Original Article

Meta-analysis on the Usefulness in Postpartum Control by Kyukichoketsuin with Methylergometrine Maleate as Control

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Abstract

[Purposes]  Evidence-based medicine (EBM) is now the established standard for selecting appropriate treatment, the basic ideas of which cannot be ignored even in the field of Kampo medicines. With this in mind, we conducted a meta-analysis (MA) for those Kampo medicines which had been administered in randomized clinical trials, as a method of establishing the evidence for Kampo medicines, and then examined the resulting data obtained for the present study. Here, we focused on the assessing the usefulness in postpartum control, using Kyukichoketsuin (KCI), with methylergometrine maleate (MME) as control.

[Methods]  We searched and collected articles published before September 2004 in Igaku Chuo Zasshi (Japana Centra Revumo Medicina) and Medline using keywords such as “Kyukichoketsuin”, etc. First we selected target articles for analysis in accordance with our inclusion criteria and examined the quality of those articles using a score system adopted by Chalmers, in 1981. Then we extracted target data from the articles in accordance with meta-analytic methods, integrated the resulting data using the DerSimonian-Laird method, and implemented sensitivity analysis to them.

[Results and Discussion]  We selected four articles for our target analysis. All four were of similar quality. When we set post-labor pains as an assessment item, and integrated three of the four articles, KCI showed that it more significantly decreased those pains compared to MME, with an integrated odds ratio of 0.32 (95% CI, 0.17−0.60). The one remaining independent article, however, in which KCI exerted statistically significant effect in height of day-five uterine fundus, indicated no higher significance through integration with the first three articles. Also, even integrating the height of the uterine fundus shown in the articles, on day four as well as the height before integration, had no significance. These results indicate that the effect of KCI for the involution of the uterus may be the same as that of MME. Regarding the volume of breast-milk lactation on day four in comparison between two test drugs, some articles showed more volume in both the KCI and MME groups, despite reaching no significant decreases in volume, with an integrated odds ratio of 0.82 (95% CI, −1.67−0.23). However, contrary to this, results for the integration of day-five breast-milk lactation volume showed an increase in the KCI group, although without reaching significant difference. Therefore, the effectiveness of KCI for breast-milk lactation could not be generally categorized as less than that of MME.

[Conclusion]  MA demonstrated that KCI was more effective in decreasing post-labor pains than was MME. We could not implement the comparable study in safety at this time. Therefore, further analysis on KCI including safety may be required to argue total effectiveness on postpartum control.

Key words:  Kyukichoketsuin, meta-analysis, methylergometrine maleate, EBM, postpartum

要旨

【目的】  EBM が治療法選択の標準となった現在，漢方薬においてもその基本を無視することは出来ない。そこで本研究は漢方薬のエビデンスを確立する一つの手法としてランダム化臨床試験（RCT）が実施されている漢方薬に対

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してMeta-Analysis（MA）を実施し、得られたデータについて検討を行った。そこで今回はマレイン酸メチルエリュゴメトリン（MME）を対照としたتقي帰調血飲（KCI）の産褥管理における有用性についての評価を行なった。

【方法】医中村、Medlineでキッチョクスジ（kyukichoketsuini）等をキーワードとして2004年9月以前に公表された論文を検索・収集した。採用基準に従い解析対象論文を選出し、Chalmersのスコアシステム（1981年）で論文の質の確認を行なった。次にMAの方法に従い評価データを抽出し、データの統合（DerSimonian-Laird法）および感度分析を行った。

【結果および考察】4論文が解析対象論文となり、これら論文の質はほぼ同等であった。後陣痛を評価項目とした3論文を統合した結果、KCIがMMEに比較し、有意に後陣痛を減弱させることが示された（統合odds ratio：0.32（95%CI：0.17~0.60））。しかし、1論文ではKCIが統計的に有意であった分娩5日目子宮底長が、統合により有意差を認めない結果となった。また分娩4日目の子宮底長は、論文同様、統合によっても有意差を認めなかった。この結果、子宮復旧に対するKCIの効果は、MMEと同等と考えられた。分娩4日目の乳汁分泌量の比較においては、何れも有意差は認められなかったものの、KCIおよびMME両方の乳汁分泌量が多いとした論文が存在していた。そこでこれらを統合した結果、乳汁分泌量が有意に多い（統合odds ratio：－8.20（95%CI：－16.17~－0.23））事がわかった。しかし分娩5日目の乳汁分泌量を統合した結果、有意差こそ認めなかったが、KCIによる乳汁分泌量が多い結果となった。このことから、乳汁分泌に対するKCIの有用性は、MME一概に劣るとも考えられなかった。

