Study Protocol

Comparing the Prophylactic Effects of Caffeine versus Placebo on the Apnea of Prematurity in Neonates of Kabul City: A Randomized Clinical Trial.

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1. **Summary:**
   - **1.1. Full Title: Comparing the prophylactic effects of Caffeine versus Placebo on the apnea of prematurity in neonates of Kabul City: A Randomized Controlled Trial.**
   - **1.2. Design:** To be able to fulfill the objective of the proposed study, a prospective double-blind randomized controlled trial with a two-arm parallel-group study will be conducted. The allocation ratio is 1:1.
   - **1.3. Setting:** The study population is preterm infants with a gestational age of ≤ 34 weeks or a birth weight of less than 1500g (very low birth weight neonates).
   - **1.4. Study setting:** This study will be conducted in Neonatal Units of Malalai, Maiwand and Shefajo hospitals in Kabul City during 2021-2022. Malalai Hospital located in the 4th district of Kabul City. This is a governmental hospital that has a Neonatal Unit of 30 beds, it also has Gynecology/Obstetrics Department. Maiwand Hospital located in the 3th district of Kabul City. This is a governmental hospital that has a Neonatal Unit of 30 beds, it also has the Pediatrics Department. Shefajo Hospital located in the 10th district of Kabul City. This is a non-governmental hospital that has a Neonatal Unit of 10 beds, it also has The Gynecology/Obstetrics Unit.
   - **1.5. Duration:** The project would be of 16 months' duration. One month for the preliminary work (training of staff and preparing of material. An estimated three preterm neonates per week will be recruited, therefore, the recruitment of participants along with data collection will take 12 months, then the data analysis and research report writing will take another 3 months. The preliminary work (training of staff and preparing of material) would be started in July, 2021. Data collection will be started in August 2021. The project will end up by November 2022.
   - **1.6. Sample Size:** Sample size is calculated. We use hypothesized a decrease of 25% in the prevalence of apnea (in preterm and very low birth weight neonates, the prevalence of apnea is about 50%) with alpha of 0.05 and power of 0.8. We estimated a required sample size of 116 preterm neonates (58 newborn babies for each group). Considering a loss to follow-up of 10%, the final sample size is 130 preterm newborn infants (65 neonates for each group).

1.7. Randomization and Blinding: For this clinical trial, participants will select by randomized sampling strategy. The randomization method will be block randomization. The packaging of the investigational products following the randomization list will be done in the Department of Statistic, Kabul University of Medical science (KUMS), labelled with a randomization code. This will maintain concealment and double blinded treatment allocation. After randomization neither the patients nor the investigator or sponsor will be aware of the treatment allocation. Patients assigned to one of the double-blinded treatments will take intravenous solution of Caffeine or distilled water. The vial will be in identical appearance packages. The involved staff of the Department of Statistics and pharmacists will be aware of the randomized treatment allocation sequence but keep the list and information concealed till closure of the database. The Department of Statistics of KUMS isn't involved in patient recruitment.

2. Pretesting of the Assessment Sheet and Data Collection Sheet:

The method of interventions, and data collection sheet will be pretested for a period of one week to assure that there are no further changes needed in the questions and signs.

3. Identification of Study Subjects: Preterm neonates who fulfill one of the following criteria will be enrolled in the study.

- ✓ Gestational age of equal or less than 34w.
- ✓ Birth Weight less than 1500g.

3.1.1. Informed consent: Data collectors will introduce themselves by reading the consent form and will take permission for participation in a study. The data collectors will be instructed to read the consent form to the anticipated participant (mother of the newborn) in Dari and Pashto and make sure that she/he understands the content of the informed consent. If the person agrees to participate in the study, then the data collector will note the name of the participant with the help of blue pen on the consent form. As minors are involved in this study the consent will be signed by the parents. In the case of illiterate participants, the thumb mark of the left thumb will be used to indicate the agreement of the participant.

3.1.2. Refusal to Participate: Try to encourage participation but forcing to participate is not allowed.

- ✓ Inform that the intervention is an important part of treatment for her preterm newborn baby and will help us understand more about the effect of such management.
- ✓ Inform that the intervention is being conducted by fully qualified personnel.

3.1.3. Documenting recruitment: Once a parent has agreed to participate in the study, assign study ID #. Assign same study ID to parent and newborn form. This may be a consecutive number with a letter indicating the cluster name. Starting two spaces will be the number starting from 01 and the last two spaces will be for the study site name.

