Challenges in herbal research: A randomized clinical trial to assess blinding with ginger

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Summary
Objective: To assess methods to blind study participants to encapsulated ginger (Zingiber officinale).
Design: A randomized double-blind placebo controlled trial.
Subjects: Eighty healthy male and female volunteers.
Outcome measures: Whether participants can accurately determine if they receive a ginger or placebo capsule and a bottle filled with ginger or placebo capsules.
Results: Forty-two subjects correctly identified the capsule they received. Of those who received placebo, over 82% correctly identified their capsule. Only 22.5% of those who received ginger correctly identified their capsule. The likelihood of guessing ginger between the groups was statistically similar (p < 0.01). 65% correctly guessed which bottle they had received (p = 0.0073). Participants receiving the bottle filled with ginger capsules successfully identified their bottle 75% of the time (p = 0.0016) compared to the 55% of the placebo group (p = 0.5).
Conclusions: Volunteers cannot determine which type of individual capsule they receive but can distinguish a bottle filled with ginger capsules.

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Introduction
Blinding in medical research is considered an important method to ensure the quality of clinical trials. Blinding in medical research reduces ascertainment bias, information bias, and observer bias.1–4 Blinding improves participant compliance, retention in clinical trials, and reduces biased supplemental or co-intervention care.1–4 Lack of blinding amongst the study personnel administering interventions may lead to performance bias as well as biased choices regarding analytical strategies and methods used.5

Three meta-analyses of clinical trials found that not blinding leads to a moderate overestimate of the effect of the new treatment.3,4,6,8

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blinding is of particular concern when the outcomes are subjective or "soft," such as with severity of nausea where ascertainment bias can play a large role, but is less of a concern for "hard" outcomes, such as mortality.1,2,4,8

Ginger’s unique aroma and taste, as well as its wide familiarity to potential study participants, challenges successful blinding. Currently, there are 19 randomized, "double-blind," placebo-controlled clinical trials examining the effect of ginger in humans. In only four of these studies did researchers attempt to assess the effectiveness of blinding or create a placebo.5–9 In none of these studies was enough information provided to determine the success of the blinding. Three of the four randomized clinical trials used coated or infused placebo capsules with the essential oils of mint or ginger, which potentially gave a treatment effect to the placebo capsules.9–11

A randomized, double-blind, parallel-arm clinical trial was performed to determine if our placebo capsules were indistinguishable from ginger capsules as evaluated by study participants, outcome assessors, and study investigators.

Methods and materials

Eligible participants included men and women over the age of 17 with no chronic illnesses and taking no medications. Individuals with a history of peptic ulcer disease, gastrointestinal (GI) bleeding from gastric or duodenal ulcers, gastrin secreting tumors, or any cancer other than basal cell or squamous cell tumors of the skin were ineligible. All study procedures were administered at the UM General Clinical Research Center (GCRC). All study participants gave written, informed consent before participating in the trial approved by the University of Michigan Institutional Review Board.

Eighty eligible participants were randomly allocated to receive either one 250 mg capsule of powdered ginger or one 250 mg capsule of placebo (lactose) both given in opaque red capsules. The block randomization scheme for the study was generated by the study biostatistician and given to the UM Investigational Drug Services (IDS). Researchers assigned the next available number to each study participant upon determination of eligibility. All participants, researchers, outcome assessors, and other study personnel, with the exception of IDS, were blinded as to which treatment the participant received. The randomization code was revealed to the researchers only when all recruitment, data collection, data entry and data management was complete.

Eighty study participants were equally allocated in a 1:1 ratio to a bottle filled with either ginger or placebo capsules. Two identical bottles, labeled number 1 and number 2, were used throughout the study. For each participant, the researchers chose one of the two bottles in an alternating manner (i.e., the first participant received bottle 1, the second participant received bottle 2, etc.) and recorded the chosen bottle number in the study participant’s file. The bottle participants received was not related to the capsule they received.

The ginger product used in this study was manufactured by Pure Encapsulations® (Sudbury, MA). Pure Encapsulation’s® ginger (Zingiber officinale) powder is a supercritical CO2 extract (22:1) standardized to contain 5% (6)-gingerol. The UM IDS placed 250 mg of the Pure Encapsulation ginger powder in size 0 red animal gelatine capsules made by Gallipot®. The placebo capsules contained lactose powder and were also prepared by the UM IDS using the same opaque, animal gelatine capsules.

