Abstract: Although all Chinese materia medica (CMM) come from nature, CMM interventions have both therapeutic effects and adverse effects (AEs). Normally, AEs in randomized controlled trial (RCT) with traditional Chinese medicine (TCM) could be divided into five types as follows: 1) AEs under proper TCM principles and guidelines, such as the toxicity (acute and chronic) and allergy; 2) AEs due to improper usage without following TCM principles, involving without following the TCM therapeutic principles, over-dosage, improper processing and preparation methods, improper formula strategy, etc.; 3) AEs due to contamination in CMM, such as heavy metal and pesticides contaminations in Chinese herbal medicine interventions, and intentional or unintentional contamination with drug(s); 4) AEs due to replacement of CMMs; 5) AEs due to drug-herb interaction. AEs of TCM should be treated properly. Overestimation or underestimation about AEs of TCM intervention will bring a wrong message to patients and health care providers. In order to give readers a more comprehensive understanding about the safety issue of study intervention, Consolidated Standards of Reporting Trials (CONSORT) for TCM should involve the background information on side effects of each CMM constituents and/or the study intervention, specific outcome assessment on AEs, the details of reported AEs and the interpretation of the AEs occurrence in a structural RCT report.

Keywords: traditional Chinese medicine; Chinese herbal drugs; clinical research; randomized controlled trials; evidence-based medicine
1 Introduction

It is generally accepted that all health interventions, including traditional Chinese medicine (TCM), should be as safe as possible prior to adopting them in clinical practice. There is a common misconception that herbal materials—including those used in TCM, known as Chinese materia medica (CMM)—are harmless to humans because they come from natural sources. In fact, TCM may cause serious adverse effects (AEs) when adulterated or used incorrectly. Although the potential toxicity of specific CMM interventions has attracted more attention worldwide as the use of herbal interventions increases, most researches on TCM continue to focus almost exclusively on establishing efficacy and effectiveness. Our previous study reported that only 30% of randomized controlled trials (RCTs) of TCM reported AEs, and most of them were too vague on this topic for readers to appropriately determine the safety of the TCM interventions studied. Better reporting on AEs in RCTs of TCM is therefore required.

The Draft Consolidated Standards for Reporting Trials of Traditional Chinese Medicine (CONSORT for TCM) were published in Chinese and English in 2007 to solicit feedback from experts in different specialties. In that draft, one checklist item addressed the reporting of safety of TCM interventions. Upon further consideration, it became apparent that a single checklist item to address the issue of safety was not enough. The extension of the CONSORT statement on reporting of harm has addressed how to illustrate the AEs in RCT of Western pharmaceuticals. Since it is essential to transparently illustrate the AEs of RCTs for all interventions, including those used in TCM, this article aims to enhance awareness of safety issues for TCM interventions by promoting improved reporting by 1) summarizing the types of AEs reported with TCM; 2) examining the impact of AEs on RCTs with TCM; and 3) formulating the reporting structure. The corresponding revisions of the draft CONSORT for TCM are also recommended.

2 Types of AEs

CMM products used in TCM can refer to materials of herbal, animal or mineral origin. Normally, AEs associated with CMM products used in TCM could be divided into five types as follows:

2.1 Unpredictable AEs Theoretically, TCM interventions are prescribed by clinical practitioners according to the golden principle of treatment based on syndrome differentiation. Even if this principle is followed, AEs cannot be entirely avoided, and toxicity (acute or chronic) or allergic reactions may occur. For example, Caulis Aristolochiae manshuricae (Guanmutong) is a commonly used Chinese herb in clinical practice, and has attracted attention for its significant nephrological toxicity in the last two decades. The major compound in C. A. manshuricae, aristolochic acid, induces acute tubular necrosis in the kidney, thus resulting in significant toxicity. But based on the Chinese medicine theories, it cannot be predicted. Allergy is another AE associated with the usage of TCM interventions including allergic shock, allergic asthma and allergic purpura. Although a previous history of allergy to herbs can remind the practitioner to be careful, this knowledge is of little value for patients who have not previously been exposed to these allergens.

2.2 AEs arising from improper use TCM drug must be used according to TCM principles, and improper usage may result in AEs. Typically, improper use involves 1) prescription without following the TCM therapeutic principles; 2) overdose; 3) improper processing and preparation methods; 4) improper formulas.

Firstly, prescriptions should be based on the TCM treatment principles. If these principles are not obeyed, potentially efficacious interventions may produce AEs. For example, Rhizoma Coptidis (Huanglian) is very cold in nature and bitter in taste. Used properly, it can clear heat, dry dampness, drain fire and expel toxicity. Used improperly, it may damage the spleen and stomach resulting in nausea, vomiting, stomachache and
loss of appetite in the short term; over the long term, improper usage may result in spleen qi deficiency. If the TCM theories are strictly followed, these AEs could be avoided.

