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Original Article

Efficacy and safety of traditional Chinese medicine for the treatment of influenza A (H1N1): A meta-analysis

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Abstract

Background: In March 2009, the first reported case infected with influenza A (H1N1) virus was identified in Mexico. The World Health Organization officially declared the outbreak to be a pandemic on June 11, 2009. The objective of this study was to evaluate the efficacy and safety of traditional Chinese medicine (TCM) in the treatment of influenza A (H1N1) infection.
Methods: We electronically and manually searched electronic databases, reference lists, and conference compilations to identify randomized clinical trials that compared the treatment of influenza A (H1N1) using TCM with a control group receiving oseltamivir or antivirus therapy. The Jadad score was used to assess trial quality. Duration of viral shedding, time to defervescence, and effective rate were taken as outcome measurements; additionally, heterogeneity analysis and meta-analysis were performed.
Results: A total of 30 studies were included in our investigation, and these studies together included 3444 cases. Based on the Jadad score, each of these studies were divided as follows: high-quality studies (n = 3), medium-quality studies (n = 2), and low quality studies (n = 25). A meta analysis was performed, which indicated that the time to defervescence between the TCM treatment group and the control group was statistically significant, the duration of viral [Influenza A (H1N1)] shedding in the integrated Chinese and Western medicine subgroups was statistically significant, but it was not statistically significant between the two groups, the effective rate between the two groups was not statistically significant. A total of 18 studies described adverse drug reactions.
Conclusion: The results of our study indicated that the mean time to defervescence in the TCM treatment group was less than noted in the control group, and that the duration of viral [Influenza A (H1N1)] shedding in the integrated Chinese and Western medicine subgroups was less than that noted in the control group. However, the available evidence does not consider the fact that the difference in duration of viral shedding and effective rate between the two groups was statistically similar. No obvious adverse events were reported in the included studies.

Keywords: influenza A (H1N1); meta-analysis; traditional Chinese medicine; treatment

1. Introduction

The influenza virus, known to be a circulating pathogen within the human population since the 16th century, is notable for its unique ability to cause recurrent epidemics and global pandemics. The ability of this virus to undergo genetic reshuffling causes unpredictable changes in its antigens and the consequent immune response leads to recurrent epidemics of febrile respiratory disease every 1−3 years. In the 20th century, three influenza pandemics occurred, which resulted in the deaths of tens of millions of people. Each of these pandemics was caused by the appearance of a new strain of the influenza virus in humans.[1−3] In April 2009, the first reported

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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case infected with influenza A (H1N1) virus was identified in Mexico. This was a novel influenza virus strain that spread rapidly around the world. Influenza A (H1N1) virus infection is associated with a high risk of severe complications and is spreading more rapidly throughout the world than other reported seasonal influenza types.[2,3] The World Health Organization officially declared the outbreak to be a pandemic on June 11, 2009.[4] Oseltamivir (Tamiflu) and zanamivir (Relenza) are approved by the US Food and Drug Administration (FDA) for use against Type A and Type B influenza infections. However, it has been thought that the development of drug resistance may limit the clinical utility of these drugs in the future.[5] Chinese herbs, which are the most important component of traditional Chinese medicine (TCM), are widely used in China. Because of the limitation of health care resources and the high cost of antiviral drugs, Chinese herbs have been recommended for preventing and treating influenza in China, especially in the poorer regions. In October 2009, China's Ministry of Health issued *Guidelines for Management of Pandemic (H1N1) 2009 Influenza*, and recommended a series of Chinese herbs for the treatment of Type A influenza A (H1N1), including extracts from natural herbs, Chinese patent medicines (including herbal injection), and principles for individually prescribed herbal decoction.[6] However, there has been no critically assessed evidence such as systematic reviews or meta-analyses on the potential benefits and harms of medicinal herbs for influenza A (H1N1) treatment to justify their clinical use and recommendation.

2. Methods

2.1. Data source and search strategy

Literature searches were conducted in the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library, MEDLINE, Embase, and the Chinese BioMedical Literature Databases, Chinese National Knowledge Infrastructure, Chinese Scientific Journal Database, China's Important Conference Papers Database, and China's Dissertation Database from their inception to November 30, 2014. We also searched ongoing registered clinical trials listed in the Chinese Clinical Trial Registry website (http://www.chictr.org/), and the International Clinical Trial Registry of the US National Institutes of Health (http://clinicaltrials.gov/). The following search terms were used either individually or in combination: "influenza," "Influenza A (H1N1)," "Chinese traditional," "Chinese herbal," "oriental traditional," "herb," "herbal medicine," "clinical trial," and "randomized controlled trial."

