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Replacement of dropouts may bias results: Comment on 'The effect of green tea ointment on episiotomy pain and wound healing in primiparous women: A randomized, double-blind, placebo-controlled clinical trial'

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Keywords

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Randomized Controlled Trials (RCT) are important for making unbiased estimates of treatment effects, but need to be performed carefully with proper analysis. While it is common to have subjects drop out of a study, this could lead to bias if they are not accounted for correctly in the statistical analysis (Wood et al., 2004; Juni, et Egger, 2005). Bell et al. show how even if the dropout rates are similar between study arms, the results for treatment effects can be biased; while having unequal dropout rates does not mean that the results will be biased (Bell et al., 2013). Therefore, it is necessary to account for the dropouts correctly, which is why Intention to Treat (ITT) analysis is preferred to provide unbiased results (Elobeid et al., 2009; Gupta, 2011; Hollis, & Campbell, 1999; Newel, 1992).

Shahrahmani et al. conducted an RCT on the effect of green tea ointment on episiotomy pain and wound healing in primiparous women (Shahrahmani et at., 2017), and in doing so, they replaced the dropouts with new participants. This presumably alleviates the problem of losing power, but it does not eliminate the potential bias of missing data from dropouts (Juni et al., 2001). Moreover, replacing dropouts can introduce new bias. The method of replacement used by Shahrahmani et al. is not clear. Referring to the ten subjects lost to follow-up (3 from the green tea group, 3 from the placebo ointment, and 4 from the group with no ointment), the authors state "subjects were replaced by other eligible women", where the original number of 33 per group is maintained for analysis. If the next person enrolled was put into the treatment group of the most recent dropout, this is not a random process. If additional subjects are needed, the next participant enrolled should be assigned randomly to one of the three groups with equal probability, in the same manner as the rest of

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the study participants, thus maintaining the randomization allocation ratio (Shibadas, & Vinu, 2018). Compromising the randomization interferes with the validity of causal inferences. Additionally, assigning a new participant to the treatment group of a dropout outside the randomization procedure might mean that the allocation is not concealed if study staff know the dropout's treatment group, which can lead to selection bias (Day, & Altman, 2000).

It is also puzzling that the researchers replaced the dropouts after they intentionally recruited extra participants to account for 20% potential attrition. The protocol submitted in the Iranian Registry of Clinical Trials (IRCT2016011225983N) does not contain any plan to replace subjects who dropout.

Because the 10 replacements were not truly randomized in Shahrahmani et al. (if our understanding is correct), they should not be included in the final analysis. An ITT analysis should be performed including the 10 participants who dropped out after randomization and excluding the 10 replacements if they were not randomly assigned to their treatment group according to the protocol.

The authors were contacted, but they were not willing to comment or share the data.

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