Secondly, over-dosage is another common reason for AEs with TCM intervention. For example, most AEs related to the root of Herba Asari (Xixin) are because of high dosages. Traditionally, the limitation of daily dosage of H. Asari is less than 3 grams, although debate exists on this topic [12]. Another typical case of over-dosage is Herba Ephedra (Mahuang). Although there is no clinical evidence from any RCT to support the effect of H. Ephedra on weight loss, it continues to be used for this indication at doses much higher than the traditional dosage, which has resulted in AEs [12].

Thirdly, the processing and/or preparation method should be selected based on reducing the potential toxicity of herbs and formulas, since improper processing and/or preparation can increase the possibility of AEs. For example, Radix Aconiti (Wutou) should only be used in its processed form and should be boiled separately for at least 45 minutes before boiling together with other components in a formula to reduce the possibility of aconite poisoning, which may lead to toxicity in patients [10].

Furthermore, failure to follow basic TCM principles during the formulation of TCM formula may result in AEs as it is well known that some CMMs are incompatible with others and should not be combined in formulations. The most important guidelines are the "eighteen incompatible herbs" and the "nineteen antagonistic herbs". At the same time, an appropriate combination of CMMs can enhance therapeutic effects and reduce harmful side effects.

2.3 AEs arising from contamination Heavy metal and pesticide contamination in TCM interventions are major concerns and can result in AEs. The growing conditions as well as the processing procedures and preparation process may contribute to these contaminations [14]. They are known to have caused serious AEs, and will continue to be a serious concern. For example, mercury contamination can cause neurological disorders and nephrotoxicity [15]. It may also result in depression, irritability, forgetfulness, confusion, tremor, sensory disturbances, visual deficits, hearing loss, movement disorders and cognitive disturbances, etc [16]. Contamination with mercury in herbs can cause serious AEs [17]. In addition, contamination from non-TCM pharmaceutical products in TCM intervention is another potential source of serious AEs. For example, a clinical trial found that PC-SPES, which is a proprietary formulation containing eight herbs that was marketed by Botanic Lab (Brea, CA) from 1966 to 2002, has side effects including reduced libido, hot flashes, diarrhoea, dyspepsia, leg cramps, nipple tenderness, and gynaecomastia, pulmonary emboli, deep vein thrombosis, a transient severe bleeding diathesis [18]. These side effects were due to product contamination with diethylstilbestrol and warfarin and caused the withdrawal of this formula from the market in 2002 [19].

2.4 AEs arising from misidentification of CMMs There are many cases of confusion in species of CMM, and there are many reasons for the various types of confusion. A particular herb used in TCM may have different subspecies, each with a different use. For example, Radix Glycyrrhiza is used in Zemaphyte for atopic dermatitis [14]. Sometimes, the incorrect species could take the place of the intended species, thus leading to AEs. The first reported toxicity case involving aristolochic acid in Hong Kong was caused by mistaken use of Aristolochia mollissima Hance (Xungufeng) instead of the aristolochic acid-free CMM Solanum lyratum Thunb (Baiying), and this misuse resulted in renal failure and malignant urothelial changes [20].

2.5 AEs arising from drug-herb interaction Potential herb-drug interactions continue to attract more and more attention due to possible AEs [21-23]. Although it is believed that TCM could perhaps play an auxiliary role when combined with Western pharmaceuticals in the management of some diseases, including certain forms of cancer, there is generally insufficient evidence to support the efficacy and safety of such combination therapies. Herbal products may interfere with the metabolic process of pharmaceuticals (e.g. pharmacokinetic interference), thus leading to AEs. For example, Ginseng, one of the most widely used dietary supplements, is well known to interact with warfarin. And also, ginsenosides exert a hypoglycaemic effect, which may enhance the actions of oral hypoglycaemic drugs and insulin [2]. Therefore, when these herbs and drugs are used together, possible negative drug-herb interaction could happen.
3 The need to concisely report AEs of RCT with TCM drug intervention

AEs associated with the use of TCM should be properly reported as overestimation or underestimation will constitute misinformation for both patients and health-care providers. In this area, evidence speaks volumes. Where does evidence come from? It comes from clinical practice, especially from clinical trials such as RCTs. It is well known that RCT is an effective tool to determine the efficacy of an intervention on a well-defined disease or a series of symptoms, and also provides valuable evidence regarding safety by identifying the potential risks and AEs associated with an intervention. Therefore, RCTs of TCM should transparently report not only efficacy, but all related AEs in the trial. Failure to report AEs will invite unjustified confidence in the safety of TCM. Sufficient details about AEs should be provided to enable readers to fully understand the safety of the herbs used. In addition, reports of AEs should be interpreted in relation to therapeutic efficacy, method of assessment, and underlying causality on the basis of both TCM theory and conventional medicine, to help readers assess the safety of specific TCM interventions.

