS, diagnosis of which will be based on the occurrence of oxygen-dependence, tachypnea, dyspnea, exclusion of other causes of respiratory failure, and the presence of a typical radiological pattern; treatment with surfactant and nitric oxide; need, type and duration of respiratory assistance (oxygen therapy, NCPAP, BiPAP, N-IMV, PTV, HFV); prenatal and postnatal steroid treatment. In addition, common complications of prematurity will be recorded: patency of the ductus arteriosus (PDA) requiring pharmacological therapy, necrotizing enterocolitis (NEC) <2 grade, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) ≤3 grade, periventricular leukomalacia (PVL), retinopathy of prematurity (ROP) of grade >3 and sepsis. In addition, mortality and the duration of hospitalization will be reported. The adapted classification of Papile et al. will be used to

classify the severity of IVH. [10]; the diagnosis of PVL will be made in the presence of cystic areas detected by cerebral ultrasound at 40 post-conceptional weeks [11]; ROP will be graded in accordance with the International Classification of ROP [12]; diagnosis of NEC will be made according to Bell's criteria [13]. Diagnosis of sepsis will be based on clinical and laboratory data (total neutrophil count, C-reactive protein) confirmed by the presence of at least one positive blood or cerebrospinal fluid (CSF) culture.

All collected data will be recorded on a web-based electronic case report form, specifically designed for this study.

Concurrent treatments

Daily treatment of patients enrolled in the study will be performed according to common practice. In particular, infants with RDS will be treated according to the criteria described in the study design. Infants will receive antibiotic prophylaxis after performance of appropriate diagnostic tests. Antibiotic therapy will be stopped after three or four days if these tests are negative. Post-natal treatment with steroids may occur in infants with severe respiratory failure during mechanical ventilation and at high risk of mortality.

The enrolled patients can be treated with the following drugs: surfactant, caffeine, doxapram, ibuprofen, paracetamol, indomethacin, dopamine, dobutamine, milrinone, adrenaline, diuretics, antibiotics, glucocorticoids, immunoglobulins, antiepileptics, nitric oxide, analgesics, sedatives.

Adverse effects

Different adverse effects have been associated to caffeine treatment, although the CAP trial and related studies did not show any significant short or long-term adverse effects of caffeine therapy [14]. We will record the following possible adverse events (AEs): tachycardia, dysrhythmia, gastro-esophageal reflux, and seizures. Diagnosis of gastro-esophageal reflux will be made on the basis of clinical signs, such as persistent crying, irritability, back-arching, feeding, and frequent awakening [15].

The collection of AEs data will last until discharge.

Statistical methods

In the absence of previous studies to use as a reference and as this is a feasibility study, it was arbitrarily decided to study 40 patients, of whom 20 will be treated with intravenous caffeine and 20 with enteral caffeine.

The clinical characteristics of the two groups will be described by calculating their mean values and standard deviations or rates and percentages.

The primary endpoint will be evaluation of the number of infants for whom administration of caffeine intravenously or enterally occurs successfully in the delivery room within 10 minutes of life. Administration will be considered a success when it is followed by the achievement of caffeine therapeutic level (8-25 µg/mL [16]) 60±15 minutes before the administration of the second dose. We decided to measure caffeine level to have objective evidence that caffeine administration has occurred successfully and that intravenous and enteral administration is equivalent or not.

The secondary objectives will be: comparison of the completion rate of intravenous versus oral administration including infants who do not reach caffeine therapeutic level; comparison of caffeine plasma level obtained with intravenous and enteral administration; evaluation of peak caffeine blood levels; assessment of frequency of MV within the first 72 hours of life in studied infants.

The primary endpoint will be assessed calculating the percentage of cases in which caffeine is successfully administered and therapeutic plasma level reached. Comparisons between infants treated with intravenous or enteral caffeine administration will be performed using the Student "t" test for continuous parametric variables, the Wilcoxon rank sum test for non-parametric continuous variables and the χ^2 test for categorical variables. A $p < 0.05$ will be considered as statistically significant.

