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# Preventive and curative effects of acupuncture on the common cold: a multicentre randomized controlled trial in Japan

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**Summary**

*Objective:* To determine the preventive and curative effects of manual acupuncture on the symptoms of the common cold.

*Method:* Students and staff in five Japanese acupuncture schools ($n = 326$) were randomly allocated to acupuncture and no-treatment control groups. A specific needling point (Y point) on the neck was used bilaterally. Fine acupuncture needles were gently manipulated for 15 s, evoking *de qi* sensation. Acupuncture treatments were performed four times during the 2-week experimental period with a 2-week follow-up period. A common cold diary was scored daily for 4 weeks, and a common cold questionnaire was scored before each acupuncture treatment and twice at weekly intervals. A reliability test for the questionnaire was performed on the last day of recording.

*Results:* Five of the 326 subjects who were recruited dropped out. The diary score in the acupuncture group tended to decrease after treatment, but the difference between groups was not significant (Kaplan–Meier survival analysis, log rank test $P = 0.53$, Cox regression analysis, $P > 0.05$). Statistically significantly fewer symptoms were reported in the questionnaire by the acupuncture group than control group ($P = 0.024$, general linear model, repeated measure). Significant inter-centre ($P < 0.001$, general linear model) and sex ($P = 0.027$, general linear model) differences were also detected. Reliability tests indicated that the questionnaire with 15 items was sufficiently reliable. No severe adverse event was reported.

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*Conclusion:* This is the first report of a multi-centre randomized controlled trial of acupuncture for symptoms of the common cold. A significantly positive effect of acupuncture was demonstrated in the summed questionnaire data, although a highly significant inter-centre difference was observed. Needling on the neck using the Japanese fine needle manipulating technique was shown to be effective and safe. The use of acupuncture for symptoms of the common cold symptoms should be considered, although further evidence from placebo controlled RCTs is required.


## Introduction

The common cold is common and, although a minor condition, is a major cause of absence from work and school. The medical cost for the treatment of the common cold is relatively high.[1,2] In the United States, adults catch on average between two and four colds each year and in 1984 the medical cost was estimated at over 35 billion dollars.[3] So a preventive therapy for this minor illness would be very welcome.

The common cold is caused by one of a several forms of rhinovirus, though antiviral drugs have been shown to be ineffective.[4] Numerous kinds of other treatment for the common cold have been proposed, and clinical research has been undertaken on oral Vitamin C,[5,6] antihistamine drugs,[7] zinc compounds,[8,9] nasal spray of chemicals,[10–12] and garlic supplement,[13] although their effects are not promising and several treatments have various side-effects.[14] No effective treatment has been established for the common cold,[15] so management consists of patient education to reduce the cost of medical interventions.[16,17]

Anecdotally, we noticed that patients attending our acupuncture clinic frequently stated that they did not catch a cold during the period when they were receiving acupuncture treatment. These reports by individuals are common and Chinese literature has suggested that the common cold is an indication for acupuncture treatment.[18,19] However, there have been no reported clinical trials of acupuncture for the symptoms of common cold until our pilot study, which clearly demonstrated the positive effects of acupuncture treatment to the neck on common cold symptoms.[20] In the present study, we planned to conduct a multi-centre randomized controlled trial (RCT), based on an estimate of adequate sample size. As it was the first multi-centre RCT, we decided to examine the overall effects of acupuncture on the symptoms of the common cold, compared with a no-treatment control group instead of a sham acupuncture group.

## Methods

### Design and settings

The present study was a multi-centre RCT with two parallel arms. Students and staff of four Japanese acupuncture schools and one university were included after giving written informed consent. This study was approved by the local ethics committees. Subjects who had symptoms of influenza were excluded. Participants were registered and randomly allocated to acupuncture or control (no-treatment) groups using a computer program. Subjects were randomized by centre to permit subgroup analysis.

