Efficacious blinding of ginger for randomized controlled trials

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Abstract

Ginger (Zingiber Officinale Roscoe) has a distinct aroma that is difficult to blind in randomized controlled trails. We tested whether packaging encapsulated ginger in blister packs leads to effective blinding. We recruited 32 healthy volunteers age 18 and up through advertisement in the University of North Carolina and the community. They were asked to examine either 1 clear gelatin capsule of 250 mg of ginger powder or 1 similar looking clear gelatin capsule of placebo (brown sugar) in a blister pack before and after opening the pack; after which they were asked to swallow the capsule. Sixty percent correctly identified capsules filled with placebo versus 23.4% correctly identified capsules filled with ginger. χ^2 tests revealed no differences between the two treatment arms in content (the majority thought they were taking a placebo), look, smell and taste of the capsules. Prior familiarity with ginger did not increase prediction rates. Our results demonstrate that ginger can be effectively blinded by packing individual capsules in blister packs.

Introduction

The gold standard in clinical research is the randomized controlled trial. Blinding the study participants, health care providers and study personnel to the assigned intervention arm is an important aspect to reduce bias. Ineffective blinding can lead to an overestimate of treatment effects.[1] However, blinding is successful in only about half of all randomized controlled trials.[2] Blinding can become difficult if participants are given clues that can identify which treatment arm they are in and in some cases, the nature of the intervention makes such clues hard to eliminate.

Ginger (*Zingiber Officinale* Roscoe) has a unique strong aroma and taste that is very familiar to most people because of its common use in food preparation and food products such as ginger snaps and ginger ale. Upon opening a bottle of ginger capsules, the aroma is very distinct. This poses a problem for blinding study participants in a placebo controlled study of ginger as a therapeutic agent. In a recent study it was found that participants receiving bottles, with capsules containing either ginger or placebo, successfully identified ginger 75% of the time compared to successfully identified placebo 45% of the time.[3] Aroma influenced the decision most. When subjects were given the capsules without the bottle, however, guessing rates were no longer different between the groups. Many randomized controlled trials of ginger have given only a single dose of ginger to participants, for example to assess the effects on post operative nausea.[4,5] Thus, ginger's aroma may not have played a significant role in unblinding the subjects as participants could be given individual capsules without containers. However in some cases ginger will need to be administered for several days or weeks such as in studies of pregnancy related nausea and vomiting.[6,7] Handing out a single dose to patients numerous times over a period of days or weeks can seriously hamper practicality and retention in a study. In such studies capsules need to be taken home by the participants. Keeping the capsules in a bottle creates unblinding because of the distinct aroma that collects in the bottle.[3] Therefore the current study is designed to determine if offering individual ginger capsules in blister packs will provide adequate blinding of the subjects.

Materials and Methods

We recruited healthy volunteers age 18 and up through advertisement in the University of North Carolina and the community. Subjects did not have a history of Inflammatory bowel disease, gall stones, bowel obstruction, ginger intolerance or ginger allergy, conditions that are counter-indications for ginger use. Subjects were asked to examine either 1 clear gelatin capsule of 250 mg of ginger powder or 1 similar looking clear gelatin capsule of placebo (brown sugar) in a blister pack before and after opening the pack; after which they were asked to swallow the capsule. The capsules are expected to dissolve in 5 min after which the volatile taste of ginger may be detected by the subjects. Therefore, fifteen min following ingestion of the capsule, subjects completed a short questionnaire in which they were asked to identify if they took ginger (yes/no), and whether the capsules smelled, looked and tasted like ginger (yes/no); 24 hours later subjects were contacted by phone to ask about side effects.

Ginger and placebo were obtained from the Professional Compounding Centers of America-PCCA and derived from the Zingiber Officinale root which was the pure ginger root powder. Ginger powder was shipped in air-tight containers to a local pharmacy, encapsulated, and packed in blister packs upon arrival. Blister packs were marked either *A* or *B*, both subjects and study personnel were blinded to the arm of the study until after analyses of the data. To assure quality, the obtained ginger root powder was sent to IBC labs and was found to a contain 2.29 mg/g of gingerols (6-gingerol, 8-gingerol and 10-gingerol combined) as well as 6-shagoals (two key active ingredients of ginger). Randomization of each subject was determined by coin toss. The study was approved by the University of North Carolina Biomedical Institutional Review Board. All subjects provided written consent before the start of the study.

Results

A total of 32 subjects participated in the study, of whom 16 received placebo and 16 received ginger. There were no drop-outs. None of the participants in the study regularly consumed ginger capsules/pills for medicinal purposes or as a dietary supplement. A total of 5 participants reported to regularly consume ginger food products such as ginger tea, candied ginger or ginger in food preparation. No adverse events were reported.

As can be seen in Table 1, subjects were better at correctly predicting placebo than ginger. In fact, the majority of subjects who swallowed ginger thought they were given placebo. Participants based this mainly on looks: 44% thought the capsule looked like it was filled with ginger, 10% of participants thought the capsule smelled like ginger, and 3% thought it tasted like ginger. Chi-square tests revealed no differences between the two treatment arms in

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Table 1. Capsule content identification.

	Capsule content correctly identified yes	no
Ginger	N=4 (25%)	N=12 (75%)
Placebo	N=10 (62.5%)	N=6 (37.5%)

Table 2. Content, look, taste and smell of capsules.

	Ginger N=16 YES	Placebo N=16 YES	Chi²/P
Capsule look like ginger?	N=7 (43.8%)	N=7 (43.8%)	χ^2=.13; P=.7
Capsule taste like ginger?	N=1 (6.3%)	N=0 (0%)	χ^2=1.0; P=.3
Capsule smell like ginger?	N=1 (6.3%)	N=2 (12.5%)	χ^2=.37; P=.5

NS, not significant

reported content, look, smell and taste of the ginger and placebo capsule (Table 2). The 1 person who thought the capsule tasted like ginger was in the ginger group, of the 3 people who thought the capsule smelled like ginger 2 were in the placebo group, and of the 14 participants who thought the capsule looked like ginger 7 were in the placebo group. Of the 5 people who regularly consumed ginger (n=4 ginger, n=1 placebo) 40% correctly identified the content of the capsules. No side effects were reported within a 24 hours period.

Discussion

Our results demonstrate that ginger can be effectively blinded by packing individual capsules in blister packs. When packaged this way, healthy volunteers cannot determine if they receive a capsule filled with ginger or placebo. Distinguishing ginger from placebo was primarily based on looks of the capsule, but visual inspection was not associated with improved identification. Those who regularly consume ginger, and thus are familiar with the aroma and taste of ginger, were also not better than chance at identifying the content of their capsules.

This study has several limitations. First, the number of subjects was small. Some results may have become significant if larger samples were included, especially since Chi² tests become less accurate with small numbers. Secondly, none of the subjects regularly consumed ginger capsules/pills, thus the results cannot be generalized to those who are familiar with ginger capsules or pills. Third, the subjects were randomized by an actual coin toss which is not an optimal method of randomization.[8]

These results have implications for trials with ginger and perhaps other herbal products as well. When using a herbal product with a distinctive look, smell, or taste, investigators need to assess the effectiveness of their blinding methods. In the case of ginger, packaging individual capsules in blister packs is an effective way to blind subjects. It is also recommended that future publications in herbal research report the blinding methods. A reported small effect of the herbal product over placebo may actually be due to ineffective blinding.[1] If investigators report careful blinding methods or a test of their blinding methods in advance this will increase the robustness of their findings.

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