Patient and public involvement

Patients and the public were not (or will not) be involved in the design, or conduct, or reporting, or dissemination plans of this research because in our study we will only anticipate caffeine treatment that will start in the delivery room rather than few hours later in the neonatal intensive care. However, if we will demonstrate that caffeine administration is feasible in the delivery room, we will involve patients and the public in the design, or conduct, or reporting, or dissemination of a subsequent trial to assess whether this strategy can decrease the need of MV in very preterm infants.

ETHICS AND DISSEMINATION

The study will be carried out in accordance with recognized ethical principles for clinical trials (Helsinki Declaration), with respect for the principles of good clinical practice in the field of clinical investigations on drugs and medical devices and applicable regulations.

The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755, march 31, 2019). Approval was obtained also from Comitato Etico Pediatrico Regione Toscana for the Careggi University Hospital of Florence, while is under submission to Comitato Etico Milano Area B for the Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico of Milan. Parents, relatives, and guardians of the enrolled patients will be given all pertinent explanations related to the study and an information sheet about the study will be provided describing the procedure and purpose of the project. Signed parental informed consent is to be obtained by a physician responsible for the study prior to the enrolment. All consents will be obtained before the delivery, possibly at the time of admission of pregnant women at risk of preterm birth.

Every effort will be made to maintain the privacy and confidentiality of patients. To facilitate this, patients' identification data (name, date of birth, medical record number) will be kept in the data set only for the time necessary, therefore the database will be de-identified and an alphanumeric code will be used. After the data has been entered, patient's sensitive data

will be anonymised by assigning a numerical identification code that will only allow identification of the patient to be traced back if necessary.

The principal investigator will be responsible for global monitoring of data and the safety of study participants. The principal investigator will be assisted by other members participating in the study.

Data will be the property of the promoter and will be shared with the investigators. Ownership of the study data will belong to the investigators involved. The results of the study will be published and may also be the subject of communications, reports or posters at conferences. We declare that the results of the study will be made available for publication.

Current trial status

Recruitment of participants started in September 2019, and the last participant is expected to reach the primary endpoint in February 2021. Primary data analysis will begin in June 2021.

Contributors All authors made substantive intellectual contributions to the trial design and manuscript. All revised the manuscript critically. CD and FM conceived of the study. AC, GM, and DM will be responsible for the neonatal care to newborns enrolled. GIM will be responsible for the laboratory measurements. LB provided statistical expertise and developed the web-based electronic case report form. All authors contributed to refinement of the study protocol, read and approved the final manuscript.

Funding No external funding was secured for this study.

Competing interests The authors declare that they have no competing interests.

Patient consent for publication Not required.

Ethics approval and consent to participate The study has been approved by the Italian Medicines Agency (AIFA: AIFA/RSC/P/32755, march 31, 2019). Approval was obtained also by Comitato Etico Pediatrico Regione Toscana.

Provenance and peer review Not commissioned; externally peer reviewed.

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Figure 1. Flowchart of the study.

Figure 2. Study timeline.

Figure 1.

Inclusion criteria	Exclusion criteria
1. Inborn infants of 25^{+0}-29^{+6} weeks of gestational age at high risk of developing RDS, who do not require MV in the delivery room. 2. Parental informed consent	1. Maternal consumption of caffeine before giving birth (> 2 cups of coffee in the 6 hours before birth); 2. major congenital malformations, chromosomal syndromes, inherited metabolic disorders; 3. fetal hydrops

