Blinding and Its Quality in Clinical Trials Conducted on Patients with Breast Cancer: A Systematic Review

Abstract

Background: Blinding is one of the critical criteria of clinical trials that prevents probable bias. Judgment regarding results of an intervention significantly depends on the quality of such studies, one of which is blinding. This study aimed to investigate blinding and its quality in clinical trials in patients with breast cancer. Materials and Methods: A systematic review was conducted on the online databases of PubMed, ScienceDirect and ProQuest using keywords, MeSH terms and grey literature. Articles were screened by predefined inclusion and exclusion criteria. They were evaluated based on the checklists introduced by Cochrane database. Results: From 22519 articles obtained at the initial stage, 20 articles remained after screening for the inclusion and exclusion criteria. Fifteen articles had used single, five: double and none had used triple or quadruple blinding. Seventeen studies had described the details of blinding. Of the 15 single blind articles, the blinded subjects were patients in five, patients and research assistants in three, research assistants in five studies, and two had not given any details. Conclusions: The majority of researchers had used the single blind method, though using double, triple or quadruple blinding increases the trustworthiness of results and increases the quality of clinical trials. The details of blinding should be explained to other researchers and for a better understanding of the method if it is to be repeated. Thereafter, nurses can apply new interventions and earn their patients’ trust and help those with breast cancer by relieving them of their disease symptoms and its treatment complications.

Keywords: Breast neoplasms, clinical trial, double-blind method

Introduction

Based on recent statistics released by the World Health Organization (WHO), cancer is the second cause of death in the world after cardiovascular disease.[1] In Iran, it is the third cause of death.[2] Different interventional studies have been conducted to evaluate the effects of different interventions aimed at relieving the symptoms of the disease and the side-effects of different therapies such as chemotherapy and radiotherapy to reduce morbidity and mortality rates in cancer patients.[3,4] Any judgment regarding the results of a research and the effect of the intervention involved significantly depends on the quality of such studies.[5,6]

Compared to other types of studies in health research, a clinical trial is the most appropriate and valuable method for evaluating the effect of a treatment.[7] High quality clinical trials should be conducted and reported to achieve this goal, and in doing so allow the audience to judge the internal consistency of the study.[8] One of the aspects of a clinical trial that indicates the extent to which it is free from probable bias is using the blinding technique.[9] After controlling the intervention and random allocation, blinding is the most significant criterion in clinical trials, which is included in many quality study tools like the Jadad scale that allocates two fifths of its score to blinding. The Cochrane checklist too is a standard, reliable, and well-known tool for assessing the quality of systematic review articles.[9,10]

Blinding is one of the methods of reducing the probability of research bias, which can affect the validity of research results.[7] It is used in different parts of research, such as, concealing data from the participants, data collector and provider, intervention provider, and even data analyzer. Thus, the biases expected to occur in different parts of an interventional study can be

How to cite this article: Matourypour P, Ghorbani A, Mahmoudi M, Binaei N, Manesh HJ, Nayeri ND, et al. Blinding and its quality in clinical trials conducted on patients with breast cancer: A systematic review. Iran J Nurs Midwifery Res 2022;27:1-7.

Submitted: 03-May-2020. Revised: 07-Jul-2020. Accepted: 16-May-2021. Published: 25-Jan-2022.
In order to investigate blinding, the standards of blinding and its types should be defined first. Blinding refers to concealing information about the type of treatment provided to a specific group of participants. Simply referring to the types of blinding used is not enough as it can be confusing to the readers. Thus, the authors need to clearly specify who has been blinded in the research process. The accurate interpretation of a clinical trial is possible when there is accurate information on the methods of design and analysis of outcomes. Previous studies indicate that blinding is one of the issues less addressed in clinical trial designs.

Subsequently, as mentioned above, a variety of biases ensue and the study results become questionable. The interpretation of clinical trials’ results depends on the quality of methods and blinding as a means to prevent bias. Given that breast cancer is the most prevalent cancer and second cause of mortality in women, a search was conducted in the Cochrane database to check whether the subject was not repetitive. We found several studies that had examined the quality of clinical trials but not specifically in patients with breast cancer. Hence, in this study we aimed to investigate blinding and its quality in clinical trials in patients with breast cancer.