Participants were given a ginger or placebo capsule and were asked to examine, smell and then swallow the capsule with water. Within fifteen minutes of ingesting the capsule, participants were asked to identify which capsule, ginger or placebo, they believed they had received. Participants were also asked to explain why they believed they received ginger or placebo by answering the following questions: "Was it the taste?"; "Was it the smell?"; "Was it the way the capsule looked?"; "Was it the way the capsule worked?".

Participants were then given a bottle filled with either ginger or placebo capsules. They were asked to examine the bottle visually and by smell. Within 15 min, participants were asked to identify whether they believed they had received a bottle filled with ginger or placebo capsules and why ("Was it the smell?"; "Was it the way the capsules looked?"). Follow-up contact via telephone or email at 24, 48, and 72 h allowed researchers to assess adverse events (AE).

Statistical analysis

Statistical analyses were performed using SAS Version 8.2. Exact tests were used to assess the statistical significance of differences between response rates. Likelihood ratio confidence intervals are reported about point estimates of proportions. The p-values for the primary protocol hypotheses of equivalence were calculated by comparing the test
statistic:
\[
\frac{(\hat{p}_G - \hat{p}_P - 0.3)^2}{\hat{v}_0}
\]
to a \(\chi^2\) distribution with 1 degree of freedom, where \(\hat{v}_0\) is the maximum likelihood estimate of the variance of the numerator under the null hypothesis. Assuming a 5% significance level, a sample size of 80 participants (40 per ginger arm, 40 per placebo arm) was selected to ensure a 75% power to reject the hypothesis that participants could detect the ginger, if the number of ginger responses in each arm were identical.

Results
Eighty participants were enrolled in the study between the dates of July 2003 and February 2004. No participants were lost to follow-up. Forty subjects received a ginger capsule and 40 received a placebo capsules; 40 subjects received a bottle filled with ginger capsules and 40 received a bottle filled with placebo capsules. All 80 randomized participants were included in the analysis (see Fig. 1).

Table 1 describes baseline study demographics and clinical characteristics by treatment group. Differences between groups by treatment are small, with the exception that all of the smokers in the study received the bottle filled with ginger capsules.

Results for the capsule
Sixty-three (79%) of the 80 study participants guessed that they had received a placebo capsule, 14 (17%) thought they had received a ginger capsule and 3 (4%) said they absolutely could not guess one way or the other. Of the 80 participants, 42 (52.5%; 41–63.8% CI) correctly guessed the identity of the capsule they received.

Over 82% (67.2–92.6% CI) of those who received a placebo correctly identified their capsule as being a placebo capsule. Similarly, 77.5% (62–89% CI) of those who received a ginger capsule guessed placebo. Only 22.5% (10.8–36.5% CI) of those participants who received ginger capsules were able to correctly identify those capsules, while 17.5% (7–33% CI) of those who received a placebo capsule also believed they had received a ginger capsule. Therefore, when comparing the two groups, the likelihood of guessing ginger, was statistically similar (\(\chi^2 = 7.47, p < 0.01\)), 22.5 versus 17.5%.

Of the 63 participants who believed they received a placebo capsule, 40 (63%; 41–63.8% CI) correctly guessed the identity of the capsule they received.

Over 82% (67.2–92.6% CI) of those who received a placebo correctly identified the capsule as being a placebo capsule. Similarly, 77.5% (62–89% CI) of those who received a ginger capsule guessed placebo. Only 22.5% (10.8–36.5% CI) of those participants who received ginger capsules were able to correctly identify those capsules, while 17.5% (7–33% CI) of those who received a placebo capsule also believed they had received a ginger capsule. Therefore, when comparing the two groups, the likelihood of guessing ginger, was statistically similar (\(\chi^2 = 7.47, p < 0.01\)), 22.5 versus 17.5%.

