Evidence-based medicine in herbal treatment: Benefit to assess quality of life (QOL)

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Abstract

Oriental medicine (including Kampo medicine) treats patients on the basis of their overall symptoms and conditions, and plays an important role in tailor-made medicine. In Oriental medicine, the condition of “acquiring a disease” is known as mibyo. The concept of treating mibyo is similar to that of improving health-related quality of life (HRQOL) which has been defined and developed in Western medicine as a subjective assessment of health-based factors from the patient’s perspective. HRQOL has been broadly defined to include the physical, psychological, social aspects of health perception and functioning. Many HRQOL scales have been developed by clinicians to assess the effect of therapeutic or preventive intervention. HRQOL scales are questionnaires for the patients, and are thus patient-reported (self-administered).

Kampo medicine is a multi-component drug system comprising more than one crude drug; however, compared with Western medicine, there is insufficient evidence in literature regarding this as it is a unique treatment system. Oriental medicine researchers have been actively discussing measures to strengthen the levels of evidence of Kampo medicine; therefore, data from randomized clinical trials (RCTs) have increased. We investigated QOL data availability in domestic and international studies regarding crude drug products. Of 1995 international studies, 39 studies evaluated QOL from international researches. For domestic research, Evidence Report of Kampo Treatment 2010 and Appendix 2011 by special committee for Evidence-based medicine (EBM), The Japan Society for Oriental Medicine (JSM), Evidence Report/ Clinical Practice Guidelines (ER/CPG-TF) summarized total 359 RCTs and one meta-analysis, 21 reports evaluated QOL, 17 reports were published after 2000. Our evaluation of these domestic and international studies suggests that QOL assessments have gradually gained widespread recognition. The levels of evidence for Kampo medicine have been increasing; however, QOL data are still very limited. The limited levels of evidence for QOL may be due to low QOL awareness, the difficulty to select QOL scale or the target patient population, and the difficulty to obtain a large number of participating patients.

Key words Kampo medicine, Oriental medicine, Herbal medicine, QOL, EBM, Mibyo, Crude drug products.

Introduction

Oriental medicine (including Kampo medicine) plays an important role in tailor-made medicine. However, one of the challenges for Oriental medicine is insufficient levels of evidence due to the uniqueness of the treatment system. Proof of efficacy or safety for a vast majority of Oriental medicine has not been fully established through an evidence-based approach. Moreover, it is imperative that Oriental medicine practitioners should accumulate scientific evidence using current...
medical practices. The integration with Western medicine's methodology would be an effective way to address the insufficient levels of evidence. Oriental medicine has a unique concept, known as mibyo treatment; the condition of "acquiring a disease" is known as mibyo. Patients with Mibyo have mental and behavioral disorders despite no abnormal laboratory test results, and their QOL is poor. Over the past few decades, QOL improvements are therapeutic goals that rival that of morbidity or mortality. The term, health-related quality of life (HRQOL) refers to how a person feels and functions in everyday life and the effects of ill health on this. The concept of treating mibyo has some similarities to Western medicine with regard to improving QOL. HRQOL scales could be used to characterize health status more efficiently. We hypothesized that QOL assessment methods could be integrated into Oriental medicine, thereby contributing to enhancement of the scientific levels of evidence.

Here we investigated the potential challenges for evidence-based medicine (EBM) by collecting QOL data on crude drug products. This review consists of three sections: 1) overview of QOL, 2) up-to-date crude drug products studies in EBM, and 3) current status of QOL assessments of crude drug products.

1. Overview of QOL

1) Historical background of QOL

Before the 1940s, an objective evaluation based on mortality rate, disease prevalence, and objective laboratory data was used in arriving at medical treatment decisions. As the prevalence of acute diseases has declined and that of chronic diseases has increased through the development of medical practice, it raises expectations for alternative to morbidity or mortality. Patients seek relief from pains through invasive medical or life-prolonging therapies; moreover, improving QOL is considered as the primary goal of treatment. Therefore, (self-administered) patient-reported outcome (PRO) from patient’s view point is considered an important factor to measure a population’s health status. Since 1940s, HRQOL has been evaluated in oncology patients in Western countries. 1,2 Thereafter, HRQOL assessment methodology has been developing more since the 1960s. 3-5 PRO is an outcome assessment that is beyond traditional efficacy and safety of a treatment methodology. In recent years, an increasing tendency towards reporting PRO results in regulatory documents and approved labels. Furthermore, regulatory agencies such as the Food and Drug Administration and the European Medicines Agency have released PRO guidelines as well. 6,7 Thus, PRO data is highly expected to support new drug applications.