Materials and Methods

This research is a systematic review conducted between 2012 and 2019. The search strategy, article selection, and evaluation of articles’ quality are explained in details below: Search was conducted in the valid medical science databases of PubMed with the MeSH term ‘single blind method’ and ‘double blind study’ and ‘breast neoplasm’ and other databases such as ScienceDirect and ProQuest with the keywords of breast cancer/neoplasm and blind study and single/double blind study on clinical trials in humans as well as the Iranian database ‘SID’ with the keywords ‘breast cancer’ and ‘Blinding’ [Table 1]. Then, the articles were evaluated based on the checklists introduced by the Cochrane database.

The inclusion criteria included, the presence of the keywords ‘breast cancer’ and ‘blinding’ in the title and abstract, the interventional nature of the research, English or Persian language articles, the intervention being conducted in the nursing field. The exclusion criteria included, not having used blinding methods, the acquisition of less than 12 points from the checklist, and the lack of availability of the articles’ full texts.

During the first stage, all the articles were reviewed by three researchers in terms of relevancy of the titles and abstracts (interventional method/application of blinding/patients with breast cancer) and irrelevant articles were removed. Then, the articles’ full texts were acquired and after omitting the names of the authors and the journals the reviewers began reviewing the articles. Thereafter, the section on the type and manner of blinding by the corresponding checklist was completed for each English and Persian article. Obtaining at least 12 scores from 20 was mandatory for inclusion. Finally, an expert on research methodology evaluated the assessment procedures on the final articles and made suggestions to be applied. After the first search we screened the final articles’ references as our second search, but no new article was found.

The checklist was designed based on the items introduced by Cochrane for systematic reviews. Its validity and reliability were measured and confirmed by ten experts in the research methodology, epidemiology, and nursing groups. The calculated Content Validity Index (CVI) was 0.87 and the reliability of all the items on the checklist was estimated at 0.92 Cronbach’s Alpha, both of which were acceptable. The checklist is demonstrated in Table 2.

Ethical considerations

This study was approved by the ethics committee of the Nursing and Midwifery Research Centre of Tehran University of Medical Sciences, Tehran, Iran (IR.TUMS.FNM.REC.1399). In this systematic review and meta-analysis, the collected data were only used for scientific purposes, and intellectual property was observed in the reporting and publication of the results.

Results

Of the 22519 articles retrieved at the initial stage of the search, first the duplicate articles were removed (6832 articles). Twenty articles were finally included in the review based on the inclusion and exclusion criteria and checklist scores [Figure 1]. The final results are shown in Table 2 in terms of the intervention, outcome, type of blinding, sample and randomization.

Target population

Clinical trials conducted on various types of patients with breast cancer were included, the risk of breast cancer incidence among this population, breast cancer survivors, those suffering from breast cancer, patients undergoing chemotherapy, patients undergoing radiotherapy, and patients awaiting surgery.

Studied variables

In the final stage, the effects of different interventions were evaluated to decrease or eliminate certain variables including fatigue, musculoskeletal symptoms, conditional and acute nausea and vomiting due to chemotherapy (intensity, duration), interventions on lifestyle, physical and mental quality of life, cognitive function and physical activity, physical function, the incidence of breast cancer, mental stress, cognitive function (memory and information processing speed),
From a total of 20 articles, 15 had used single, 5 had used double and neither study had used triple or quadruple blinding. Of the 15 single blind articles, the blinded subjects were patients in five studies, they were patients and research assistants in three studies and were research assistants in five studies. Two studies failed to explain the blinded subjects and their details. In five articles, double blinding was used. In these studies, except for one study, the details of blinding had not been mentioned. In the remaining four cases, blinding had been performed on the samples and the researcher and the samples and subjects, who analyzed data on the samples and the physician/nurse/other member of the treatment team were unaware of the intervention type.

**Discussion**

Of the 20 final articles retrieved from nursing – related studies, 15 had used the single blind method while five studies had used double blinding. No study had used triple or quadruple blinding. This is not a desirable finding, as unintentional systematic bias may occur and it can threaten the reliability of the research results, which can be minimized by blinding. Polit and Beck introduced blinding as a technique that can reduce bias through single, double, triple and quadruple blind methods. The greater the number of blinded parties in the research, the lower the probability of bias that is out of the researcher’s control. Thus, indicating the importance of employing robust methods in clinical trials to raise the validity of results.