### Intervention

An acupuncture needle (disposal stainless needle, 0.14 mm diameter, Seirin Co. Ltd, Japan) was gently inserted into Y points (special point) on the neck bilaterally. The points are located about 1.5 cun (the width of finger) lateral to the midline. The Y point was used by a famous Japanese acupuncturist, Yoneyama Hirohisa for treating pain in the throat. The anatomical structure of the Y point has not been clarified, but it is located near the submandibular triangle. The occurrence of *de qi* sensation projecting deep into the deep throat was taken as a sign of the correct location and direction of insertion of the needle. The acupuncture needle was gently manipulated (using the 'sparrow pecking' technique) to induce *de qi* and continued for 15 s bilaterally. Acupuncture treatments were performed twice a week for 2 weeks (4 treatments), and follow-up period was set for 2 weeks. The trial ran for four weeks starting in the last week of January.

### Outcome measures

The main outcomes were the incidence of the common cold reported in a common cold diary (CCD) and the rating of symptoms of 15 items of the common cold questionnaire (CCQ). Subjects were asked to record the daily condition of their common cold

Table 1 Questionnaire for common cold symptoms (CCQ).

| | | |
|---|---|---|
| 1 | Snivel | None, slight, moderate, severe |
| 2 | Sniffle | None, slight, moderate, severe |
| 3 | Throat pain | None, slight, moderate, severe |
| 4 | Paresthesia | None, slight, moderate, severe |
| 5 | Cough | None, slight, moderate, severe |
| 6 | Sputum | None, slight, moderate, severe |
| 7 | Sneeze | None, slight, moderate, severe |
| 8 | Shiver | None, slight, moderate, severe |
| 9 | Head ache | None, slight, moderate, severe |
| 10 | Muscle-joint pain | None, slight, moderate, severe |
| 11 | Nausea-vomit | None, slight, moderate, severe |
| 12 | Diarrhea | None, slight, moderate, severe |
| 13 | Fever | None, slight, moderate, severe |
| 14 | Degree of common cold | None, slight, moderate, severe |
| 15 | General condition | None, slight, moderate, severe, worst |

in a binary form (yes or no) for 4 weeks in the CCD. They were also asked to answer the CCQ consisting of 15 categorical items with four or five levels (Table 1). The questionnaire was completed four times on each day of acupuncture treatments (the control subjects also did this on the same days) and twice weekly after the final treatment. A total of six CCQ records were obtained in each subject. On the final recording day, the same questionnaire was completed twice at 90 min intervals to confirm its test-retest reliability.

In one centre, blood samples were collected from the subjects, after obtaining additional informed consent, to measure blood cell counts, CD markers and cytokines. These data will be reported as a separated paper.

### Data analysis

Common cold diary (yes/no) data from both groups were analyzed initially by Kaplan–Meier's survival analysis, then Cox regression analysis was performed to analyze the data in detail. An analysis by the general linear model (GLM) of repeated measures was also used[21,22] instead of the conventional repeated measure of ANOVA, in order to analyze various parameters such as group, sex, centre and interactions simultaneously. Egret (Cytel Inc.), SPSS 7.5 for Windows and Medical Pack (SPSS Inc.) were used for data analysis.

## Results

A total of 326 subjects were registered and allocated to either the acupuncture group ($n = 163$, 99 males, 64 females) or the control group ($n = 163$, 101 males; 62 females). There was no significant difference between the groups regarding age and sex (Table 2). Five subjects dropped out (three in the acupuncture group and two in the control group).