2) Definitions of QOL

Various controversies exist regarding the definition and concept of QOL, but QOL is almost equivalent to the concept of health defined by the World Health Organization (WHO). The WHO introduced a broader definition of health as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (preamble in the charter in 1947). 8,9 QOL includes the physical, psychological, and social aspects of health perception and health functioning. QOL has broader meanings such as satisfaction for life and a reason for living. However, these are usually affected by external factors (economic status or residential environment), and it has been reported that external factors should be excluded in the health care field; namely, QOL should be limited only to health-related aspects. HRQOL is utilized to assess the impact on the patient’s daily life and health status thought therapeutic or preventive intervention. 5,10,11

3) QOL assessment methodology

The PRO assessment is a key to assess HRQOL. PRO data provides valid evidence of health status from the patient’s perspective. 10 Table 1 displays a summary of frequently utilized HRQOL scales, 5,11 which are classified into preference-based, single index measures, and profile measures.

A preference-based, single index measure is frequently utilized for health economic research. Preference-based scales, such as the EQ-5D, 12,13 the SF-6D 14 and the Health Utilities Index, 15 are standardized multi-dimensional health state classifications. 16 Preference-based scales differ substantially from the functional status or health status assessments. These values were used for each scale to generate a scoring algorithm, from which a single utility score could be deduced for
Table 1  Health-related QOL scales

<table>
<thead>
<tr>
<th>Category</th>
<th>Scale name</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preference based measure</td>
<td>EQ-5D, HUI, SF-6D</td>
<td>Economic research</td>
</tr>
<tr>
<td>Profile measure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generic measure</td>
<td>SF-36, HADS, SIP, NHP, WHOQOL</td>
<td>Clinical research, Epidemiology research</td>
</tr>
<tr>
<td>Disease specific measure</td>
<td>KDQOL, RDQ, DLQI</td>
<td>Clinical research, Clinical trial</td>
</tr>
</tbody>
</table>

Modified from the source: Ikegami; 2001\(^1\), Takegami; 2009\(^1\)

EQ-5D: EuroQOL 5D, HUI: Health Utilities Index, SF-6D: Short-Form-6Dimensions
SF-36: Short-Form-36 Health Survey, HADS: Hospital Anxiety and Depression Scale, SIP: Sickness Impact Profile, NHP: Nottingham Health Profile, WHOQOL: The World Health Organization Quality of Life
KDQOL: Kidney Disease Quality of Life, RDQ: Roland-Morris Disability Questionnaire, DLQI: Dermatology Life Quality Index

each health state. Reports regarding the use of preference-based QOL measures are increasingly common in the medical literature. These measures offer an advantage over functional or health status measures, as they incorporate individual attitudes toward functional status, pain, and disability, etc.\(^1\) The EQ-5D is a preference-based self-administered scale. Here a single value obtained from the responses to five questions represents the subject’s health status; the five questions include the dimensions of health, (1) mobility, (2) self-care, (3) usual activities, (4) pain/discomfort, and (5) anxiety/depression. For each dimension, patients selected one of three graded responses for each dimension that indicate no problem, some problems, or severe problems with the activity. Thereafter, QOL values are calculated using a scoring algorithm derived from community time trade-off values assigned to various health states comprising the five dimensions. EQ-5D scores are reported on a ratio scale anchored on 0.0, the value of “dead,” and 1.0, the value of “perfect health.”\(^12,13\)

The profile measures are further classified into generic and disease specific scales. Generic scale such as the SF-36,\(^18,19\) the Hospital Anxiety and Depression Scale,\(^20\) and the WHO Quality of Life\(^21\) provide quantitative alteration in health status and social functioning in a wider population from health subjects to patients, using one standard scale. The profile measures are expressed in several profiles or subscales.

The SF-36 is a generic self-administered scale. The SF-36 contains 36 questions including eight multi-item subscales: (1) physical functioning, (2) physical role limitations, (3) bodily pain, (4) general health perception, (5) vitality, (6) social functioning, (7) emotional role limitation, and (8) mental health. These eight scales provided the basis for calculating the Physical Component Summary and the Mental Component Summary scores. Subscale scores were computed by summing across items in the same scale and then transforming raw scale scores to a range from 0 to 100. Higher scores on summary measures and all eight subscales represent a better HRQOL.\(^18,19,22\)

Disease specific scale such as the Kidney Disease Quality of Life,\(^23\) and Dermatology Life Quality Index (DLQI)\(^24\) are scales to assess the impact for health status on daily, social functioning from a specific disease. The sensitivity of the disease specific scale is high, but it is not possible to compare the health status between patients with two different diseases.