Results for the bottle
Fifty-two participants (65%) correctly guessed which bottle they had received (\(p = 0.0073; 55–75\%\) CI).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ginger capsule (n = 40)</th>
<th>Placebo capsule (n = 40)</th>
<th>Ginger bottle (n = 40)</th>
<th>Placebo bottle (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age ± S.D. (year)</td>
<td>34.4 ± 11.9</td>
<td>37.2 ± 15.5</td>
<td>37.5 ± 13.1</td>
<td>34.1 ± 14.4</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>4 (10)</td>
<td>3 (8)</td>
<td>7 (18)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>32 (80)</td>
<td>30 (75)</td>
<td>32 (80)</td>
<td>30 (75)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>24 (60)</td>
<td>26 (65)</td>
<td>25 (63)</td>
<td>25 (63)</td>
</tr>
<tr>
<td>African–American</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>3 (8)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3 (8)</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (20)</td>
<td>6 (15)</td>
<td>6 (15)</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Native American</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>2 (5)</td>
<td>4 (10)</td>
<td>4 (10)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>
When separated into participants who received the ginger and placebo bottles, those participants who received the placebo bottle were not able to correctly identify their bottle. Only 55% (n = 22) of those who received the placebo guessed their bottle assignment correctly (p = 0.5271; 40–70% CI). In contrast, those who received the bottle filled with ginger capsules were able to identify which bottle they were assigned 75% (n = 30) of the time (p = 0.0016; 62–88% CI).

Only 10 participants claimed that the way the bottle looked influenced their choice, while 66 participants stated that the aroma or smell of the bottle influenced their decision, thus the bottle’s aroma was significantly associated with the participant’s choice (p < 0.04). In contrast, the appearance of the bottle was not significantly associated with which bottle a study participant chose (p = 0.68).

We suspected that the strong ginger aroma was going to be the hardest aspect of the herb to blind. Thus, we decided to examine if the aroma dissipated or intensified over the course of the study. After adjusting for how the bottle looked and smelled we determined that the date of participant enrollment was highly significant for a participant...
to conclude that he had received a ginger bottle (p = 0.01). Gender, age, race/ethnicity, and smoking status were not significantly associated with the ability to correctly identify the content of the bottles.

Adverse events

Four adverse events were reported: “light-headedness”, “dizziness”, “shakiness”, and mild GI upset. Adverse events were split evenly between the placebo and ginger group.

Discussion/conclusions

We found that healthy adult volunteers cannot determine whether they received a ginger or placebo capsule. Participants’ age, gender, race/ethnicity, and smoking status were not predictive of being able to correctly identify which capsule they were assigned. Moreover, participants’ perception about the way the capsule looked, smelled, worked or tasted was not predictive of choosing the correct capsule. In contrast, study participants were able to correctly identify which bottle (filled with ginger or placebo capsules) had been assigned. The bottle’s aroma but not the appearance was predictive of the study participants’ choice. The ginger aroma appeared to diminish over the course of the study and thus, the earlier a participant was enrolled in the trial the more likely that participant was to choose the ginger bottle.

The rate of adverse events was low in this trial with only four non-serious events reported, making it difficult to compare any differences between ginger and placebo. The AEs were evenly distributed across the two groups with gastrointestinal side-effects being the most common. However, in contrast to other trials that found more instances of GI AEs in the ginger group ours GI AEs were evenly distributed across the two groups. The difference in our study is most likely due to the extremely short duration (one dose of 250 mg) of ginger ingestion as compared to taking ginger capsules over several weeks.

Our results have wider implications for herbal research. Most herbal RCTs do not assess the effectiveness of the blind in their studies. If any assessment is conducted it is carried out during or after the conclusion of the study and rarely is included as a priori hypothesis, calling into question the robustness of the results. The possibility of ineffective blinding may not be an issue in many herbal studies where the phytomedicine in question has a neutral taste, appearance, and aroma profile, although this neutrality maybe difficult to assess. However, when using any distinctive herbal product blinding can become a challenge. Lack of blinding tends to lead to an overestimation of effect size of about 19%. Thus, in studies were only a modest effect is found in favor of the herb and the blind is in question the benefit can all be attributed to lack of blinding and not to any specific effect of the herbal product.

Healthy adult volunteers cannot determine which type of individual capsule they receive but can distinguish a bottle filled with ginger capsules. It is therefore our recommendation that researchers using powdered standardized ginger root place ginger capsules in blister packs in future RCTs. By using blister packs participants only receive individual capsules. This minimizes the distinctive aroma capsules contained when grouped in a bottle. We also recommend that clinical trials testing herbal products systematically evaluate the effectiveness of their blinding procedures ideally before starting the clinical trial or if this is impossible embedded as an a priori hypothesis within the trial.

References

