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The Choice of Population and Outcomes in Neonatal Trials on Hyperbilirubinemia: Are They Relevant? An Analysis of Cochrane Neonatal Reviews

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Abstract
Background: Neonates with jaundice are usually managed according to their serum bilirubin despite an unclear overall correlation between bilirubin levels and patient-important outcomes (PIOs) such as kernicterus spectrum disorder (KSD). ***Objectives:*** We examined data from Cochrane Neonatal reviews to assess whether conditions that constituted KSD were included as key outcomes and how commonly they occurred in the population studied. ***Methods:*** We identified Cochrane reviews, published till November 2017 that evaluated interventions for neonatal jaundice (NNJ). We extracted the following information at the review and study levels: included population, outcomes assessed (in particular, whether PIOs such as KSD were listed as the primary outcomes), as well as their cumulative incidence in the reviews. ***Results:*** Out of 311 reviews, 11 evaluated interventions for NNJ with 78 randomized controlled trials (RCTs) included. Among the reviews, a total number of 148 outcomes were predefined and 30 (20.3%) were PIOs related to KSD, with 11 (36.7%) listed as primary outcomes. Among the 78 included RCTs (total participants = 8,232), 38 (48.7%) enrolled predominantly high-risk and 40 (51.3%) enrolled predominantly low-risk population. A total number of 431 outcomes were reported, and 40 (9.2%) were PIOs related to KSD (of which 37 were from studies with high-risk infants), with 13 (32.5%) listed as primary outcome. Cumulatively, no infant developed KSD across all studies. ***Conclusions:*** There is suboptimal representation of PIOs such as KSD in neonatal trials and Cochrane reviews on NNJ. Over half of the trials included populations with very low risk of KSD, which does not represent judicious use of resources. Amidst our continued search for a more reliable surrogate marker for NNJ, studies should evaluate the whole spectrum KSD alongside serum bilirubin in high-risk populations with sufficiently significant event rates, as this will make the trial methodologically feasible, with findings that will impact the population concerned.

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