Two authors (J.-H.L. and R.-Q.W.) conducted the literature search and study selection, and data were extracted independently. The extracted data included authors and title of the study, year of publication, study size, age and sex of the participants, details of methodological information, name and component of Chinese herbs, treatment process, details of the control interventions, outcomes (e.g., total effective rate), and adverse effects reported for each study. Disagreement was resolved by discussion, and consensus was reached through a third party.

2.2. Inclusion criteria

The following inclusion criteria were applied: (1) study cases were confirmed to be infected by H1N1 strain, according to diagnostic criteria that China's Ministry of Health has promulgated the "Influenza A (H1N1) Diagnosis and Treatment Program" (third edition, 2009); (2) study included key interventions for medical treatment, including any type of medicine, such as TCM; diagnosis and treatment using various types of Chinese medicine formulations (e.g., Chinese medicine, herbs, herbal extracts, and other active ingredients) or integrated TCM and Western medicine or these in combination with other therapies, with the control group receiving Western medicine or placebo; (3) randomized controlled trials (RCTs) or controlled clinical trials.

2.3. Exclusion criteria

Studies were excluded based on the following criteria: (1) if the study was a repetition of an existing study already presented in the published literature; (2) if the control interventions contained medicine; (3) if the study involved nonclinical trials of key interventions for TCM (such as animal testing, *in vitro* experiments); and (4) if the study control was unreasonable, without comparable clinical trials.

2.4. Extraction of data

Data were obtained directly from medical reports. When not explicitly stated, data were derived from graphs, tables, or charts included in the reports or data supplements. The data collected included the following: report location (country, state, and city), report dates, and authors. Extracted data included the duration of viral shedding, time to defervescence, and effective rate.

2.5. Trial quality assessment

Two authors (R.-Q.W. and W.-J.G.) evaluated the quality of the included trials. The quality of included trials was assessed using the Jadad Score to address the following criteria[7]: (1) description of the method for determining the sample size; (2) randomization; (3) description of generated random sequence; (4) description of allocation concealment; (5) blinded; (6) double blind; (7) describing the number of participants lost, where the lost or quit test proportion was less than 10%. If a study meets all of the aforementioned seven criteria, we assign the study a Jadad score of 7 (i.e., 1 point for each criterion met). The quality of trials was assessed as follows: total score of 0−2, low quality; total score of 3−4, medium quality. total score of 5−7, high quality. Two reviewers independently evaluated the studies. In the event of disagreement, further

discussion and consultation were undertaken involving a third-party opinion.

2.6. Statistical analysis

Data were summarized using relative risk (RR) with 95% confidence intervals (CIs) for binary outcomes, or mean difference (MD) with 95% CI for continuous outcomes. RevMan (version 5.0.17) was used for data analyses. However, meta-analysis was utilized if the trials had a good homogeneity of study design, participants, interventions, control, and outcome measures, which were assessed by examining I^2 (a quantity that describes approximately the proportion of variation in point estimates due to heterogeneity rather than sampling error). Publication bias were to be explored by funnel plot analysis if sufficient studies were found. If we had identified a sufficient number of randomized trials, we had planned to perform sensitivity analyses to explore the influence of trial quality on effect estimates. The quality components of methodology included adequacy of generation of allocation sequence, concealment of allocation, double blinding, etc.

3. Results

3.1. Description of studies

We retrieved a total of 287 citations from the aforementioned databased. Then, upon reading the titles and abstracts, duplicates were eliminated and research purposes in the papers were evaluated. At this point, 153 articles were available. Then studies, interventions, and outcome variables that did not meet the necessary requirements were eliminated, which brought down the available articles to 83. The total number was further reduced by 21 when studies using random method and unreasonable control groups were excluded. The final 30 studies included two English medical literatures. The remaining were all Chinese literature (Table 1). Again, we used the Jadad criteria to evaluate the quality of the evaluation; once the assessment was completed, three studies were designated as high-quality literature,[8–10] two as medium quality,[11,12] and 25 as having low quality.[1–7,13–38] None of the included studies reported sample size estimation, and had a maximum sample size of 300 cases,[32] a minimum of 46 cases,[35] and all studies were grouped using a stochastic approach but with no referral documents to hide a random allocation scheme. In addition, three studies described the use of blinding.[8,10,28] Although all of the studies reported use of a random method, only 10 detailed the random method used,[8,10–12,14,23,25,27,28,31] and five studies described participant lost and exit records.[8,10,11,21,28,37] There were 18 studies that described the adverse drug reactions,[8–12,14,15,19–21,23,26–28,30–32,34] eight studies that addressed experimental group therapy in Integrated Chinese and Western medicine studies,[11,17,21,25,34,36–38] and 22 that involved simple TCM treatment studies. In most of the studies, the control group received phosphate oseltamivir treatment (28 studies); only two studies used other antiviral drugs.[14,25] The basic characteristics of these studies are shown in Table 1.