The DLQI is a disease-specific self-administered scale to evaluate the impacts of dermatological diseases. The DLQI contains 10 questions in six multi-item subscales: (1) symptoms and feelings, (2) daily activities, (3) leisure, (4) work and school, (5) personal relationships and (6) treatment. DLQI scores are 1-30, with 0 being the best and 30 being the worst.\(^24\)

The Scientific Advisory Committee of Medical Outcomes Trust defined the criteria to perform QOL scale assessments.\(^25\) In addition, Takegami & Fukuda added some modification to the criteria as shown below.\(^1\)

1) conceptual and measurement model, 2) respondent and administrative burden, 3) reliability, reproducibility, 4) validity, 5) standardization, 6) sensitivity/accuracy, 7) measurable range, 8) responsiveness, 9) cultural and language adaptation, 10) interpretability
Clinicians need to consider these 10 criteria when they select scales. If the appropriate QOL scale is not selected, the data obtained from those scales may lead to inaccurate interpretation. Clinicians also need to select appropriate patient population. It is difficult to obtain reliable responses if the patient’s condition is not stable due to circadian change, repeated aggravation or remission of symptom, e.g. in patients with cognitive dysfunction or Parkinson disease.11

2. Up-to-date crude drug product studies in EBM

In general, clinical trials such as randomized control trials (RCTs) and double-blind RCTs provide highly reliable evidence.26,27 Oriental medicine using crude drug products is a unique and personalized medication system. It is difficult to exclude bias in clinical trials using crude drug products with very unique smells, tastes, and colors, which makes it difficult to mask those features and prepare an unidentifiable placebo. The insufficient levels of evidence are very critical in Oriental medicine compared with Western medicine. The levels of evidence for crude drug products was evaluated before 2000,28,29 and the overall quality of evidence for RCTs was poor, but it has improved gradually over time. Clinicians are conducting crude drug product RCTs, domestically and internationally, to obtain scientific evidence.30,34 For example, one clinical report for the treatment of allergic rhinitis29 was evaluated as high evidence.35 However, the overall quality and levels of evidence for crude drug products are insufficient compared with Western drugs. Although the levels of evidence have improved gradually over the past few decades, it needs to be addressed.

Kampo medicine as crude drug products is widely used in medical practice in Japan. An EBM Special Committee appointed by the Japan Society for Oriental Medicine (JSOM) was established in 2001 to enhance EBM in Japan. Subsequently, experts reviewed data,

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>No. of reports</th>
<th>Total No. in 1986-2011 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1986-2010 (35)</td>
<td>2011 (36)</td>
</tr>
<tr>
<td>Infections</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Cancer</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>Blood Diseases including Anaemia</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and Endocrine Diseases</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric/Behavioral Disorders</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System Diseases</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Eye Diseases</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Ear Diseases</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Cardiovascular Diseases</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory Diseases</td>
<td>42</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal, Hepato-Biliary-Pancreatic Diseases</td>
<td>53</td>
<td>4</td>
</tr>
<tr>
<td>Skin Diseases</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Diseases of the musculoskeletal system and connective tissue</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Genitourinary Tract Disorders</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>Ante/Post-partum Diseases</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Symptoms and Signs</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>Post-anesthesia and Postoperative Pain</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Ante/Post-partum Diseases : Meta Analysis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Extrinsic Injuries/Diseases</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Others</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>346</td>
<td>14</td>
</tr>
</tbody>
</table>

Modified from Evidence Reports of Kampo Treatment35,36
The number of structured abstracts for RCT are shown by disease.

* The number in parentheses indicates the percentage of structured abstracts by disease in total 360 ones
accumulated as evidences for Kampo medicine and released Evidence Reports. These reports are all based on RCTs (including quasi-randomized controlled trial, cross-over study, meta-analysis) using approved drugs in Japan and were published after 1986. Reports in which the quality of the study drug was poor were excluded. As a result of this comprehensive review, of the 415 reports, 345 RCTs and one meta-analysis were selected and the structured abstracts with expert review comments were presented. In 2011, 16 new RCTs were identified and 14 structured abstracts reports were added.37)

Table 2 displays the number of RCTs by disease category on the basis of the Evidence Report of Kampo Treatment 2010, Appendix 2011 (JSOM, ER/CPG-TF).36,37) 7) Gastrointestinal, hepato-biliary-pancreatic diseases”, “respiratory diseases”, “genitourinary tract disorders” and “cancer” are the most frequently reported disease categories. The ratios of reports in each category out of the 360 reports are 15.8%, 12.2%, 9.4%, and 8.6%, respectively. Some studies were well-designed; for example, the run-in period was incorporated into the study design, and the pre-data and post-data for one individual were compared.39) These reports were evaluated as high evidence levels. However, the number of patients enrolled was not sufficient, patient demographics were not well balanced, statistical analyses conducted were insufficient, or data interpretation was incorrect in several reports. Although researchers continue to integrate EBM methodology into Kampo medicine, the levels of evidence still need to be improved further.