### Common cold diary (CCD)

The numbers of subjects positive for the common cold at enrolment were 28 in the acupuncture group and 36 in the control group. There is no statistically significant difference between the groups (chi-square test, $P > 0.05$). Fig. 1 shows the Kaplan–Meier survival functions of the subjects who had no common cold symptoms in the diary (CCD) in the two groups. During the experimental period (14 days), the survival probability of the acupuncture group reduced more rapidly than that of the control group, but this tended to reverse at the end of trial (14 days follow-up period). There is no statistically significant difference between

Table 2 Results of the random allocation to the acupunture or control group.

| Center | Acupuncture | | | Control | | |
|---|---|---|---|---|---|---|
| | Male | Female | Total | Male | Female | Total |
| A | 34 | 9 | 43 | 32 | 10 | 42 |
| B | 23 | 12 | 35 | 24 | 11 | 35 |
| C | 15 | 18 | 33 | 17 | 17 | 34 |
| D | 16 | 20 | 36 | 17 | 19 | 36 |
| E | 11 | 5 | 16 | 11 | 5 | 16 |
| Total | 99 | 64 | 163 | 101 | 62 | 163 |
| Mean age | 28.2 | 28.8 | 28.5 | 28.9 | 28.2 | 28.6 |
| S.D. | 7.4 | 8.4 | 7.8 | 8.2 | 7.6 | 8 |

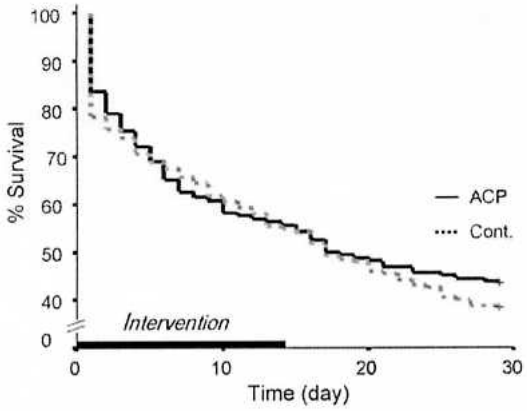


**Figure 1.** Survival curves of the acupuncture and control groups. At each time point, subjects who entered "yes" in the CCD were deleted from the survivors. Acupuncture: solid line; control: dotted line.

the survival curves (log rank test, $P=0.53$). Mean and 95% CI of acupuncture and control group were 17[15,19] and 16,[15,18] respectively. The Cox regression analysis was performed to evaluate the influence of sex, age and group. The probabilities of the differences of sex, age and group in the total sample were 0.834, 0.583 and 0.721, respectively. No significant difference between five centres in the preventive effect was detected ($P=0.07$, 0.52, 0.66, 0.76, 0.87, respectively).

Fig. 2 shows a profile plot of estimated marginal means (EMM) of the CCD incidence by GLM analysis. The EMM represents the interaction of the group (acupuncture and control) and time (28 days) on the CCD incidence, which is also modified by the covariates such as sex and centre. Higher values of EMM indicate a higher incidence of common cold. In the acupuncture group (solid line), EMM values tend to decrease during the acupuncture stimulation period (intervention: thick horizontal bar).

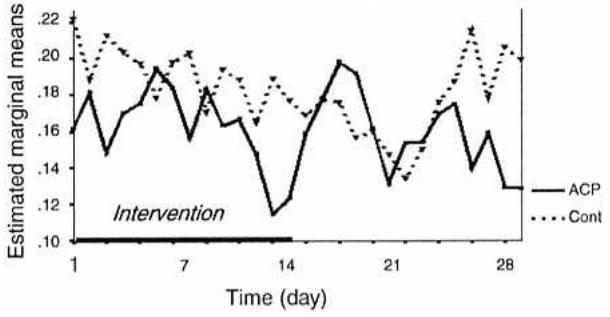


**Figure 2.** A profile plot of the CCD scores by day and group. In the acupuncture group, a marked decrease of the estimated marginal means (EMM) of the CCD score was observed at the end of the treatment. Horizontal bar shows intervention period (14 days) Acupuncture: solid line; control: dotted line.

