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Balancing Demand for Universally Improved Health Outcomes with Need for a Local Standard of Care

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Abstract

The United States, along with other resource-rich countries, leads global health care by advancing medical care through randomized controlled trials (RCTs). While most medical research is conducted in these resource-rich areas, RCTs, including replications of previous trials, are additionally carried out in low- and middle-income countries. On the basis of positive findings from several RCTs conducted in high-income countries, the Antenatal Corticosteroids Trial (ACT) evaluated the effectiveness of antenatal corticosteroids in reducing neonatal mortality in low- and middle-income countries. ACT, however, was undertaken in dramatically different health care infrastructures and did not confirm the results of previous studies. We argue that it is neither clinically appropriate nor ethically acceptable to extrapolate findings from one region to another without accounting for the disparate cultural values, goals of care, and health services infrastructure that impact clinical outcomes.

Introduction

As the gold standard of clinical research, randomized controlled trials (RCTs) produce generalizable results when properly conducted. However, in the quest to improve global health, it is easy to overlook issues of generalizability, which depends on the sample of participants being representative of the target population. Results of an RCT conducted in one country might not generalize to another due to differences in patient characteristics, social determinants of health, national economic status, health care infrastructure, health services, and legal context. While a well-done RCT ideally acknowledges and accounts for participant-level clinical and demographic differences, the social and health systems in which care is provided in the target population can mistakenly be assumed to be constant rather than variables in the health care equation [1, 2].

These difficulties are highlighted by the discrepant results of two RCTs on antenatal glucocorticoid administration to prevent neonatal respiratory morbidity—the Antenatal Corticosteroids Trial (ACT) and the Antenatal Late Preterm Steroids (ALPS) trial [1, 2]—

conducted in different regions. The lessons learned from these trials present bioethical considerations that need to be taken into account when endeavoring to improve health outcomes globally. After analyzing both overlooked clinical assumptions and ethical issues, we argue that it is neither clinically appropriate nor ethically acceptable to extrapolate findings from one region to another without accounting for the disparate cultural values, goals of care, and health services infrastructure that impact clinical outcomes. In our diverse and global health care system, it is important to remember that, ultimately, all care is local.

Clinical Context

Antenatal corticosteroids (ACS) as a means of reducing adverse neonatal outcomes in at-risk preterm births first came to light in 1972 [3]. These steroids are given to pregnant mothers at risk for preterm delivery to improve neonatal respiratory function. In the United States, evidence strongly supports the use of ACS to help reduce respiratory distress syndrome and death in preterm infants less than 34 weeks of gestational age, and the decrease in neonatal morbidity and mortality nationally following preterm birth is thought to be strongly related to glucocorticoid administration [1, 4-6].

The majority of trials evaluating the effectiveness of ACS limited use to a gestational age of less than 34 weeks until the publication of the ALPS trial in 2016. The ALPS trial was a large, multicenter, RCT conducted in the United States that sought to determine whether ACS had a role in improving neonatal outcomes when given in the late preterm period from 34 weeks 0 days to 36 weeks 5 days [1]. The ALPS trial demonstrated a positive impact from administering late preterm ACS, including reduced rates of resuscitation at birth, surfactant use, transient tachypnea of the newborn, and bronchopulmonary dysplasia [1]. The study did not detect a significant difference in rates of maternal infection (chorioamnionitis or endometritis) between groups, and there were no neonatal deaths in either study arm. As a result of the ALPS trial's findings, the American College of Obstetricians and Gynecologists expanded its recommendations on ACS therapy for fetal maturation to include consideration of routine administration to pregnant women between 34 weeks 0 days and 36 weeks 6 days who were at risk of preterm birth within 7 days and who had not received a previous course of ACS [5].

Given the success of ACS in the United States and other high-income countries such as Finland, Brazil, Spain, United Kingdom, New Zealand, and the Netherlands, among others, the World Health Organization (WHO) has recommended the use of ACS for women at risk for preterm delivery to help improve preterm birth outcomes [7, 8]. The National Institutes of Health published a conference report addressing the expanded use of ACS in low-income countries to help reduce high rates of neonatal death and morbidity attributed to prematurity [9]. In general, antenatal corticosteroids are recommended for use in low-income countries, ideally at a hospital with high-level care

[9]. But these recommendations warrant caution as they also acknowledge a lack of data regarding the efficacy of ACS in these countries.

In response to this need, the WHO recently announced plans for two upcoming trials to further evaluate the efficacy of ACS use in low-income countries [10, 11]. The two trials will look at ACS use in gestational ages 26 weeks 0 days to 33 weeks 6 days and 34 weeks 0 days to 36 weeks 0 days, respectively. The RCTs will be held in Bangladesh, India, Kenya, Nigeria, and Pakistan at hospitals with sufficient levels of maternal and newborn care [10, 11]. These trials, also known as the WHO Antenatal Corticosteroids for Improving Outcomes in Preterm Newborns (WHO ACTION) trials, will seek to answer questions raised by the results of the ACT trial given the limitations of generalizability to the diverse populations that exist in low- and middle-income countries [10, 11].