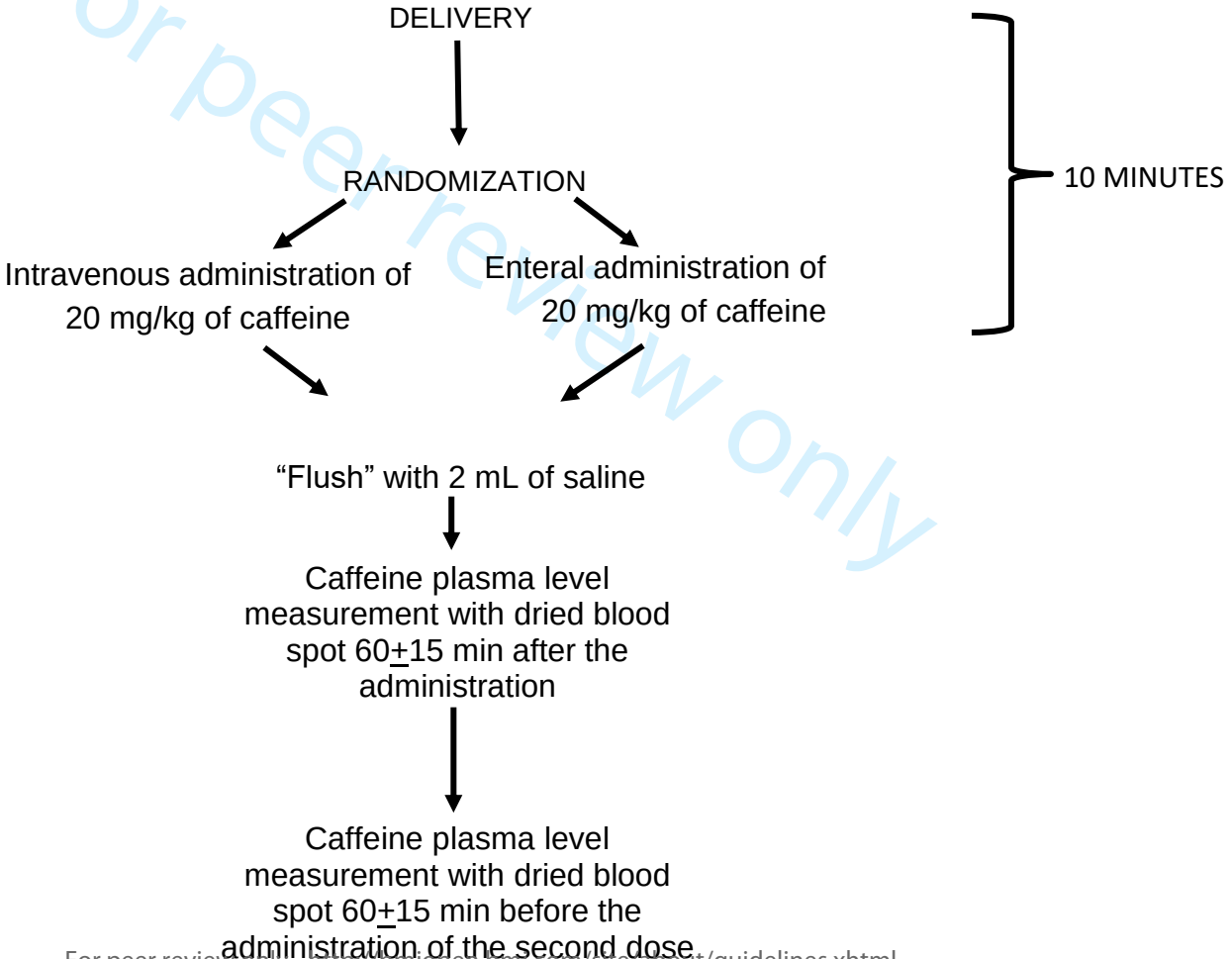

Figure 2.

	Before randomization	Randomization	60±15 min after caffeine administration	1 h before next caffeine administration	Within 72 h of life	Within 7d of life	Discharge or death
Informed consent	X						
Inclusion and exclusion criteria	X						
Clinical characteristics	X						
Maternal data	X						
Pregnancy diseases	X						
Antenatal steroids	X						
Type of delivery	X						
Apgar score	X						
Caffeine administration		X					
Caffeine plasma level			X	X			
Adverse events			X	X	X	X	X
Surfactant treatment			X	X	X		
Type and duration of respiratory assistance			X	X	X	X	X
Sepsis, PDA, IVH, LPV, NEC, BPD, ROP			X	X	X	X	X

PDA: Patent ductus arteriosus; IVH: intraventricular hemorrhage; PVL: periventricular hemorrhage; NEC: necrotizing enterocolitis; BPD: bronchopulmonary dysplasia; ROP: retinopathy of prematurity.