**Table 3** Summary of the general liniear model (GLM) analysis on the CCD and CCQ.

| Center | CCD | CCQ |
|---|---|---|
| A | $P=0.198$ | $P=0.035$ |
| B | $P<0.001$ | $P<0.001$ |
| C | $P=0.360$ | $P=0.029$ |
| D | $P=0.945$ | $P=0.643$ |
| E | $P=0.644$ | $P=0.218$ |
| Total | $P=0.325$<br>Center × group,<br>$P=0.003$ | $P=0.024$<br>Sex differentiation,<br>$P=0.005$ |

Missing data were replaced by surrounding medians.

On the other hand, EMM values of control group (dotted line) gradually decrease with fluctuation for about 20 days then rapidly increase at the end of trial (28 days).

Table 3 summarizes the significance level in each of the five centres calculated by GLM analysis using CCD and CCQ data. Although no significant group difference was observed (summed data of five centres, $P=0.325$), a highly significant positive effect of acupuncture was detected in centre B ($P<0.001$). In centre A, a tendency towards a negative effect of acupuncture was observed although it was not statistically significant ($P=0.198$). A significant interaction between group and centre ($P=0.003$) was also detected. This indicates that the effects of acupuncture depended on the centre in which it was given.

## Common cold questionnaire (CCQ)

The effects of acupuncture on EMM during the acupuncture treatments (four sessions) and 2 weeks of follow-up are shown in Fig. 3. The smaller val-

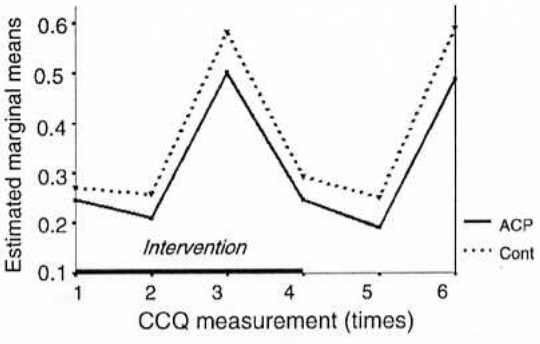


**Figure 3.** A profile plot of the CCQ scores by time and group. In the acupuncture group, EMM values were smaller than those of the control group in all six measuring points, indicating positive effects. Horizontal bar shows intervention period (four treatments within 2 weeks) Acupuncture: solid line; control: dotted line.

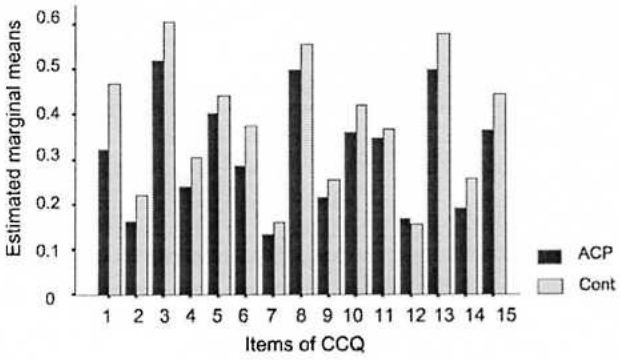


**Figure 4.** A profile plot of the CCQ scores by items and group. In the acupuncture group, the EMM values of all items (1–15) were smaller than that of the control, except for the item 12. This indicates that the positive effects of acupuncture are not restricted in the specific symptom such as throat pain.

ues of EMM for the acupuncture group (solid line) indicate that acupuncture reduced the symptoms recorded by CCQ compared with those of the control group (dotted line). Fig. 4 shows the 15 items of EMM for each group. Among the 15 items, acupuncture (solid column) shows smaller values for EMM than the control group (grey column) except for the item 12 (diarrhoea), indicating that acupuncture tended to improve almost all items in the CCQ.

Table 3 also summarizes the results of analysis by GLM using CCQ (15 items) data. There was a significant positive effect on the symptoms of common cold in the acupuncture group ($P=0.024$, between-group comparison). However, it should be noted that a significant negative result ($P=0.035$) was detected in centre A. A significant difference between the two sexes ($P=0.005$) was also detected.