4. Intervention Process:

Three MD Doctors (Pediatrician or Neonatologist), one for each Neonatal unit, will be hired for 12 months of the intervention period. The process of intervention is as follows:

4.1. Phase I (Before the intervention): Before the intervention, a list of 130 randomized codes would be provided by the statistician. The pharmacist will prepare 130 identical appearance vials of caffeine citrate and distilled water with specific randomized code number prepared by the statistician. The statistician and pharmacist must keep the list of randomized codes securely until the end of the intervention.

4.2. Subject selection: Each week about 3-5 codes will be selected randomly and the related vial will give to newborn babies fulfill one of the following criteria:

- ✓ Gestational age ≤ 34 weeks.
- ✓ Birth Weight less than 1500g.

4.3. The patient selection process would be continued along with the intervention process until the completion of 130 preterm neonates (65 for the Caffeine group and 65 for the Placebo group)

4.4. Phase II (Intervention Process):

150 preterm neonates will be managing by prepared intravenous solution, 1ml/kg as the initial dose on the first day of life, and then 0.5 ml/kg daily as the maintenance dose for the first 10 days of life. The pharmacy would provide these solutions in vials with a specific codes and its 1ml will contain either 20mg of Caffeine citrate or distilled water. Neither the staff of research nor the patients' parents will know the composition of the mention solutions. Therefore, at the end of the intervention, 65 preterm neonates would be managed by Caffeine citrate 20 mg/kg intravenously as the initial dose on the 1st day of life, and then 5 mg/kg intravenously daily as the maintenance dose for the first 10 days of life. The other 65 preterm neonates would be given the same amount and duration of distilled water.

5. Assessment of effects:

At the end of the intervention, the list of randomized codes and related information of intervention would be disclosed The effects will assess by the research statistician and PI. The evaluation will perform by comparing the primary and secondary outcomes between two groups.

5.1. Primary outcomes:

✓ The risk of Apnea defined as the cessation of respiration exceeding an arbitrary duration of 20 s, or <20 s but with bradycardia, cyanosis or oxygen de-saturation. The apnea will be diagnosed by Cardio-respiratory Monitor.

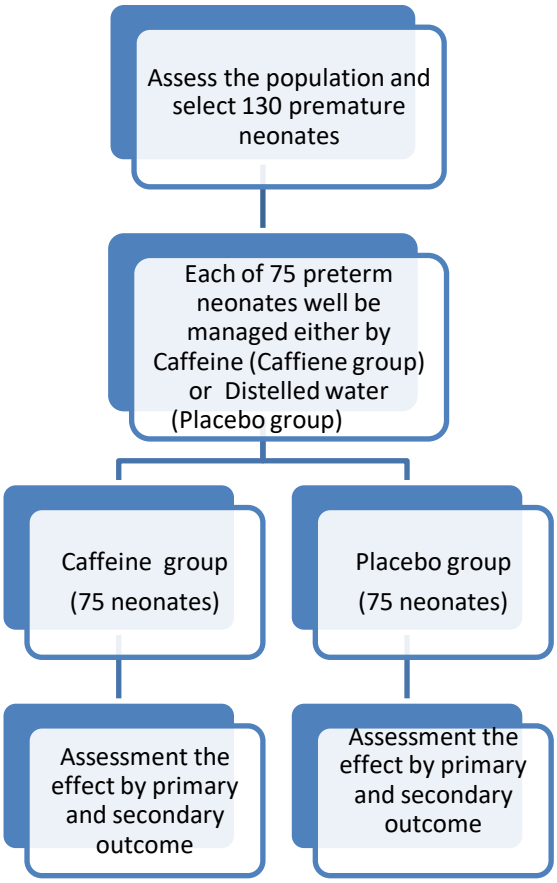
✓ The total duration of apnea demonstrates in days and the number of apnea attacks during 24hr.

✓ The gestational age at birth shows in weeks, which determine by LMP or antenatal maternal ultrasound or gestational age assessment by neonatal heel-toe distance.

5.2. Secondary outcomes:

- ✓ Secondary variable is risk of neonatal death during the intervention.

5.3. Assessment of effects: The effects of drugs both groups would be compared by RR, Mean ± SD and P-value of data.



Flow chart of research

6. Training of the data entry officer:

One data entry officer will be hired for 6 months. The data entry officer will also be trained by PI. He will be given training on how to read the filled data forms. Code book will be introduced to data entry officer. A Stata/SPSS spread-sheet made by PI will be given to the data entry officer. He will be trained on how to enter the data from the filled forms into the spread sheet. The PI will request the data entry officer to enter the data for five study participants in front of the PI. The mistakes done in this process by the data entry officer will be communicated to them.