In the dark: an experimental study in distinguishing an authentic herbal substance from a sham herbal substance

John Hung Yang Lee

A thesis submitted as partial requirement for the degree of
Master of Science by research

Faculty of Science
University of Technology, Sydney
July 2012

CERTIFICATE OF AUTHORSHIP/ORIGINALITY

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

Production Note:
Signature removed prior to publication.

Signature of Candidate-John Lee

Acknowledgement

First and foremost I would like to thanks my supervisor Associate Professor Christopher Zaslawski for his time and effort he has put in in helping me design, collect the data and assist with writing certain sections of this thesis. I would also like to thank my wife and children who assisted me on several occasions with some of the technical aspects of computing. Also for statistical assistance Dr Narelle Smith was invaluable.

Finally thank you to the many participants who assisted me by volunteering and participating in the three studies. Last but not least I would like to thank Dr Chun Lin Zhou for her assistance in helping me recruit participants at the UTS outpatient clinic.

UNIVERSITY OF TECHNOLOGY
LIBRARY
SYDNEY

Contents Page

Chapter I 1

1.1 Background to the studies 1

1.1.1 The randomized controlled trial (RCT) and its features 1

1.1.2 Blinding assessment 2

1.1.3 Chinese medicine herbal medicine RCT 4

1.2 Aim of the research 6

1.3 Format of thesis 6

Chapter II Literature Review 9

2.1 Search strategies 9

2.2 Blinding in randomised controlled trials 9

2.3 Blinding in herbal medicine RCTs 11

Chapter III Methods 16

3.1 Overview of the three studies 16

3.2 Recruitment 17

3.3 Setting 17

3.4 Materials 18

3.4.1 Herbal substance 18

3.4.2 Sham materials 19

3.4.2.1 Study one 19

3.4.2.2 Study two 20

3.4.2.3 Study three 22

3.5 Data collection 24

3.6 Procedure for evaluating the substances 25

3.7 Statistical Analysis 26

3.8 Statistical power 27

Chapter IV Results 28

4.1 Participants 28

4.2 Participant previous herbal medicine experience 29

4.3 Choice results for study one (Pilot) 29

4.4 Choice results for study two 31

4.2.2 Reasons for choice 34

4.2.2.1 Visual appearance 34

4.2.2.2 Odour 36

4.2.2.2 Taste 37

4.3 Consistency of choice across the three tests 40

4.4 Choice results for study three 41

4.4.1 Results for visual appearance 42

4.4.2 Results for Odour 43

4.4.3 Results for Taste 45

Chapter V Discussion 47

Chapter VI Summary and future directions 51

References 52

Appendices 59

List of Tables Page

Table 2.1: Levels of difficulty in blinding and associated factors for each level 14

Table 2.2: Levels of perceived risk of unblinding 15

Table 4.1: Gender and herbal experience status of participants for all three studies 28

Table 4.2: Types of herbal delivery modes previously used. 29

Table 4.3: Participant choice response for taste 35

Table 4.4: Reason given by the participants concerning their choice and the odour of the substance 36

Table 4.5: Reason given by the participants concerning their choice and the taste of the substance 37

Table 4.6: Participant responses for the participants concerning the visual appearance and their previous experience with Chinese herbal medicine 39

Table 4.7: Participant responses for the participants concerning odour and their previous experience with Chinese herbal medicine 39

Table 4.8: Participant responses for the participants concerning taste and their previous experience with Chinese herbal medicine 39

Table 4.9: Frequency of incorrect and correct responses from participants receiving the placebo and herbal substance for the visual appearance evaluation 42

Table 4.10: Reason given by the participants concerning their choice and the visual appearance of the substance and their choice response 43

Table 4.11: Frequency of incorrect and correct responses from participants receiving the placebo and herbal substance for the odour evaluation 44

Table 4.12: Reason given by the participants concerning their choice and the odour of the substance and their choice response 44

Table 4.13: Frequency of incorrect and correct responses from participants receiving the placebo and herbal substance for the taste evaluation 45

Table 4.14: Reason given by the participants concerning their choice and the taste of the substance and their choice response 46

