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LETTER

Letter to the Editor Regarding 'A Multicentre, Randomised Clinical Trial to Compare a Topical Nitrizinc® Complex Solution Versus Cryotherapy for the Treatment of Anogenital Warts'

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DIGITAL FEATURES

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Dear Editor,

We have read with great interest the randomized controlled trial (RCT) by Pontini et al., who compared two provider-administered treatments for anogenital warts (AGWs): nitrizinc complex solution and cryotherapy [1]. These authors found the nitrizinc complex solution to be as effective as cryotherapy for the treatment of small AGWs, with a better tolerability profile and a lower rate of recurrence.

In this study by Pontini et al., treatments were administered every 10 days for a maximum of four treatment sessions: nitrizinc complex solution was applied until the lesion took on a yellowish–white color, and cryotherapy was applied for a few seconds [1]. Regrettably, the authors provided no further details on the application of the treatments. An insufficient description of application procedures is a common occurrence in RCTs of AGW treatments. Thus, a recent meta-analysis of cryotherapy found that treatment delivery [intensity (aggressive vs. gentle), duration, use of spray or cryoprobe] was not sufficiently standardized, making it difficult to compare treatment effectiveness across studies [2]. To ensure comparability of future RCTs, the delivery of cryotherapy could be standardized as follows: (1) apply treatment to lesions until bleaching occurs; (2) bleach for 5 s; (3) perform two freezing cycles; (4) re-evaluate patients at 15 days; (5) repeat procedure every 15 days until AGWs are completely destroyed for a maximum of four sessions [3].

A high risk of bias has been identified in RCTs of AGW treatments. This is largely

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explained by the fact that blinding of participants and care providers is difficult or impossible to achieve in the case of provider-administered treatments [4, 5]. Although Pontini et al. [1] ensured that the effectiveness of the nitrizinc complex solution and cryotherapy was evaluated by someone other than the physician administering treatment, lack of blinding may have resulted in the physician's lack of conviction in his or her own actions and poor adherence to trial protocol, placebo effects, or early patient withdrawal from the study [6]. The following measures have been proposed to ensure blinding in RCTs of provider-administered treatments [7, 8]: (1) performing a fake procedure (e.g., using similar but non-functional equipment); (2) not informing the patient of the study hypothesis at inclusion, while nevertheless respecting ethical guidelines; and (3) blinding the medical/paramedical team to the study hypothesis. In the context of dermatology, photographing lesions may be a suitable method for blinding evaluators [6].

Pontini et al. evaluated AGW recurrence at 1 and 3 months [1]. However, given that AGW recurrence has been shown to be fairly common 6 months after treatment [9–11], they should also have done so at 6 and 12 months. Lastly, it should be noted that while ablative therapies (surgery, electrosurgery, CO_2 laser) are more effective than patient-administered treatments in the short term [4, 9], the latter may be superior in the long term due to their immunomodulatory effects.

We are grateful to Pontini et al. [1] for pursuing research in this area despite the development of preventive vaccination for human papillomavirus, the indirect effectiveness of which on AGWs is well documented [12]. Indeed, vaccination coverage remains insufficient worldwide [13], indicating that AGWs will continue to be of concern for years to come. In the future, RCTs that avoid bias and respect CONSORT reporting guidelines should evaluate the effectiveness of AGW treatments according to: (1) the sex of the patient; (2) the anatomical location of AGWs (cutaneous vs. mucosal); (3) the number of AGWs; (4) the size of AGWs; (5) whether AGWs are new or recurrent; and (6) whether the patient is immunocompromised [6].

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

Peer Review. Please note, contrary to the journal's standard single-blind peer review process, as a letter this article underwent review by a member of the journal's Editorial Board.

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