Gingyogedokusan versus oseltamivir for the treatment of influenza: Bayesian inference using the Markov chain Monte Carlo method with prior pilot study data

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ABSTRACT

Aim: Gingyogedokusan (GGGS) is a herbal medicine approved for upper respiratory infections in Japan, and could be utilized for the treatment of influenza. We conducted a multi-center, prospective trial, comparing GGGS against oseltamivir in patients with influenza, but failed to include enough participants for conventional analysis. We further conducted a Bayesian analysis, however, using the Markov chain Monte Carlo (MCMC) method, by utilizing our original data.

Methods: We used our data from 2010 and 2011, which compared GGGS and oseltamivir. A total of 10 patients were diagnosed with influenza and enrolled in the study (six for GGGS and four for oseltamivir). We conducted MCMC to elucidate posterior distributions for outcomes. Outcomes were time to alleviation of symptoms, time to recovery of activity level, time to recovery of health status, and time to resolution of fever.

Results: Calculated mean time to alleviate symptoms was 3.99 days for GGGS, while it was 5.66 days in the oseltamivir group (difference of 1.66 days, 95% credible interval: −3.64 to 6.46). The posterior probability of the mean time for the oseltamivir group being longer than that for the GGGS group was 69%. Likewise, that probability was 81% for recovery of activity level, 86% for health status, and 24%, for fever resolution.

Conclusion: According to Bayesian analysis, GGGS appears to have superiority over oseltamivir in resolving symptoms, although fever may resolve earlier with oseltamivir use. This is a proof of concept study, to encourage further research into the efficacy of GGGS for the treatment of influenza.

KEY WORDS: Bayesian statistics, gingyogedokusan, influenza, oseltamivir

INTRODUCTION

Western medicines such as neuraminidase inhibitors or capsid-dependent endonuclease inhibitor are frequently used for the treatment of influenza, but they have several shortcomings. First, these medicines work only against influenza viruses, and are not effective against other pathogens causing influenza-like symptoms. Second, given that widely used rapid influenza diagnostic test kits (RIDT) are not very sensitive in detecting influenza [1], these medications might not be utilized for many patients who are judged not to have influenza on false-negative RIDT. Third, these medications may induce viral resistance over time if used excessively [2–7]. The cost and potential side-effects are also concerning, especially during the season when many develop the disease [8–10].

After pandemic influenza in 2009 (influenza A/pandemic H1N1 infection worldwide), we conducted a multi-center, randomized controlled trial to demonstrate the efficacy of gingyogedokusan (GGGS) compared with oseltamivir, the most popular neuraminidase inhibitor, for the treatment of influenza, to identify an alternative to conventional influenza treatment regimens. We were not, however, able to include a sufficient number of participants as scheduled, partly because there was an atmosphere of panic during and after the 2009 influenza pandemic in Japan, and because academic societies strongly...
recommended the use of neuraminidase inhibitors for all patients with influenza [11], although such practices were not necessarily common abroad [12,13]. As a consequence, assigning patients to a group that had no provision for neuraminidase inhibitors became almost impossible. With only a small number of participants, we ended up publishing the result as a pilot study, not proving the efficacy of GGGS, but rather suggesting the necessity for further studies [14].

While the frequentist approach handles point estimation and asks if a null hypothesis is rejected, the Bayesian estimation method uses an interval estimation approach and determines the likelihood of the null hypothesis being correct [15,16]. The Bayesian method allows us to determine how likely it is that there is a difference in treatment outcomes between GGGS and an ordinary neuraminidase inhibitor, unlike the previous pilot study.

We therefore used our original data in a stochastic mathematical model to calculate posterior distributions, in order to compare parameters on the treatment effectiveness of GGGS over oseltamivir.

**METHODS**

**Model**

The current study compared clinical outcome parameters between GGGS and oseltamivir for the treatment of influenza. Each parameter consisting of continuous variables in our original study was used in the present analysis, and we compared the posterior probability of the difference in means of each outcome, assuming them to have a normal distribution but different variances, as parameters mu[i] and sigma[i], respectively. We also assumed that the prior distribution of mu is non-informative prior, given that there was no previous clinical data with which to make an assumption of prior distribution. We set four separate sampling sequences, each consisting of 1000 random samples (including 500 samples discarded for convergence) to calculate posterior distributions and posterior means and variance (mu and sigma), and these means were compared for difference, in order to calculate the posterior distribution of the probability of GGGS being better than oseltamivir for each parameter. The region of practical equivalence (ROPE) was arbitrarily determined from −0.5 days to 0.5 days. The null value is declared to be rejected if the 95% highest density interval (HDI) falls completely outside the ROPE, and the null value is declared to be accepted if the 95% HDI falls completely inside the ROPE. All 95% credible intervals (CrI) were calculated using HDI. Obtained posterior means and their differences were evaluated using Gelman–Rubin statistics and visual inspection of the trace plot. We used R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and the probabilistic programming language Stan (Stan development team, https://mc-stan.org/) for all Bayesian analyzes.