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INFORMATION SHEET
FOR PARENTS/LEGAL GUARDIAN

Study title: Study protocol: treatment with caffeine of the very preterm infant in the delivery room: a feasibility study

Protocol code, version, and date: CAFSP01, version 1.0, 01/04/2018

Study promotor: Careggi University Hospital of Florence

Principal Investigator: Prof Carlo Dani, Division of Neonatology Careggi University Hospital of Florence.

Dear Parents / Guardian,

We ask you to accept participation to this study only after having carefully read this information sheet and having had a thorough interview with the investigating physician who will have to dedicate the time necessary to fully understand what is proposed.

Why we do this study

Caffeine is a drug that is administered to all very preterm infants from the first hours of life to prevent the onset of apneas, caused by the immaturity of the breathing center, in order to reduce the risk of endotracheal intubation and mechanical ventilation. This study aims to evaluate in a small group of newborns whether the early administration of enteral or intravenous caffeine is already possible in the delivery room in the first minutes after birth. If the study will be successful, it will be possible to plan a further larger study to see if administering caffeine so early is beneficial in reducing the risk of mechanical ventilation in comparison with the current later use.

What are the characteristics of this study and what participation in the study entails

Newborns of gestational age of 25^{+0}-28^{+6} weeks who are at high risk of developing respiratory distress syndrome and who did not require mechanical ventilation in the delivery room will be eligible in the study.

In case you decide that your daughter / son can participate in the study, after signing the consent form, she/he you will receive a dose of caffeine within 10 minutes of birth enterally, through a

nasogastric tube, or intravenously through the umbilical vein. The choice of the route of administration of the drug will take place in a randomized manner, ie random. Subsequently, and only in cases in which the administration has been successful, the dosage of the concentration of caffeine in the blood will be carried out approximately one hour after the administration and one hour before the next dose, to objectively confirm that the administration has taken place. effectively. The dosage will be performed on small amounts of blood taken from the puncture of the newborn's heel and collected on a special card during other samples that would still be performed for the monitoring of these very preterm newborns. The dosage will be performed at the Laboratory of Chemistry and Clinical Pharmacology of the A. Meyer Pediatric Hospital in Florence. The samples will be anonymized and will be kept for 7 years in the same laboratory.

Benefits and risks of participating in the study

Although an immediate direct benefit from participation in the study cannot be demonstrated, if the next larger study will demonstrate that caffeine administered in the delivery room is effective in preventing mechanical ventilation, it can be inferred that the infants treated in this preliminary study have had the advantage of a lower risk of endotracheal intubation and mechanical ventilation. The conclusions of this study and the subsequent study could therefore contribute to improving the care of preterm infants.

Caffeine is a drug used in all very preterm infants and it is considered so safe that in clinical practice it is not recommended for its blood dosage to be sure that the safe therapeutic concentration is not exceeded. Possible side effects reported in the newborn are tachycardia (which disappears when the drug is discontinued) and seizures in case of overdose. However, since tachycardia always precedes seizures, the withdrawal of caffeine that follows the onset of tachycardia effectively prevents the potential for seizures. Therefore, participation in this study, since it encompasses administering caffeine a few hours (1-4) earlier thatn it would anyway, will not include additional risks compared to common clinical practice.

What happens if you decide not to take part in the study or to withdraw from the study

Participation in the study is entirely voluntary. If you decide not to take part in the study, your daughter / son will not suffer any penalty or loss of future benefits to which he would otherwise be entitled at the Careggi University Hospital.

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INFORMATION REGARDING THE PROCESSING OF PERSONAL DATA

Data controllers and related purposes

The Neonatal Intensive Care Unit of Careggi University Hospital which proposed the study that has been described to you, for the areas of its competence and in accordance with the responsibilities provided for by the rules of good practice, will process personal data of your child, in particular those on health and, only to the extent that are indispensable in relation to the objective of the study, exclusively in relation to the implementation of the study.

