Although effective treatments exist to prevent painful vaso-occlusive episodes in patients with sickle cell disease (ie, hydroxyurea), finding therapies to reduce the severity or duration of episodes once they have begun has proved elusive. Inhaled nitric oxide, intravenous magnesium, and intravenous sevuparin have been tried without success. In 2001, JAMA published a phase 3 multicenter, randomized, placebo-controlled clinical trial of poloxamer 188 in 255 children and adults with sickle cell disease hospitalized with a vaso-occlusive episode.1 In that study, Orringer et al found a modest, statistically significant reduction in the duration of the episodes with poloxamer 188 vs placebo (141 hours vs 133 hours; difference, 9 hours; P = .04).

In this issue of JAMA, Casella and colleagues2 present the results of a phase 3, randomized, placebo-controlled clinical trial of poloxamer 188 conducted in 66 hospitals in 12 countries. The investigators enrolled 388 children and adults with sickle cell disease and moderate to severe pain requiring hospitalization. The primary outcome was time to last dose of parenteral opioids. The trial found no significant difference between the groups, suggesting no evidence of a beneficial effect of poloxamer (81.8 hours in the poloxamer 188 group and 77.8 hours in the placebo group; difference, 4.0 hours; 95% CI, −7.8 to 15.7).2

Why did these trials come to such different conclusions? The most likely explanation is the choice of primary outcome. In the study by Orringer et al,1 the primary outcome was time from randomization to crisis resolution. The resolution of pain is subjective, and the criteria to determine crisis resolution established by the investigators were extremely stringent and difficult to implement, leading to a high proportion of participants with incomplete documentation. Also, incomplete documentation occurred more often in the placebo group than the intervention group, resulting in more imputation of missing values for the placebo group, which favored the poloxamer 188 group. In the trial by Casella et al,2 a different, more easily verified primary outcome was selected, with data available for 99% of participants.

The trial by Casella et al2 was completed in 2016, 5 years ago, and is much older than the randomized clinical trials that JAMA usually publishes. Why did the editors decide to accept this report? Two factors influenced the decision.

The first is that JAMA published the trial by Orringer et al,1 and the editors thought it was important for these contradictory results to be published. The second relates to the reason for the delay after trial completion. The neutral results of the study were announced in 2016 when the trial was completed. The company that funded the trial, Mast Therapeutics, was immediately sold to another company, SAVARA, including the rights to the trial. According to the authors, the new company reportedly was not interested in publishing the results and the data were no longer available to the investigators. Although it took several years, ultimately one of the investigators reported that he was able to use his own resources to allow completion of the analysis, an important and noteworthy commitment to the scientific process.

Results of studies, especially clinical trials that are time and resource intensive, should be published in a peer-reviewed journal, regardless of whether the outcomes were positive or negative. The results of clinical trials should not be discarded because of financial interests, disinterest, or shift in priorities on the part of the funders.3 Not publishing negative results can lead to research duplication, as well as waste of the resources committed to the trial. In addition, individuals participate in research expecting that their efforts will contribute to the base of knowledge, and it is unfair and perhaps unethical to disregard the data and findings based on their participation in studies. Although not relevant to poloxamer 188, which has not been approved by the Food and Drug Administration, an available drug with positive findings in a randomized clinical trial might be prescribed; if a subsequent negative trial was not published and the drug continued to be used, funds may be spent needlessly and patients may be exposed to drugs with potential harm.

The report by Casella et al2 in this issue of JAMA adds to the evidence base and illustrates some of the challenges in finding effective treatments for patients with sickle cell disease. The investigators deserve recognition for their determination to publish the results of this study.

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