【結論】MAによりKCIは後陣痛の減弱においてMMEに比較し有用性が高いことが示唆された。しかし今回は安全性に関する比較は行なえなかったため、産褥管理の総合的な有用性を述べる上では今後、安全性を含めた解析が必要であると思われる。

キーワード：キッチョクスジ、メタアナリシス、マレイン酸メチルエリュゴメトリン、EBM、産褥

Ⅰ. Introduction

Evidence Based Medicine（EBM）has become rapidly prevalent since it had been advocated in 1991, and being established as one of the vital idea in the medical field. EBM is defined as a clinical and epidemiologic methodology to seek for the best scientific evidence available for decisions in individual patient treatment, and as an idea to give treatments based on scientific evidences without relying on conventional experiences or intuition of individual physicians. As the scientific evidences in this case, the study results of experimental medicine or reasoning of pathological physiology are not prioritized, but the results of clinical studies, especially of randomized clinical studies are regarded as important.

Now that EBM has been established as the standard to select as an appropriate treatment, even the Kampo medicine, Japanese traditional medicine, could not ignore the idea of EBM. Therefore, the establishment of a clinical study design or of assessment method of Kampo medicines based on biostatistics are required to adequately assess the usefulness of Kampo medicines.

On the other hand, meta-analysis is one of the study techniques which can overview total outcomes of the clinical studies on the same theme being already published, and that can draw the results from the studies. Its study purposes involved are as follows：i. Enhancement of statistical power by increasing sample size；ii. Determination of uncertainty, when discrepancies among study results are present；iii. Improvement of effect size such as effective-size or effective-number；iv. Discovery of answer to what one did not understand at the early stage of a study；and etc. Resultant outcomes obtained from randomized clinical studies with meta-analysis are considered very important for implementation of EBM, with a rating as level 1 evidences in the classification of Agency for Healthcare Research and Quality (its name was changed in 1999 from Agency for Health Care Policy and Research).

In consideration of above mentioned, as one of the techniques to establish the evidence of Kampo medicines, we adopted to conduct meta-analysis for Kampo medicines and then reviewed the resultant outcomes obtained in this study. We chose Kyukichoketsuini（KCI）as the study drug, because in our previous exploratory study on the pharmacoeconomic analysis of Kampo medicines, we confirmed that several randomized clinical studies have been conducted for it. And we assessed its usefulness in postpartum control in comparison with Methylergometrine Maleate（MME）.

Ⅱ. Methods

We searched the documents of clinical study on
Fig. 1 Screening of articles

Fig. 2 The Chalmers score according to references
KCI in "Igaku Chuo Zasshi" published between year 1983 to 2004. As the search formula, kyukichoketsu in (Japanese or English) /AL was used. Also we searched them in Medline published between year 1966 to 2004 from Ovid Online data base using a key-word, "Kyukichoketsu in". Then among all literatures obtained, we adopted those literatures which met the all following criteria:

A) An Original article
B) An randomized controlled trial
C) A study on puerperants consisted of primiparous and multiparous who had normal vaginal delivery.
D) A study which uses KCI as a investigational drug and also MME as a control drug.
E) More than one assessment parameter among height of the uterine fundus, breast-milk lactation, and the severity of post-labor pains was reviewed for the efficacy of the treatment.

We analyzed the articles matching to above criteria, and then extracted necessary data. Data contents involved the background of study targeted patients; sample numbers; randomized methods; masking methods; the dosing methods of investigational and control drugs including dose, dosing frequency per day, and dosing days; concomitant medications; and study endpoints. If study end points data were shown just graphically without numerical values, we measured points on the graph with calipers and converted graphical values to numerical values. The extracting procedure of these data were done independently by another investigator than one who integrated the data to keep study validity.

