Ethical Issues with Placebo Use In Neonatal Research

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Summary:

While we cannot deny the benefits and evidence generated by placebo-controlled trials in neonatal research, using any painful procedure or agent with potential side effects should be viewed critically. The neonate has the right to personal respect. All ethical and moral principles should be followed when performing research on neonates.

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A placebo is an inactive substance that looks like the drug or treatment being tested. In research, a placebo is used as a control when studying the effect of certain drugs or treatments. Intramuscular (IM) injection of a placebo into neonates causes pain, and there have been concerns about its use in randomized controlled trials (RCT). A recent article discussed this issue and concluded that placebo injections are neither necessary nor ethically acceptable in neonatal research (1). Examples of unnecessary IM placebo include IM saline injection in 30 control babies while studying the safety of stannsoporfin in neonatal jaundice (2). Firstly, the drug is new; secondly, the drug is not a life-saving drug; third, there are better alternatives available to treat neonatal jaundice.

In another study (3), premature neonates received a placebo intravenously every 48 hours for six doses, followed by sham injections three times a week until postmenstrual age (PMA) of 32 weeks (6-7 days), so a preterm infant born at 22 weeks would have received approximately thirty subcutaneous injections (3 per week times ten weeks, 32-week PMA). How could we justify the magnitude of this injustice? In addition to the pain associated with these subcutaneous sham injections, there is a potential risk of infection related to breaching the skin integrity, which is colonized with bacteria. The other example is using saline IM injection of 484 infants while studying the effect of the RSV vaccine(4).

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IM injections hurt, which is an adverse event. So, how can we justify using an IM placebo during RCT in neonates? A placebo's perceived or potential benefits are irrelevant to the study subject. This defeats the fundamental ethical principle of beneficence.

When we look at oral placebo use in neonates, we also see a problem. The choice of a suitable placebo substance is essential. In a recent paper, the investigators used a high sugar-containing oral solution in the control group of neonates with neonatal opiate withdrawal syndrome (NOWS) (5). They used a simple syrup USP (Humco, Sucrose 85% weight per volume; Purified Water; Citric Acid; 0.1% Methylparaben or equivalent). The authors aimed to look at the effect of a drug (ondansetron) in reducing the severity of NOWS symptoms, judged by a score (Finnegan score). This score has 21 components, many of which would be affected by oral sucrose administration. For example: crying, tremors, sucking and feeding, and stools. Sucrose is an active substance used as a non-pharmacological agent during minor painful procedures in neonates. Why shouldn't they use water? This is an example of a breach of the second ethical principle, non-maleficence.

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The third crucial ethical principle in research is autonomy. Neonates are incapable of consenting to any intervention. Parents, as surrogates, make all the decisions and are mostly unaware/or told of the pain associated with placebo injections. The fourth principle is also breached during the placebo. Using a painful procedure (IM injection) for research purposes is performed; it is an act of unduly burden imposed, which is injustice.

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Axelin and Salanterä (6) reviewed multiple studies and found that in 75% of the studies, the infants suffered pain during the research with a placebo, and 25% of the journals did not have ethical guidelines for submitted manuscripts. Fleischman (7) looked at the ethical issues in neonatal research involving human subjects and described specific categories of permissible research based on levels of risk. The first category is no greater than minimal; the second is a prospect of direct benefit; and the third is a minor

increase over minimal. A painful placebo or placebo with potential side effects is beyond these criteria.

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We cannot deny the benefits and evidence generated by RCT in neonatal research. DeMauro et al. (8) stated that RCTs are needed to improve neonatal care, identify better care practices, uncover useless or harmful therapies, reveal new knowledge gaps, and improve outcomes. However, using any painful procedure or agent with potential side effects should be viewed critically. The neonate has the right to personal respect. All ethical principles should be followed when performing research on neonates.

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Author contribution: *Dr. Manzar conceptualized and wrote the draft.*

Funding and financial support: *None*

Conflict of interest: *None*

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