Prior to the announcement of the WHO ACTION trials, the first randomized controlled trial analyzing ACS use in low-income countries was published in 2015. In an effort to expand ACS use and evaluate its feasibility and effectiveness in low- and middle-income countries, Althabe et al. launched a cluster-randomized trial in six countries with high rates of premature birth via the ACT trial [2]. Pregnant women before 36 weeks of gestational age at risk for preterm delivery were randomized to receive ACS in Argentina, Guatemala, India, Kenya, Pakistan, and Zambia. Health care practitioners were trained to identify women with signs of labor and medical conditions that could necessitate an indicated preterm delivery. They also received instruction on how to accurately estimate gestational age, as the availability of ultrasonography was limited. The primary outcome measured was 28-day neonatal mortality among infants less than the 5th percentile for birth weight to act as a proxy for preterm gestational age. Despite the increased use of ACS in the study treatment arm, however, the study found no difference in neonatal mortality between the treatment and control arms, an overall small increase in neonatal mortality in the study population as a whole, and an increased rate of maternal infection in the women who received ACS [2]. These findings came as a surprise given the publication of 30 trials demonstrating a positive benefit and showing a reduction in perinatal death, neonatal death, and respiratory distress syndrome [8]. These incongruent results raised questions regarding the generalizability of previous trials.

Addressing Overlooked Clinical Assumptions in Research

The comparison of the ALPS trial to the ACT trial calls attention to several overlooked implicit clinical assumptions. The ACT trial investigators are thoughtful when addressing the challenge of determining gestational age by looking at birth weight less than the 5th percentile as a proxy for length of pregnancy. As the authors acknowledge, one weakness of the study is that term infants with intrauterine growth restriction were possibly included while missing preterm infants with higher birth weights, both of which could have contributed to lack of an observed positive effect since gestational age has a greater impact on lung development than weight. This is in stark contrast to the ALPS

study conducted only using participants with excellent dating of their pregnancies due to the availability of prenatal care and antenatal ultrasounds.

It is also crucial to consider several assumptions one might make about a disease and subsequent treatments in another global territory. Disease pathology might not be the same between regions. In fact, data suggest that the underlying etiology for preterm birth varies based on geographic location [12]. For example, higher rates of infections such as HIV, STDs, and malaria are thought to be partly related to the exceedingly high rates of preterm birth in Africa [13]. If rates of infection as a cause of preterm birth are higher in low-income regions, it would be reasonable to predict that ACS use in this population could lead to a higher incidence of maternal sepsis as steroids also act as an immune suppressant [14]. In fact, in a systematic review of 21 RCTs evaluating the effects of ACS use, 8 did show a trend, though not statistically significant, of increased puerperal sepsis [8]. Therefore, along with studying the heterogeneity in results of ACS administration between high-income and low-income countries, researchers should also investigate the potentially varying basis for preterm birth in low-income countries.

Medical care should also not be taken as an isolated event in time. Proper follow up and long-term care must be a consideration for premature infants. For example, it is unclear the extent to which the lack of skilled attendants at birth and decreased availability of adequate postnatal care impacted the results of the ACT trial. The ACT trial's criteria for cluster centers was based upon birth registries with at least 300 births annually, whether these occurred at homes or facilities [2]. While the study interventions also included training in essential newborn care, there is no mention of quality assurance among health care practitioners. The majority of women did deliver in health care centers but there were still reported home births [2]. Additionally, there were differences between the treatment and control group regarding type of skilled attendant and delivery location [2]. Women in the treatment arm tended to deliver in a clinic with a nurse as the skilled attendant, whereas the control arm had more hospital deliveries with physicians. Taken together, the divergent outcomes between the ALPS and ACT trials might be explained by the variation in study methodology, especially the study populations, as well as the varying health care infrastructures in which care was provided.

Ethical Challenges in Extrapolating Research Findings Globally

The disparate results of the ALPS and ACT trials demonstrate the importance of an adequate understanding of the cultural context as well as the risks of insufficiently accounting for the health services environment of different countries when attempting to extrapolate research findings. Physicians have an ethical responsibility to be mindful of potential hazards or challenges that exist in underdeveloped countries that might impede or undermine patient care when applying successful treatments that have only been studied in specific target populations.

In addition to assumptions made about a disease's epidemiology, it is imperative to be mindful of a region's values, goals of care, health care infrastructure, and resources when bringing treatments abroad or designing replications of previous research trials. While the ACT trial was successful at increasing rates of ACS administration in six low- and middle-income countries [2], increasing neonatal and maternal care overall poses a more difficult challenge, since a substantial proportion of women deliver in their homes [12]. It might not be culturally desirable, or logistically feasible, for these women to deliver in a hospital [15]. Economic status and local resources also deserve attention when considering the application of biomedical research findings. For example, the cost-benefit ratio of a variety of interventions for improving maternal and infant health can differ within low-income regions. Using the number of disability-adjusted life years averted, a metric that combines both mortality and morbidity in order to determine the cost of disease burden, one report found ACS to be the *least* cost-effective intervention among others such as breastfeeding support, tetanus toxoid vaccines, and treatment of syphilis in South East Asia [16]. Thus, resources might better be allocated in these countries to interventions known to have greater impact on population health than ACS.

Designing an ethical research study, especially in the era of global health, requires thoughtful balance. The study should be conducted in populations that are sufficiently narrowly demarcated to account for the relevant variations in culture and in health systems that might impact the results. An appropriate response to this dilemma is demonstrated in the new WHO ACTION trials, as previously discussed [17]. However, the study population should also be sufficiently broadly defined to potentially include as many patients as possible and not exclude groups of people from having the opportunity to serve as research participants. Finally, the group of people serving as research participants must have the opportunity to directly or indirectly benefit from the results.

Conclusion

The medical community is thus left with the challenge of how to reconcile different results from research trials conducted in a global health care system comprised of varying cultural contexts and health care infrastructures. The global health care community must push itself to be thoughtful and critical when seeking to apply results from RCTs conducted in resource-rich regions to an entire international community. Furthermore, it is imperative to realize that while the desire to improve health outcomes must be global, such efforts should be cognizant of local values, culture, resources, and health care infrastructure. While the actual medical care and thus standard of care recommendations might vary between regions given these differences, conducting research globally remains of high importance.

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