Then we assessed the quality of extracted article using Chalmers' scoring system published in 1981[1]. We use our ratings on the assessment not for weighting study, but for referring information to integrate extracted articles, because it was said that no appropriate rating system which could excluded subjective variation caused by a rater etc. was present now. When we could extract multiple articles which focused on the same study end points, we integrated their measurement outcomes with a meta-analytic method. Microsoft® Office Excel 2003 version was used to make a calculation. Nonuniformity of outcomes among articles was tested with Cochran's Q test at 5% of significance level. When no nonuniformity was observed, a summary odds ratio and its 95% coincidence interval were calculated with the Der Simonian-Laird method[8], a random effects model. With the result of these, we statistically assessed the usefulness of KCI in the height of the uterine fundus, breast-milk volume, and the severity of post-labor pains.
### Included Studies

<table>
<thead>
<tr>
<th>Height of the uterine fundus (cm; Mean+/−SD) on day 4</th>
<th>Height of the uterine fundus (cm; Mean+/−SD) on day 5</th>
<th>Breastmilk volume (ml/day; Mean+/−SD) on day 4</th>
<th>Breastmilk volume (ml/day; Mean+/−SD) on day 5</th>
<th>Post-labor pains (Number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.4+/−0.7</td>
<td>−</td>
<td>83.8+/−21.2</td>
<td>−</td>
<td>7</td>
</tr>
<tr>
<td>11.8+/−2.8</td>
<td>−</td>
<td>92.1+/−7.1</td>
<td>−</td>
<td>14</td>
</tr>
<tr>
<td>9.7+/−3.0</td>
<td>8.9+/−2.4</td>
<td>−</td>
<td>−</td>
<td></td>
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<tr>
<td>11.1+/−3.2</td>
<td>10.5+/−2.7</td>
<td>−</td>
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<tr>
<td>9.6+/−2.2</td>
<td>9.7+/−2.8</td>
<td>243.7+/−142.5</td>
<td>180.0+/−102.3</td>
<td>9</td>
</tr>
<tr>
<td>9.5+/−2.2</td>
<td>9.6+/−1.7</td>
<td>215.2+/−160.3</td>
<td>158.4+/−86.6</td>
<td>17</td>
</tr>
</tbody>
</table>

of post-labor pains with MME as control. The respective reasons we chose the study end points above were as follows: The decreased height of the uterine fundus was a judgment criterion for the postpartum involution of the uterus. A good volume of breast-milk was vital to feed a newborn. And less post-labor pains are necessary to attain the improvement of postpartum QOL.

Regarding sensitivity analysis, the calculation results of integrated odds ratio were analyzed with the Mantel-Haenszel method, a fixed effects model, and were compared to each other; then the impact of these results was assessed (sensitivity analysis).

On the other hand, those data which had the same study end points but had different assessment methods were investigated for the impact on their conclusions by adjusting the extracting methods and implementing sensitivity analysis (sensitivity analysis).

### III. Results

1. Research results According to our research methods, 44 articles were extracted consisting of 42 articles from “Igaku Chuo Zasshi” and 2 articles from "Medline". Among them, 5 articles met inclusion criteria. Of 2 articles out of the 5 analyzed, the same clinical study from different points of views and with the same data were obtained, thus we employed one from which more study end points were available. This resulted in total 4 articles for analysis targets (Fig.1).

2 Qualitative assessment of the articles Chalmers’ scoring system which had maximum 100 points gave the 4 articles 22, 21, 28, and 32 points respectively (Fig.2). We defined that each target article was almost the same in quality due to this results, thus, we considered no differentiation of the articles was required when we integrated them. Regarding the randomization methods of them, one article adopted envelope method, another alternating assignments, and remaining two had no description. No article adopted masking method among analysis target articles.

3 Articles’ contents Among 4 articles each dose and daily dose of KCl and MME were the same, however, respective dosing days of KCl varied from 5 to 28 days while those of MME were the same 5 days. Therefore, we limited the study target period as 5 days starting from the postpartum date and extracted all data for each study end point so that we could compare the end point among articles. This led to the re-
Fig. 3  Mean difference (Height of the uterine funds: Day 4)

Fig. 4  Mean difference (Height of the uterine funds: Day 5)
sults that the same study endpoints among total 4 articles were found in 3 and 2 articles dealing with the height of the uterine fundus on postpartum day 5 and in 3 with the severity of post-labor pains (Table.1).