Of the 15 single-blind articles, the blinded subjects were patients in five studies; they were patients and research assistants in three studies and were research assistants in five studies. Two studies failed to give any explanations regarding the blinded subjects and their details. In five articles, the double blind method was used. Seventeen out of 20 studies had described the details of their blinding, although some studies had not done so. The quality with which clinical trials are conducted and describing blinding along with its details are of great importance, as nurses can use reliable research results that can improve patient care. Therefore, blinding along with other positive advantages of the method like multi-group random allocation, and allocation concealment can increase the quality of a clinical trial and yield more accurate and reliable results. Paying attention to blinding improves the quality of such

| Search term | PubMed | ScienceDirect | ProQuest | SID* |
|-------------|--------|---------------|----------|------|
| (Single-blind method or double-blind study) and breast neoplasm MeSH | 642 | 4941 | 16585 | 30 |
| (Breast cancer OR neoplasm) and blind study and (single and double study) Keywords | 321 | 4941 | 16585 | 30 |
| Total | 963 | 4941 | 16585 | 30 |

*SID: Scientific Information Database
Matourypour, et al.: Blinding and its quality in clinical trials contributors

### Table 2: Clinical trials conducted on breast cancer in the field of nursing that have used the blind method

| Authors          | Year | Type of Blind Method | Intervention                                                                                   | Outcome(s) Assessed                                                                 |
|------------------|------|----------------------|------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Gok Z et al.     | 2019 | Single               | The participants were randomly assigned to either a 12-week PMR* or MM** intervention or to the Control Group (CG). The intervention group continued PMR or MM for 20 minutes every day, for a total of 12 weeks. The CG received only a single attention-matched educational session (15 min) on breast cancer before the start of the paclitaxel regimen. Data were collected at baseline, week 12, and week 14. | Fatigue, Functional Living Index-Cancer (FLIC)                                        |
| Franco L et al.  | 2016 | Single               | In the preoperative holding area, subjects received 2 drops of oil, either 2% LFO (lavender fleur oil) or UO (unscented oil), inside a plastic oxygen face mask for 10 min. | Anxiety and vital signs before and after aromatherapy                                 |
| Ho RTH et al.    | 2016 | Single               | The intervention included six 1.5-h DMT*** sessions provided twice a week over the course of radiotherapy. | Perceived stress, anxiety, depression, fatigue, pain, sleep disturbance, and quality of life |
| Larkey L et al.  | 2016 | Double               | The intervention group (QG/TCE****, SQG******, ES*******) met weekly for an hour during the 12 weeks of the intervention. | The primary outcome (fatigue) and secondary outcomes (anxiety, depression, sleep quality, cognitive function, and physical activity) were assessed at baseline, immediately and 6 months after the intervention. |
| Larkey LK et al. | 2016 | Double               | Twelve weekly sessions of QG/TCE were compared to sham Qigong (SQG), a gentle movement control intervention similar to QG/TCE but without focusing on breathing and the meditative state. | Mental and physical QOL, cognitive function (Functional Assessment of Cancer Therapy-Cognitive Function, overall levels of physical activity and body mass index (BMI) were assessed at 3 time points. |
| Matourypour et al.| 2016 | Single               | Therapeutic touch was applied to each patient once for 20 min on the aura (human energy field) focusing on the solar chakra. | Chemotherapy-induced vomiting                                                      |
| Vanaki et al.    | 2016 | Single               | Therapeutic touch was carried out for both (test and placebo) groups prior to their first chemotherapy appointment (once for about 15-20 minutes). | Nausea duration and frequency                                                      |
| Kerrison et al.  | 2015 | Single               | Delivery of a text-message reminder 48 h before appointment, which included the time, date and venue of the appointment, as well as information about rescheduling if unable to attend. | Breast screening end codes at the initial appointment and again 60 days thereafter. |
| Brown JC et al.  | 2015 | Single               | Twice-weekly slowly progressive weight lifting or standard care. | Physical function                                                                  |
| Stagl et al.     | 2015 | Single               | A 10-week, group-based Cognitive Behavioral Stress Management (CBSM) intervention (n=120) for the test group and/or a 1-day psychoeducational seminar for the control group (n=120). | Survival and recurrence 8-15 years post-enrollment.                                      |
Table 2: Contd...

