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Aromatherapy Versus Oral Ondansetron for Antiemetic Therapy Among Adult Emergency Department Patients: A Randomized Controlled Trial

To the Editor:

April et al[1] conducted an intriguing trial comparing aromatherapy with ondansetron in adult emergency department (ED) patients with nausea. The authors conclude that among ED patients with nausea, aromatherapy provides greater nausea relief than oral ondansetron. It was unexpected to see aromatherapy reported as outperforming a known, potent antiemetic. On close review, we have identified some methodological issues that may have influenced the results and conclusions drawn.

Most important, this study was effectively an unblinded trial. Isopropyl alcohol has a very noticeable smell that cannot be masked. Participants in the aromatherapy arm correctly identified it in 53% (42/80) of those exposed compared with only 9% (7/80) of those in the oral ondansetron arm. As such, subjects and the investigators (who were mostly physicians and who doubled as study personnel collecting the data) were most likely aware of the intervention allocation.

Second, the effect size in the ondansetron-only group was underestimated and biased toward the isopropyl alcohol arms because of inappropriate timing of data collection. The primary outcome (effect on nausea) was assessed 30 minutes after administration of both medications, yet peak serum level and time of maximal ondansetron effect occur at least 2 hours after oral administration.[2] This finding is highlighted in Figure 3 of their article, which depicts the ongoing reduction in nausea in both ondansetron study arms that begins only at 30 minutes postadministration. Furthermore, when "nausea therapy satisfaction" measured at disposition was examined nearly 3.5 hours later, it was significantly higher among patients administered ondansetron only compared with both of the isopropyl alcohol inhalation groups.

The ondansetron dose used (4 mg) was too low; most studies that have demonstrated effectiveness of oral ondansetron use doses of 8 mg in patients weighing greater than 30 kg.[3] Thus, adults receiving oral ondansetron in the study were administered a subtherapeutic dose and had the benefits quantified at a point when one would not yet expect to observe significant antinausea effects.

These limitations must be taken into account when the study results are interpreted.[1] Although it is tempting to adopt an appealing, easy-to-implement solution such as aromatherapy for the treatment of nausea, perhaps a more appropriate conclusion would be that aromatherapy provides some early nausea relief and requires further study to confirm whether its use as an adjunct to ondansetron provides benefit.

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2. VanDenBerg CM, Kazmi Y, Stewart J, et al. Pharmacokinetics of three formulations of ondansetron hydrochloride in healthy volunteers: 24-mg oral tablet, rectal suppository, and iv infusion. *Am J Health Syst Pharm*. 2000;57:1046-1050.
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In reply:

We thank Freedman et al[1] for their letter in regard to our randomized trial comparing nausea relief with aromatherapy versus oral ondansetron. We found that patients allocated to arms receiving aromatherapy reported greater nausea reduction at 30 minutes.[2] This finding adds to the growing literature demonstrating that aromatherapy has efficacy in treating nausea in the emergency department (ED) setting.[3] That said, Freedman et al[1] highlight several important study limitations.

First, blinding is difficult for any investigation of aromatherapy and was imperfect in our study. We might have improved blinding by exposing patients not allocated to receive isopropyl alcohol to an alternative aromatherapy agent with a similar smell or by exposing all patients in both arms to an additional background scent (eg, scented oils). However, we suspect the antiemetic effect of isopropyl alcohol is due to olfactory distraction. Consequently, we anticipate that any trial exposing all arms to some form of aromatherapy would likely show clinical equipoise. Indeed, the anesthesia literature suggests that a variety of aromatherapy agents reduces postoperative nausea, suggesting that this effect is not unique to isopropyl alcohol,[4] although the latter is likely to be more readily available in the ED setting courtesy of ubiquitous alcohol pads.

In regard to our selection of 30 minutes postintervention as the time to collect our primary outcome of nausea reduction, we agree that ondansetron is unlikely to achieve full effect within this period. However, insofar as this time horizon potentially biases our results against ondansetron, a longer time would arguably bias our results against aromatherapy. Although the time of primary outcome measurement should take into consideration the pharmacokinetic profiles of the agents under investigation, equally important is the relevance of that period to clinical practice. In the case of ED treatment of nausea, we believe most emergency physicians would find a wait of 2 or more hours for nausea relief to be untenable. Hence, although inhaled isopropyl alcohol may not provide superior nausea relief compared with oral ondansetron during longer periods, our finding that it achieves superior nausea relief at 30 minutes postintervention is itself a clinically important result. Similarly, patients receiving inhaled isopropyl alcohol reported greater satisfaction, as reflected by lower satisfaction visual analog scale scores at ED discharge (we designated lower visual analog scale scores as more satisfied to maintain consistency with the pain and nausea scores for which lower values were more desirable because they reflected less severe symptoms). Nevertheless, it is not our contention that aromatherapy should supplant ondansetron but rather that it may supplement this commonly used agent. The nausea relief reported by patients allocated to the study arm receiving both of these interventions speaks to the potential efficacy of this therapeutic strategy.

We concede that our ondansetron dosing (4 mg) may have been subtherapeutic. We selected this dose as the amount of drug commonly administered in the ED setting for the treatment of undifferentiated nausea. Future research might examine whether higher ondansetron doses would yield different findings.

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