4 Nonuniformity test No study endpoint with a statistical nonuniformity was observed in analysis in this present study.

5 Meta-analysis

5.1 Comparison of the height of the uterine fundus on postpartum day 4. There were 3 arti-
cles which compared the height of the uterine fundus on postpartum day 4. Among them, no statistical significance was shown with average difference at integration, −0.54 (95% CI, −1.31 to −0.23). Thus, usefulness of KCI over MME was not found (Fig.3).

5.2 Comparison of the height of the uterine fundus on postpartum day 5. There were 2 articles which compared the height of the uterine fundus on postpartum day 5. Of them, no statistical significance was shown with average difference at integration, −0.79 (95% CI, −2.45 to −0.88). Thus, usefulness of KCI over MME was not observed (Fig.4).

5.3 Comparison of breast-milk volume on postpartum day 4. There were 2 articles which compared breast-milk volume on postpartum day 4. Among them, statistical significance was shown with average difference at integration, −8.20 (95% CI, −16.17 to −0.23). This result showed that KCI caused significantly less breast-milk volume than MME on postpartum day 4 (Fig.5).

5.4 Comparison of breast-milk volume on postpartum day 5. There were 2 articles which compared breast-milk volume on postpartum day 5. Of them no statistical significance was observed with average difference at integration, 6.23 (95% CI, −0.48 to 12.93). Therefore, usefulness of KCI over MME was not observed (Fig.6).

5.5 Comparison in the number of patients with the severity of post-labor pains. There were
3 articles that compared the severity of post-labor pains. Each article had different assessment standards in post-labor pains. Each consisted of “the number of patients who felt post-labor pains as suffering”, “the number of patients who took an internal analgesic drug”, and “the number of patients whose post-labor pains were classified by Visual Analogue Scale (hereinafter referred to as VAS) values ranging 1 to 10 points”. Although these post-labor pains did not show completely the same event, we decided to integrate them into “the number of patients who felt post-labor pains as suffering”, when implemented meta-analysis. Then, we extracted data based on the hypothesis that “the number of patients who took an internal analgesic drug” was almost the same as “the number of patients who felt post-labor pains as suffering”, and integrated both the data directly. Regarding “the number of patients by VAS values”, we made a hypothesis that the number of patients who marked 3 or more than 3 scores of VAS values on postpartum day 1 when the maximum numbers of them were included was almost the same as “the number of patients who felt post-labor pains as suffering”, and then integrated both the data. These procedures resulted in 0.32 (95% CI, 0.17~0.60) of integrated odds ratio consisted of “the number of patients who felt post-labor pains as suffering” in the 3 articles, when KCI was compared to MME, and showed the statistically significance of KCI for MME. This demonstrated that KCI significantly more decrease post-labor pains than MME (Fig.7).

6 Sensitivity analysis

6.1 Sensitivity analysis(1) Severity of post-labor pains were analyzed in sensitivity analysis using a fixed effects model (the Mantel-Haenszel method). The resulting odds ratio, 0.32 (95% CI, 0.17~0.60), with this method was approximately equivalent from that of a random effect model (the DerSimonian-Laird method). Therefore, we considered the both analytic methods should not have caused any different results.

6.2 Sensitivity analysis(2) As mentioned above, while in the assessment of the severity of post-labor pains we used 3 or more than 3 of VAS values as “the number of patients who felt post-labor pains as suffering”, in this sensitivity analysis we changed score of VAS values to 5 or more than 5 scores and analyzed data using the random effects model (the DerSimonian-Laird method). The resulting integrated odds ratio, 0.32 (95% CI, 0.16~0.63), by this analysis was approximately equivalent from that in the setting with 3 or more than 3 of VAS values. In addition, the fixed effects model (the Mantel-Haenszel method) also showed almost the same integrated odds ratio, 0.30 (95% CI, 0.15~0.60). Thus, we concluded the both analytic methods should not have caused any different results (Fig.8).