**Medication**

Gingyogedokusan is a herbal medication containing extracts from plants and animal products. GGGS is approved for over-the-counter (OTC) use to treat upper respiratory infection in Japan. The GGGS preparation is a mixture of nine plants and one animal ingredient. The following were mixed with trehalose, magnesium aluminometasilicate, hydroxypropyl methylcellulose, anhydrous silicic acid, and corn starch to make a 7.5 g extract (daily dose for adults): Lonicera japonica Thunb. 4.26 g; Forsythia suspensa Thunb. 4.26 g; Mentha arvensis L.var.piperascens MALINV. 2.556 g; Schizonepeta tenuifolia Briq. 1.704 g; Glycine max Merr. (fermented soybean) 2.136 g; Glycyrrhiza globa 2.556 g; Platycodon grandiflorum A. DC 2.556 g; Lophatherum gracile Bronn. 1.704 g; seeds of Arctium lappa L. 2.136 g; and powdered horn of Saiga tatarica 0.132 g. GGGS was provided by Rhoto pharmaceutical (Osaka City, Osaka, Japan).

Oseltamivir is an oral neuraminidase inhibitor used for the treatment of influenza.

**Brief account of the previous study**

The previous study was an open-label, unblinded, randomized, multi-center, prospective comparative study, comparing GGGS with oseltamivir in the management of influenza and influenza like illness. The study was conducted at five outpatient clinics in the Kansai area, Japan. Subjects were healthy persons aged between 16 and 40 years old. Patients with influenza-like illness (ILI) were eligible for enrollment in the study. GGGS 2.5 g was given three times per day orally for 5 days, and oseltamivir 75 mg was provided twice daily orally for 5 days. The study was conducted from 12 January 2010 to 24 March 2011. Axillary temperature was recorded twice per day (morning and evening) and the severity of seven predetermined symptoms (nasal stuffiness, sore throat, cough, muscle aches, tiredness or fatigue, headache, and feverishness) were individually rated by the patients, daily up to day 7 using a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe) as in previous studies [17–19]. Additionally, an 11-scale subjective activity level (0, not able to do anything; 10, usual activity level) and subjective health status (0, the worst health status the patient can think of; 10, the best health status of the patient) was recorded daily up until day 7.

The study was originally planned to enroll approximately 100 patients, but it was decided to terminate the study in March 2011 due to an unexpectedly low number of subjects enrolled and a lack of funding.

The original study was approved by the Institutional Review Board at Kobe University School of Medicine (#988), and it was registered in the University Hospital Medical Information Network Clinical Trials Registry (trial number UMIN000002676).

Details of the trial have been reported previously [14].
Outcomes

The outcomes were all clinical: (i) time to recover from symptoms, defined as all symptoms recorded either absent or mild [18–20]; (ii) time to subjective activity level score ≥8; (iii) time to subjective health status ≥8; and (iv) time to body temperature resolution to <37°C for 24 h.

RESULTS

The original study enrolled 15 patients, of whom 10 were positive for influenza virus on reverse transcription–polymerase chain reaction (RT-PCR). All influenza viruses were A/pandemic H1N1 2009. Six of these patients were randomized to receive GGGS and four received oseltamivir. They all completed the treatment, and became well. The previous study noted that the overall effectiveness of GGGS was largely similar to oseltamivir, even in those with influenza infection confirmed on RT-PCR. For example, mean time to resolution of symptoms was 3.2 days for GGGS and 3.6 days for oseltamivir [14].

Patient characteristics are listed in Table 1. As per the inclusion criteria, no patient had any underlying medical condition.

For time to resolution of symptoms, posterior mean time to achieve outcome in the GGGS group was 3.99 days (95% CrI: 1.34–6.29), while it was 5.66 days in the oseltamivir group (95%CrI: 0.83–9.74; Fig. 1a). The difference of the

Table 1 | Patient characteristics

| Characteristics                  | GGGS Mean ± SD or n (%) | Oseletamivir Mean ± SD or n (%) |
|----------------------------------|--------------------------|---------------------------------|
| Age (years)                      | 27.0 ± 8.0               | 29.5d ± 5.8                     |
| Male                             | 5 (83)                   | 2 (50)                          |
| Completion of medication         | 6 (100)                  | 4 (100)                         |
| Virus type                       | A/pandemic H1N12009      | 6 (100)                         |
| Smoking                          |                          |                                 |
| Current smoker                   | 0                        | 1 (25)                          |
| Ex-smoker                        | 1 (17)                   | 1 (25)                          |
| Non-smoker                       | 5 (83)                   | 2 (50)                          |
| Baseline body temperature (°C)   | 37.8 ± 0.7               | 37.6 ± 0.7                      |
| Baseline symptom score           | 7.5 ± 5.6                | 7.5 ± 4.0                       |
| Baseline activity level          | 5.8 ± 2.1                | 5.3 ± 1.9                       |
| Baseline health status           | 4.0 ± 1.7                | 6.0 ± 2.2                       |

GGGS, gingyogedokusan.