Integrating with Western methodology is one of the ways to enhance the levels of scientific evidence. It will be no easy task to identify ways to build evidence on the basis of the unique Kampo medicine system. As known, the levels of evidence for RCTs are generally higher than those for case series and case reports. However, JSOM has reported that case series have the potential to provide clinically beneficial evidence. If we underestimate the value of case series, we may lose some beneficial medical inputs. Case reports possibly provide clinically important data so that clinical physicians can make treatment decisions efficiently. These studies have a chance of becoming a trigger for new medical findings that will lead to future treatments and the best medical practice.40)


The mibyo treatment in Oriental medicine is a method of prevention before the health status deteriorates. There are few very clear medical symptoms or abnormal laboratory test results under mibyo condition, and QOL is poor. Successful mibyo treatment requires meticulous observations from the patient’s perspective and no abnormal laboratory test results. In this regards, the basic concept of mibyo treatment is considered to somewhat resemble QOL improvement, which was developed in Western medicine. We believe that QOL assessment methodology may be appropriate for crude drug products (including Kampo medicine) and may contribute to accumulating evidence. Thus, we investigated the availability of QOL data in domestic and international studies that evaluated about crude drug products. We searched published studies available in PubMed, as of July 2011. “QOL”, “randomized controlled trial” were the search terms, and a total of 1995 reports were identified. Thereafter, Kampo medicine (therapy) or (traditional) Chinese herbal medicine (therapy), or Chinese herbs, or Chinese medicinal plants, were additionally searched within the 1995 reports and 39 reports were identified. A majority of these studies were reported from China. Nevertheless, one of the reasons for the less number of reports may be the limited number of English studies as most studies related to crude drug products are written in local languages. As shown in Fig.1-A, 30 of the 39 studies were published after 2005. This indicates that the awareness for QOL in crude drug products remains very low, but has increased since 2005. We also searched the Evidence Report of Kampo Treatment 2010, Appendix 2011 (JSOM, ER/CPG-TF). The RCTs assessing QOL as one of their outcome measures, were 21 of 359 RCTs and one meta-analysis(total of 346 in 2010 report and 14 in 2011 reports).36,37) Seventeen of 21 RCTs were published after 2000, and 13 were published since 2005 (Fig.1-B). Table 3 displays the number of RCTs evaluating QOL as an outcome measure based on the Evidence Report of Kampo Treatment 2010, Appendix 2011 (JSOM, ER/CPG-TF).36,37) The total number of RCTs evaluating QOL was 21 of the 360 (Table 2), which is < 6% of the total(5.8%). The ratios of RCTs evaluating QOL in each
disease category were 22.7% (5/22) in “symptoms and Signs”, 12.7% (7/55) in “gastrointestinal, hepato-biliary-pancreatic diseases”, 6.8% (3/44) in “respiratory diseases”, 5.9% (2/34) in “genitourinary tract disorders” and 6.5% (2/31) in “cancer”, respectively.

As a result of our review, disease specific QOL assessment scales related to gastrointestinal system such as the Gastrointestinal Symptom Rating Scale and King’s Health Questionnaire were mainly used. In addition, the SF-36 and WHQOL as generic scales were used. These scales are valid and reliable. The number of reports that assessed QOL is still very limited; however, but researchers are making efforts to introduce QOL assessments into Kampo medicine. The reason behind this limited data may be due to low awareness regarding the benefits of using QOL assessment. Moreover, it might
be difficult to understand the criteria to select the most appropriate QOL assessment scale for target patients. Another reason is the difficulty in collecting a sufficient number of responses in Japan. Because a large number of responses is normally required to prove statistical significance, to obtain a large number of participating patients from the limited number of hospitals in Japan is often challenging; thus, but multiple hospital collaboration may be necessary.

The levels of evidence to evaluate the effect of Oriental medicine remain low, but the interest and expectation for QOL increasing. Some research reported that the condition of mibyo can be assessed by the SF-36 of generic scale and categorized into several patient groups. One patient group comprises patients in whom lifestyle guidance without pharmacotherapy is effective, whereas another specific patient group requires Kampo treatment in addition to lifestyle guidance.

Thus, it is necessary to identify the patient groups that respond effectively to crude drug products. We expect that the QOL concept and methods for QOL assessment will be used more widely and utilized appropriately. Further education may be needed to enhance QOL awareness.

Conclusion

Insufficient levels of evidence are critical in crude drug products studies, and many activities are on-going to enhance the levels of evidence. Since 2000, the quality of evidence in crude drug products has been getting increased domestically and internationally since 2000. QOL assessment is one of the possible areas to integrate Western EBM methodology into Oriental medical practice effectively, although awareness for QOL is still low. We expect that QOL assessments will be utilized more frequently in future crude drug products studies.

Acknowledgments

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