COMMENTS AND RESPONSES

Comparison of Negative Pressure Wound Therapy Using Vacuum-Assisted Closure With Advanced Moist Wound Therapy in the Treatment of Diabetic Foot Ulcers: A Multicenter Randomized Controlled Trial

Response to Blume et al.

We have read with interest the article by Blume et al. (1) in which the authors interpret the presented results as supporting evidence that negative pressure wound therapy (NPWT) is as safe as and more efficacious than advanced moist wound therapy (AMWT) to treat foot ulcers in diabetic patients. NPWT is widely applied, although the evidence base is weak and existing trials are frequently affected by methodological flaws (2,3). In our opinion, the presented results should be interpreted with more caution.

One of the major reasons for the limited validity of the results is the high proportion of censored subject data (33%, $n = 111$) in this unblinded trial. Even though NPWT can hardly be studied in a blinded fashion, an open study design, principally, carries a high potential for bias.

This could have been minimized by a blinded committee assessing clinical outcomes and objectifying study decisions, leading to discontinuation and censoring (e.g., "withdrawal by investigator," the second most frequent reason for discontinuation in this trial). The criteria for discontinuation are not clearly stated, and comparability in censoring over time cannot be assessed because data on the number of subjects at risk are not presented in Fig. 2. This should be considered when interpreting the Kaplan-Meier analysis of "time to complete ulcer closure" because this analysis is based on the assumption that being censored is not related to prognosis. In this context, we are wondering how "ineffective therapy" could be a reason to exclude patients in a trial conducted to prove whether an intervention is effective. We are not sure how to interpret the difference between the presentation of the results in this figure and in the text: according to the text, 43.2% (NPWT) and 28.9% (AMWT) of patients had complete ulcer closure until day 112. In Fig. 2 it seems that at day 112, ~58% (NPWT) and ~38% (AMWT) have complete closure.

To confirm the results of the intent-to-treat analysis, an analysis including only patients who complete the active treatment phase is used ($n = 120$ in each group). We were not able to reproduce these numbers using the data presented in the flow diagram.

Another major point of criticism is the primary end point definition. Complete ulcer closure defined as skin closure without drainage or dressing is an important outcome, but it has to be followed up adequately to ensure that wound closure was permanently successful, in particular when it was achieved by surgery. In fact, the authors state that ulcer closure was followed at 3 and 9 months, but, unfortunately, these crucial data are not presented.

Finally, we are not convinced by the arguments for the postulated equivalence of safety. It is unclear whether safety analysis was taken into account for sample size calculation and whether the power was sufficient. That no significant differences were found may not lead to the conclusion of equivalence without further exploration. Moreover, numerically, more cases of infection ($n = 11$ vs. $n = 4$) and of major secondary amputations are observed under NPWT ($n = 5$ vs. $n = 4$). We suggest that in future trials the abovementioned issues should be considered and all efforts be made to rule out potential sources of bias.

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References

1. Blume PA, Walters J, Payne W, Ayala J, Lantis J: Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. *Diabetes Care* 31:631–636, 2008
2. Gregor S, Maegele M, Sauerland S, Krahn JF, Peinemann F, Lange S: Negative pressure wound therapy: a vacuum of evidence? *Arch Surg* 143:189–196, 2008
3. Peinemann F, McGauran N, Sauerland S, Lange S: Negative pressure wound therapy: potential publication bias caused by lack of access to unpublished study results data. *BMC Med Res Methodol* 8:4, 2008