4 Structure for reporting AEs

In order to give readers a comprehensive understanding about the safety of TCM interventions, background information on known or suspected side effects of each CMM constituent in the study intervention, as well as specific outcome assessment on AEs, details of reported AEs, and the interpretation of the AEs should be included in a report of AEs in RCTs of TCM.

4.1 Background information on AEs Before a TCM intervention enters into an RCT, initial analysis and review of the safety of the intervention is necessary. The safety background information of the TCM drug should be briefly summarized. The data may come from literature review or preclinical pharmacology/toxicology testing.

4.2 Specific outcome assessment Outcome measures specific to safety surveillance should be addressed, as well as details regarding other assessments related to treatment efficacy. Selection rationale, concrete assessment method, and reference standards should also be defined and explained. If the occurrence of specific AEs is to be used as one of the terminal evaluation criteria, its underlying rationale should also be determined and described.

4.3 Details of reported AEs All AEs discovered in treatment and control groups, regardless of severity, must be transparently reported. The details should include clear definition of each AE, time of occurrence, frequency in each group, degree of severity, and number of cases who withdrew or reduced their dose due to AEs. If no AEs were reported, authors should declare that "no AEs were reported", instead of not mentioning AEs at all in the RCT report.

4.4 Interpretation All AEs reported should be interpreted, in terms of both TCM theory and conventional medicine, if applicable, including a discussion of the potential underlying causality.

5 Recommendations for revision of CONSORT for TCM

To better reveal the safety issues of CMM intervention, further modifications to the draft of CONSORT for TCM, with the addition of the following descriptive text to the item numbers were indicated and summarized in Table 1.
Table 1  Recommendations for revision of CONSORT for TCM

<table>
<thead>
<tr>
<th>Topic</th>
<th>Item</th>
<th>Additional description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Background</td>
<td>2</td>
<td>State the AEs of each CMM in the study intervention and explain with the theories of TCM and conventional medicine, as appropriate.</td>
</tr>
<tr>
<td>Objective</td>
<td>3</td>
<td>If the trial addresses both efficacy and safety, the objectives should state this.</td>
</tr>
<tr>
<td>Intervention</td>
<td>5</td>
<td>Precisely list the method to minimize the toxicity of the intervention (e.g., special preparation, prolonged boiling process, etc.), if applicable.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>State any available information on safety assessment (e.g., acute toxicity test, chronic toxicity, and quality control on contamination, etc.).</td>
</tr>
<tr>
<td>Outcome</td>
<td>6</td>
<td>List the outcomes specific on safety issue with definition, concrete assessment method (e.g., how, when, and by whom, etc) and standard reference.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Address the principles of study termination on safety issue, if applicable.</td>
</tr>
<tr>
<td>Statistical method</td>
<td>12</td>
<td>Describe the methods used to present and determine the safety issue.</td>
</tr>
<tr>
<td>Participant flow</td>
<td>13</td>
<td>Identify the number of withdrawals or those reducing dosages due to adverse effects in each group.</td>
</tr>
<tr>
<td>Outcome and estimation</td>
<td>17</td>
<td>Describe the results with regard to safety for each group and the estimated effect size and its precision (e.g., 95% confidence interval).</td>
</tr>
<tr>
<td>Ancillary analysis</td>
<td>18</td>
<td>Describe any subgroup analysis and exploratory analysis on safety issues.</td>
</tr>
<tr>
<td>Adverse event</td>
<td>19</td>
<td>Report all AEs of each group in detail (e.g., name with clear definition in terms of TCM and/or Western medical terms, nature, time of occurrence, frequency, any recurrence, and degree of severity). If there are no adverse events to report, explicitly declare &quot;no AEs should be reported&quot;.</td>
</tr>
<tr>
<td>Interpretation</td>
<td>20</td>
<td>Interpret the adverse effects in terms of TCM theory and conventional medicine, and identify the potential underlying causes and any interaction with co-medications, if applicable.</td>
</tr>
</tbody>
</table>

6 Conclusion

The safety of an intervention is as important as its efficacy. AEs are a significant aspect of drug safety. In order to provide a clear profile of the safety of TCM intervention(s) in an RCT report, reporters should 1) present and discuss any information with regard to safety based on literature review or preclinical studies; 2) concisely describe the assessment protocol; 3) completely list any and all AEs that occurred in their trials; and 4) discuss possible causes. We wish these guidelines can help researchers improve their reporting of AEs and thereby improve the quality of their studies, and also help readers critically evaluate the safety profile of tested interventions.

REFERENCES

7 Vanherweghem JL, Depierreux M, Tielemans C, et al. Rapidly progressive interstitial renal fibrosis in young women; association with slimming regimen including...


10 Li D. Literature review of eighty-five cases of allergy due to usage of traditional Chinese medicine. Fujian Zhong Yi Yao. 2007; 38(3): 44. Chinese.


14 Kang Yum E, Oransky SH. Chinese patent medicine as a potential source of mercury poisoning. Vet Hum Toxicol. 1992; 34(3); 235-238.