| Authors              | Year | Type of Blind Method | Intervention                                                                 | Outcome(s) Assessed                                                                 |
|----------------------|------|----------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Dostal AM et al.[29] | 2015 | Double               | Administration of four oral GTE, **capsules containing 1315 mg±116 total catechins per day (843±44 mg as Epigallocatechin-3-gallate (EGCG)) for 12 months. | Mammographic density, circulating reproductive hormones, and biomarkers of breast cancer risk. |
| Bao et al.[30]       | 2014 | Double               | Patients were randomized to an 8-week-long Real Acupuncture (RA) group or Sham Acupuncture (SA) group. | Menopausal symptoms, depression, anxiety and depression, sleep quality, quality-of-life. |
| Tambour M et al.[31] | 2014 | Single               | Group A: Complete Decongestive Therapy including manual drainage Group B: Complete Decongestive Therapy without manual lymphatic drainage. | Lymphedema (%) from baseline to 7 months, body weight (kg), patient sensation of heaviness, sensation of tension and quality of life. |
| Anderson et al.[32]  | 2014 | Single               | Intervention participants were scheduled for a one-hour lifestyle coaching session (face-to-face) and up to six fortnightly follow-up telephone consultations for three months. | Body weight, waist circumference, eating and alcohol habits, and physical activity. |
| Carlson et al.[33]   | 2013 | Single               | Mindfulness-Based Cancer Recovery (MBCR) consisted of eight weekly group sessions, 90 minutes each, plus a 6-hour workshop between weeks 6 and 7 for a total of 18 contact hours. Supportive expressive therapy consisted of 12 weekly group sessions, 90 minutes each, and equal contact hours for MBCR. 6-weeks of relaxation acupressure compared to stimulatory acupressure or standard care. | Mood, stress symptoms, quality of life, social support, spirituality and post-traumatic growth immediately before and after the interventions, and 6 and 12 months later. |
| Zick et al.[34]      | 2012 | Single               | Participants, investigators, study nurses and all study staff were blinded. | Fatigue, depression, anxiety, self-efficacy, sleep quality. |
| Von Ah et al.[35]    | 2012 | Single               | Working memory and processing speed educational sessions, including ten 1-hour training sessions conducted in small groups of 3-5 breast cancer survivors over 6-8 weeks. | Working memory and processing speed, perceived cognitive functioning, anxiety, fatigue, quality of life, intervention satisfaction, acceptability. |
| Zhuang SR et al.[36] | 2012 | Double               | Chinese medicinal herbs. | Cellular immunity. |
| Zwerenz et al.[37]   | 2012 | Single               | Short-term psychodynamic psychotherapy (up to 20±5 sessions). | Depression and quality of life |
| Matourypour et al.[38]| 2013 | Single               | Patients were not aware of the intervention (placebo group). | Nausea |

*PMR: Progressive Muscle Relaxation, **MM: Mindfulness Meditation, ***DMT: Dance Movement Therapy, ****QG/TCE: Qigong/Tai Chi Easy, ******ES: educational support, *******SQM: “sham” Qigong group (movements without a focus on the breath and meditative state), 8GTE: Green Tea Extract

In fact, attention is paid to the quality of studies in terms of design to enable the generalization of their results, at the same time that analyzing the quality of the reported studies because of their significant impact on patient care.
findings is of great value to the readers and/or users of research results.\textsuperscript{15}

Since blinding is one of the criteria for evaluating the quality of research, double or even triple or quadruple blind methods are recommended. Given that this kind of methodology has higher quality the results of a clinical trial that has employed this methodology can be trusted more too. Thus, future overviews on other factors affecting the quality of the methods employed, such as sampling, sample size calculation formula, data collection, etc., are also suggested.

This research has certain limitations. We did not have access to the full texts of some of the articles, despite the correctness of their titles and abstracts and their suitability for inclusion in the review. Moreover, limiting the language of the articles to English/Persian and restricting our search to four databases were other limitations of our study, whereas, other databases could contain further relevant and valuable researches.

**Conclusion**

Blinding has a critical role in preventing bias, so using double, triple or quadruple blinding increases the trustworthiness of clinical trial results. Thus, in any clinical trial, it should be clearly specified who has been blinded to raise the trustworthiness of results. Thereafter, nurses can apply new interventions and earn their patients’ trust and help those with breast cancer by relieving them of their disease symptoms and its treatment complications by using such trustworthy results.

**Acknowledgments**

This research has been approved by the Nursing and Midwifery Care Research Center of Tehran University of Medical sciences under project number 47816.

**Financial support and sponsorship**

Tehran University of Medical Sciences

**Conflicts of interest**

Nothing to declare.

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