The processing of personal data of your child is essential for the study: refusal to provide them will not allow to participate in the study.

Nature of the data

The physician who will follow you in the study will identify you with a code: data concerning your daughter/son collected during the study will be recorded, processed and stored for at least 7 (seven) years from the conclusion of the study. Only the physician and authorized persons can link this code to your child.

Processing methods

The data, also processed by means of electronic means, will be disclosed only in a strictly anonymous form, for example through scientific publications, statistics and scientific conferences.

Exercise of rights

You can exercise the rights listed in art. 7 of the Privacy Code (eg. Access the data of his / her son / daughter, integrate them, update them, rectify them, oppose their treatment for legitimate reasons, etc.) by contacting the trial center directly and in particular Prof. Carlo Dani, Neonatal Intensive Care Unit of Careggi University Hospital, telephone 055 7948421.

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Further information

There are no additional costs for you resulting from participation in the study. You will not receive any financial compensation for participating in the study. The protocol of the study proposed to you was drawn up in accordance with the Standards of Good Clinical Practice and the Declaration of Helsinki, and was approved by the Ethics Committee of the Tuscany Region, Pediatric Section, on April 15, 2019.

For further information and communications during the study, the following staff will be available: prof. Carlo Dani, phone 055 7918421, email cdani@unifi.it

_____ ___/___/_____ _____

Name of physician who gives Information sheet Date Hour

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INFORMED CONSENT FOR PARENTS/LEGAL GUARDIAN

Study title: Study protocol: treatment with caffeine of the very preterm infant in the delivery room: a feasibility study

Protocol code, version, and date: CAFSP01, version 1.0, 01/04/2018

Study promotor: Careggi University Hospital of Florence

Principal Investigator: Prof Carlo Dani, Division of Neonatology Careggi University Hospital of Florence.

I, the undersigned (mother/legal guardian)
_____ born on ___/___/_____resident in _____ address _____
phone_____

I, the undersigned (father/legal guardian)
_____ born on ___/___/_____resident in _____ address _____
phone_____

Of the minor _____ born on ___/___/_____

I declare that I have received from Doctor _____ exhaustive explanations regarding the request to participate in the study, as reported in the information sheet, of which I was given a copy on _____ at _____ (indicate date and time of delivery).

I declare that the nature, purpose, procedures and benefits of the study have been clearly explained to me.

I also DECLARE that:

1. I have read and understood the information sheet provided regarding the research project and forming part of this consent;
2. I was given the opportunity to ask any question to the investigator of the study and I received satisfactory answers;
3. I was given sufficient time to reflect on the information received and to discuss it with third parties;
4. I was informed that the study protocol and all the modules used have had the favorable opinion of the competent Ethics Committee;
5. it was clearly explained to me that I can decide that the minor does not take part in the study and that such decisions will not modify in any way the relations with the treating doctors and with the facility where I am being treated;
6. I have been informed that the results of the study will be disclosed to the scientific community, protecting the identity of the minor in accordance with current privacy legislation.
7. I am aware that I must receive a copy of this informed consent.

Therefore I DECLARE TO:

☐ **WANT** ☐ **NON WANT**

that the minor participate in the study

_____	___/___/_____	_____	
Name of minor	Date	hour	
_____	___/___/_____	_____	_____
Name of mother/legal guardian	Date	hour	Signature
_____	___/___/_____	_____	_____
Name of father/legal guardian	Date	hour	Signature

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	Page 12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	PAGE 8/9

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Page 3
	6b	Explanation for choice of comparators	Page 4
Objectives	7	Specific objectives or hypotheses	Page 3,4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Page 4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Page 4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Page 4
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 4,5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 5
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 6,7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Page 7,8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Page 7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Page 4-6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Page 4,5
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Page 4,5
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	--
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Page 6
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Page 6

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Page 8
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Page 7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Page 8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Page 8,9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	N/A
	31b	Authorship eligibility guidelines and any intended use of professional writers	Page 8,9
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	-N/A