IV. Discussion
This study demonstrated that KCI could significantly alleviate post-labor pains compared with MME. This result may be obtained by using meta-analysis with enhanced statistic power to emphasize the evidence of alleviating post-labor pains that had already been shown as statistic significant among 3 articles.

However, contrary to the result above, meta-analysis denied the statistical significance (p=0.0071) of the height of the uterine fundus on postpartum day 5 which had been noted in one article. And the statistical significance of the height of the uterine fundus on postpartum day 4 was neither found in articles nor in meta-analysis. With these results, we considered the effectiveness of KCI for the involution of the uterus was almost equivalent to that of MME.

It is said that the beneficial effects of increased lactation of breast-milk volume involve the better growth of infants due to increased breastfeeding volume, consciousness raising of motherhood due to increased breastfeeding volume and frequency, inhibition of the development of stasis mastitis, and etc. Between 2 articles which compared lactation of breast-milk volume between KCI and MME, one article showed KCI caused more, however, while another noted MME did more. On this subject we conducted meta-analysis to determine the incompatibility between the results of 2 articles, and elicited the result that KCI produced significantly lower breast-milk volume lactation with integrated odds ratio: −8.20 (95% CI, −16.17~−0.23). This was considered a negative result on the effectiveness of KCI. However, the results of meta-analysis of breast-milk volume lactation on day 5 demonstrated more volume in KCI group with integrated odds ratio, 6.2276 (95% CI, −0.48~12.93) no marked significance.
Since the combination of study articles was different
between for on day 4 and day 5 analysis, the opposition
results was observed between day 4 and day 5.

In addition, we thought the study on safety should
be implemented to refer to the total usefulness in
postpartum control, however, we could not employ
meta-analysis from the randomized controlled study
at this time, because only one article was present
which had the assessment items on safety as a meas-
urement outcome among 4 targeted articles.

MME is one of the ergo-alkaloids and the deriva-
tive of the ergotamine which has been used for an
induction study for coronary spasm. As compared
with the ergotamine, its effect is stronger in uterine
contraction effect and weaker in vasoconstriction ef-
fect. It is said that even its weak vasoconstriction ef-
fect sometimes induce the angina pectoris, myocar-
dial infarction, atriocentric block by contracting
coronary artery[11]. MME also may cause side effect
such as increased blood pressure, nausea and vom-
ting, and chest pressure sensation. Therefore, the
package insert of MME indicates that the admin-
istration of it should be contraindicated for the pa-

tients with a serious ischaemic heart disease or the
history of it, and be carefully given for the patients
with high blood pressure, a heart disease or an oc-
cclusive angiopathy[20].

Whereas KCl, written in “Man-byo-kai-shun”, is
said that according to the idea of the Kampo medici-
ne it can recover patients into normal physiologic
conditions by nourishing Qi and blood, and by
quickening the blood. It is composed of 13 crude
drugs: Botan-pi, Yakumo-so, Senkyu, Touki, Jio,
Kou-bushi, Uyaku, Chinp, Shoukyo, Byakujutsu,
Bukuryo, Taiso and Kanzo. As serious side effects
written in the KCl’s package insert, KCI includes
pseudo-aldosterone and myopathy[20], however, these
are not solely resulted in KCI preparation, but in all
preparations which contain Kanzo. Although ano-
rexia and stomach discomfort are also referred as
the other side effects in it, these are also one of the
general side effects in Kampo preparations. As far
as a package insert is concerned, KCI may be safer
than MME. In order to prove the usefulness in post-
partum control of KCI further more in the future, it
may be required that those randomized clinical stud-
ies that can accumulate the measurement outcomes
for safety, and meta-analysis that can analyze safety
outcomes.

As was referred earlier, meta-analysis is proved
with high appropriateness as level 1 evidence in
AHRQ classification. But as a matter of course, even
meta-analysis can not provide perfect evi-
dences with the presence of bias being affected from
unpublished studies. The present study is not per-
fecly free from this kind of publishing bias. We
may need to fully take care of this point of view,
when we still use meta-analysis method to establish
the evidences of Kampo medicines.

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