## Reliability of the CCQ

A reliability test was undertaken on the final day of recording. Cronbach's alpha value for the repeated CCQ measurement was 0.892 (0.90, 0.94, 95% CI) and test of reliability using ICC (intra-class correlation coefficient) was 0.998. These results clearly show that the CCQ we used was sufficiently reliable for the evaluation of common cold symptoms.

## Incidence of adverse events

A total of 1280 acupuncture needle penetrations were made in this RCT and 10 minor adverse events were reported. They included subcutaneous bleeding (four cases), paraesthesia in the throat (five cases), and throbbing (one case), giving an incidence rate of 0.8%. No severe adverse events were reported.

# Discussion

This is the first multi-centre RCT to investigate the effects of acupuncture on the symptoms of common cold and a significantly positive effect was demonstrated in the CCQ, though not in the CCD, compared with the no-treatment control group.

## No-treatment control group and volunteer bias

In the present clinical trial, students and staff of acupuncture schools were used as subjects. The majority of subjects had previous experience of acupuncture treatment and were familiar with the sensation elicited by acupuncture needling (*de qi*). So we used no-treatment controls instead of sham treatment such as minimal acupuncture.[23] We would like to emphasize that previous experience of acupuncture and confidence in the efficacy of acupuncture influences the effect of acupuncture.[24] When we started the present RCT we considered it was more important to demonstrate the effects of acupuncture as a whole (including non-specific effects) on the symptoms of common cold as this is the first RCT in this area.

We assumed that the subjects' expectation of the efficacy of acupuncture was very strong and that a clear difference between the outcome of the acupuncture and control groups might be seen. Our expectation seems to have been rejected. The effects of acupuncture were not obvious and a statistically significant negative effect was found in centre A, where the pilot study had been done with clear positive results.[20] The reason why a significant negative result occurred in centre A is not clear, but suggests that the subjects' expectation may not have been as strong as we had supposed. We could not, of course, exclude this possibility in our results. Another factor that should be considered was the fact that the subjects in the no-treatment control group may have received acupuncture and moxibustion treatments in the course of their training during the experimental periods, which might reduce the difference between the groups. The differences in training among different acupuncture schools might also lead to difference outcomes, although random allocation of subjects might reduce this effect.

The major benefit of using student subjects in this RCT was the very small dropout rate. Our consent form clearly informed subjects that entry and withdrawal were completely voluntary. We paid only a small amount of money (¥2000) to registered subjects to cover their expenses and compensate

them for their time, in order not to offer any financial inducement. We found the majority of subjects were interested in the methodology of this RCT, and understood the importance of generating evidence for the efficacy of acupuncture by RCTs. This was important from an educational point of view and probably contributed to the lack of dropouts.

## Effect of acupuncture on the symptoms of common cold

In this RCT a significant decrease in common cold symptoms was produced by acupuncture needle manipulation on the neck. Various drugs and procedures have been used in attempts to treat the common cold, but no effective treatment has yet been established.[4–13] It is therefore significant that acupuncture had a positive effect and it may be a possible alternative treatment for the common cold. The mechanism of acupuncture for common cold symptoms has not been clarified. The fundamental pathological processes of the common cold are believed to be the response to infection by rhinoviruses. It is therefore reasonable to assume that acupuncture reduces common cold symptoms by activating the immune system.[25–28] Although it has been pointed out that a single acupuncture treatment had no immediate effect on immune activity,[29] our results demonstrated that some cumulative effects were observed after multiple acupuncture treatments (see Fig. 1).

In this study we used the Y point, which has been used for pain relief of the throat, and we expected strong and specific effect on the item 3 (throat pain) in the CCQ. However, the effects of acupuncture were not restricted to throat symptoms (see Fig. 4) since almost all items were improved in the acupuncture group. This supports the suggestion that general effects such as the potentiation of the immune system might be produced by needling the Y points.