Figure 1 | Posterior probability density function of true time to resolution of (a) symptoms, (b) activity level, (c) subjective health status and (d) fever in patients taking (-----) gingyogedokusan or (---) oseltamivir for the treatment of influenza.
also indicated convergence across four chains. Given that all values of Rhat were <1.1, and all trace plots of it fell inside ROPE, meaning that 95% fell completely outside the ROPE, thereby indicating that the null value was rejected.

With regard to subjective activity level, posterior mean time to achieve the outcome in the GGGS group was 4.89 days (95%CrI: 3.75–6.19), while it was 6.06 days in the oseltamivir group (95%CrI: 2.76–9.60; Fig. 1b). The difference in the means was 1.17 days (95%CrI: –2.69 to 4.53), and the posterior probability of the mean time for the oseltamivir group being longer than that for the GGGS group was 81%. For HDI, 3.93% of it fell inside the ROPE, again indicating that the null value was rejected.

For subjective health status, posterior mean time to achieve outcome in the GGGS group was 4.90 days (95%CrI: 2.90–6.95), while it was 6.62 days in the oseltamivir group (95%CrI: 1.67–9.74; Fig. 1c). The difference of the means was 1.73 days (95%CrI: –3.29 to 5.65), and the posterior probability of the mean time for the oseltamivir group being longer than that for the GGGS group was 86%. For HDI, 2.47% of it fell inside the ROPE, indicating rejection of the null value.

For time to resolution of body temperature, the posterior mean time to achieve outcome in the GGGS group was 3.51 days (95%CrI: 2.78–4.28), while it was 3.06 days in the oseltamivir group (95%CrI: 1.48–4.65; Fig. 1d). The difference of the means was –0.44 days (95%CrI: –2.32 to 1.28), and the probability of the mean time for the oseltamivir group being longer than that for the GGGS group was 24%. For HDI, 8.70% of it fell inside the ROPE, indicating rejection of the null value.

Obtained posterior means and their differences were checked for convergence using Gelman–Rubin statistics and by visually inspecting trace plot. Convergence was confirmed given that all values of Rhat were <1.1, and all trace plots also indicated convergence across four chains.

**DISCUSSION**

This secondary Bayesian analysis has demonstrated that for most clinical outcomes, the probability of GGGS being better than oseltamivir was high, although the posterior 95% HDI of differences for all parameters contained the value of zero. Therefore, even using the Bayesian method, the presence of difference between the two arms could not be definitively confirmed. Still, using this method, we were able to show that GGGS was more likely to be better than oseltamivir for several parameters. The only probability that was not high was the probability of GGGS being better than oseltamivir in time to resolution of body temperature: that is, 24%. Whether oseltamivir is better than GGGS in decreasing body temperature, or whether they are similar in that regard is a matter of debate, but the difference of only 0.44 days might be clinically meaningless, or it might be due to chance alone. Overall, we found that the probability of GGGS being better than oseltamivir for the treatment of influenza was high.

When we conducted the prospective trial, there was a shortage of participants due to the prevailing attitude that everyone with influenza should be treated with neuraminidase inhibitors, which precluded conventional frequentist statistical analyses with sufficient analytical power. Now we have re-analyzed the data using a Bayesian estimation method, which tells us how likely one group is to outperform the other for a single outcome, even in the case of a limited number of enrolled patients [16]. With existing data, we were able to assess posterior distribution using the MCMC method. The probability of GGGS being better than oseltamivir is derived from Bayesian statistics, which does not assume a null hypothesis, hence P-value, which is frequently used in clinical studies [15]. The method is an ideal alternative to conventional clinical trials, when the number of participants is not likely to have sufficient power to conduct statistical analysis based on a null hypothesis.

Obviously, the present results are not a finite conclusion on the superiority of GGGS over oseltamivir. Further prospective clinical trials to validate the present findings are necessary. The present findings, however, are a good proof of concept that justifies inclusion of traditional Chinese medicines such as GGGS in the alternative treatments for influenza, given that first-line medications do have their own problems, as already discussed.

In conclusion, we conducted secondary Bayesian analyzes on the effectiveness of GGGS for the treatment of influenza compared with oseltamivir, and the probability of GGGS being better in terms of clinical outcomes was high. Further studies are needed to confirm the present findings.

**CONFLICT OF INTEREST**

The previous, underlying, prospective trial was funded by Rhoto pharmaceutical, but no funding was received for the present study. The authors declare no other conflicts of interest.

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