List of Figures Page

Figure 1.1: Flow sequence of literature search 10

Figure 3.1: Visual appearance of substances used in the study 1 21

Figure 3.2: Visual appearance of substances used in study 2 21

Figure 3.3: Visual appearance of materials used in study 3 (powder form) 23

Figure 3.4: Visual appearance of materials used in study 3 (encapsulated form) 24

Figures 4.1: Responses to the questions concerning odour 30

Figures 4.2: Responses to the questions concerning visual appearance. 30

Figures 4.3: Responses to the questions concerning taste 31

Figure 4.4: Participant choice response for visual inspection 32

Figure 4.5: Participant choice response for odour 33

Figure 4.6: Participant choice response for taste 34

Figure 4.7: Consistency of choice for those participants who initially selected correctly for the visual assessment 40

Figure 4.8: Consistency of choice for those participants who initially selected correctly for the odour assessment 41

Figure 4.9: Consistency of choice for those participants who initially selected correctly for the taste assessment 41

Abstract

Background: The randomised controlled trial (RCT) is currently the "gold standard" for assessing the efficacy of a therapeutic intervention. One important aspect of an RCT is the blinding of various parties involved in the trial. Blinding is similar to randomization, in that its goal is to distribute participant expectancies evenly across the two or more groups. The assessment of blinding has been fraught with complications and associated with methodological difficulties. A review of the literature found very poor and limited reporting of the success of blinding in not only pharmaceutical studies, but also many Chinese medicine RCTs. In addition the special qualities of Chinese herbal medicine such as taste, odour, color and texture make it very difficult to blind trial participants. Because of these reasons it was decided to undertake a series of experiments to determine whether a credible sham substance could be developed for use in a clinical trial for Chinese herbal medicine.

Methods: Three separate studies were undertaken in sequential order between 2009 and 2011, with the second and third study attempting to improve on each previous study. In all three studies the primary aim was to evaluate whether a greater proportion of participants could correctly identify an authentic herbal substance when comparing to a sham substance using visual, odour and taste assessments. The first study was a pilot involving eleven participants. The aim of this study was to pilot the data collection process and determine whether the initial materials were suitable for the study.

The second study involved 81 participants. This study improved on the initial pilot

study in several ways. There was an increase in participants and an opaque eye pad was used during the tasting phase to effectively blind the participant. In addition a closer colour matching of the three sham substances to the herbal substance was achieved.

The third and final study involved only two substances, a refined sham substance and the herbal substance. Participants were randomly given only one of the two substances and asked whether they believed the substance to be a' herbal' or 'placebo' substance or 'didn't know' using a questionnaire. In this study there was no comparison with more than one substance as occurred in study one and two. This study improved on the first and second study by improving the taste and colour of the sham substance in order to be comparable to the herbal substance.

Results: For study one a one proportion test found that for both odour ($p=0.484$) and visual appearance ($p=0.077$) the number of participants correctly selecting capsule B as the herbal substance was not significantly different from what may have been selected by chance. This was not the case for taste where significantly more participants correctly selected capsule B as the herbal substance ($p=0.004$) compared to the other three substances.

For study two, in all three assessments (visual, odour and taste) a statistically greater percentage of participants selected the herbal substance than the comparator sham substances ($p<0.0001$ in all three cases).

For the final study a similar proportion of subjects in both groups believed they were observing and smelling an authentic herbal substance ($p=0.435$ for observing

and p=0.443 for odour) suggesting effective blinding. However, similar to the two earlier studies a statistically larger proportion of subjects receiving the authentic herbal substances believing they were tasting a herbal substance (p=0.002) compared to the sham herbal substance group.

Conclusion: This is the first time that a series of studies have been undertaken that have attempted to identify important cues and features that may threaten participant blinding in a herbal medicine trial. It was shown that with refinement it was possible to blind for visual and odour assessments but the sense of taste remained in all three studies a difficult human sense to blind. This obviously presents a problem for any herbal clinical trial where there is the opportunity for participants to break open a capsule and taste the contents. The studies have further demonstrated the need for pre-trial blinding for Chinese herbal studies and that a concerted effort should be made to develop a similar looking, smelling and tasting sham substance compared to the verum intervention arm. If possible inert materials, flavouring and colouring agents should be used. If this is not possible potentially active materials that have been shown to be irrelevant for the particular condition can be an option.