## Inter-centre difference of acupuncture effects and sex difference

It was obvious that the effectiveness of the acupuncture treatment was quite different in each centre. The most surprising fact was that acupuncture had a significantly negative effect in centre A, where clear positive effects were demonstrated in the pilot study. The technical level of acupuncture treatment at that centre is considered to be of a very high standard and their staff are involved in training at the other centres, so technical issues should not be the cause of the anomalous result. A difference in the interaction between the acupuncturist and the subjects in each centre is a possible reason for the difference in outcome.

A significant sex difference in common cold symptom was also detected, with the effects of acupuncture on females tending to be smaller than on males. This suggests that the effect of acupuncture on the symptoms of the common cold might be dependent on sex hormones. However, as far as we know, there have been no reports on sex differences in acupuncture efficacy, although sex differences in the incidence of fibromyalgia is well known.[30] One possible explanation for this difference is that the acupuncturists might be have been overly careful to avoid the bleeding in female subjects, as the Y points bleed easily, and may have given insufficient stimulation. If the sex difference is based on the actual mechanisms of acupuncture, it is a very interesting phenomenon and needs to be clarified in a future study with an appropriate protocol.

## Measurement of symptoms of common cold and reliability of CCQ

We used two types of questionnaire, the CCD yielding binary information about the incidence of common cold, and the CCQ. The comparison of CCD and CCQ data showed several contradictions in the questionnaire. The subjects who answered "no" in the CCD tended to mark "slight or moderate" in several items of the CCQ. Fig. 5 summarizes the relation of the answers yes/no in the CCD and total count of the CCQ items (1–13). This kind of discrepancy might arise from the criteria each subject used to respond "yes" in the CCD. We need clearer in-

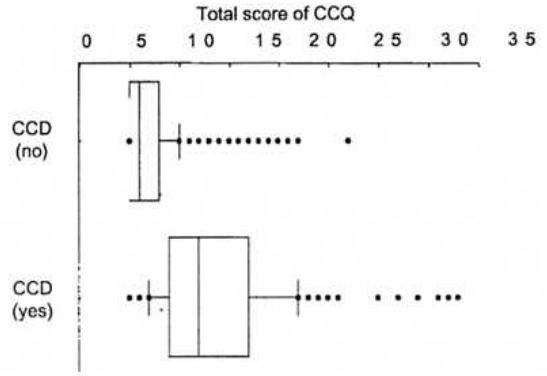


**Figure 5.** Relationship between the CCD counts and CCQ scores. The summed scores of CCQ (items 1–13) are shown in a box plot. The subjects who answered "no" in the CCD questionnaire responded with relatively high scores in the CCQ questionnaire. A negative response to CCD was not matched by absence of symptoms according to the CCQ.

structions with more precise definition for the CCD. On the other hand, the reliability of the CCQ was shown to be very high. The fact that a positive result was obtained in the present RCT using the GLM analysis of CCQ data and not by CCD data strongly supports the use of CCQ in future clinical trials.

## Acupuncture procedures and adverse effects

In the present study we chose the sparrow pecking technique to the Y points in the neck. The Y points are not standard acupuncture points, but have been frequently used to treat throat pain in the western area of Japan, and the present procedure (gentle sparrow pecking with a thin acupuncture needle), which is very common in Japanese acupuncture practice, has been shown to be effective in the pilot study of this RCT.[20] We had several training periods to learn the correct location and correct manipulation for eliciting the acupuncture sensation in the throat.

The Y point region in the neck is rich in blood vessels and nerves, but few adverse events such as subcutaneous bleeding (0.8%) were reported. This rate seems to be higher than that previously reported from Japan (0.14%), but this survey included acupuncture treatment to the body and extremities.[31] These data demonstrated the safety of fine acupuncture needling to the neck with gentle manipulation by the Japanese acupuncturists, although it may appear to be quite a dangerous manoeuvre.

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