3.2. Time to defervescence

There were 17 studies that reported time to defervescence, including three of the high- and medium-quality studies.[8,11,12] We first analyzed the high- and medium-quality studies. After the test for heterogeneity ($p = 0.13$, $I^2 = 50\%$), a lower heterogeneity was noted by applying a fixed effect model (MD = 0.02, $p = 0.87$), although the difference between the two groups was not statistically significant. The total sample size in these 17 studies was 1564 cases, and statistical analysis was performed by calculating MD. Subgroup 1 included studies employing pure Chinese medicine treatment ($n = 13$ studies): in five of these studies, the time to defervescence was more than the control group, but in the eight remaining studies, it was lesser than the control group. After the test for heterogeneity ($p = 0.23$, $I^2 = 21\%$), Subgroup 1 was found to have a lower heterogeneity. Application of the fixed effects model (MD = −0.11, $p = 0.009$) indicated that the difference was statistically significant (i.e., the time to defervescence in the pure Chinese medicine group was less than that of the control group). Subgroup 2 integrated Chinese and Western medicine therapy studies ($n = 4$). In this subgroup, the average time to defervescence was less than that noted in the control group. After the test for heterogeneity ($p = 0.82$, $I^2 = 0\%$), no heterogeneity was noted in Subgroup 2. Application of the fixed effects model (MD = −0.25, $p = 0.008$) indicated that the difference was statistically significant using a fixed effects model (i.e., the time to defervescence in the integrated Chinese and Western medicine treatment group was less than that of the control group). The data of Subgroups 1 and 2 were combined by hypothesis testing. An analysis of these data indicated statistical significance ($p < 0.05$). Based on this result, it is clear that average time to defervescence in the TCM treatment group was less than that of the control group (Fig. 1).

3.3. Duration of viral shedding

There were 12 studies that reported the duration of viral shedding, including two of the high- and medium-quality studies.[10,11] We first analyzed the high- and medium-quality studies. After the test for heterogeneity ($p = 0.47$, $I^2 = 0\%$), a lower heterogeneity was noted by applying the fixed effects model (MD = 0.26, $p = 0.06$), and the difference between the two groups was not statistically significant. The total sample in these 12 studies was 1469 cases, and statistical analysis in these studies was performed by calculating MD. Subgroup 1 included nine pure Chinese medicine studies, and Subgroup 2 included three integrated Chinese and Western medicine studies. After a test for heterogeneity ($p = 0.02$, $I^2 = 56\%$), Subgroup 1 was found to have a lower heterogeneity. Application of the fixed effects model (MD = 0.07, statistic $Z = 0.96$, $p = 0.34$) indicated that there was no statistical difference between the groups. After testing for heterogeneity ($p = 0.41$, $I^2 = 0\%$), Subgroup 2 was found to have a lower heterogeneity. To estimate the combined effect, subgroups within each study were combined to affect sample size,

Table 1
Study basic characteristics.

Study	Sample		Sex (male/female)		Age		Randomization	Random method	Sample size estimate	Lost and exit	Blind	Interventions		Treatment time (d)		Outcomes	Jadad scale
	Experimental group (E)	Control group (C)	E	C	E	C						E	C	E	C		
Chen et al[14] 2010	48	47	Unclear	Unclear	Unclear	Unclear	Yes	Random number tables	No	No	No	Fanggan decoction	Antiviral drug	3–5	3–5	A, B	2
Liu et al[15] 2010	64	60	30/34	35/25	19.8 ± 3.7	19.64 ± 1.4	Yes	Unclear	No	No	No	Lianhuaqingwen capsule	Oseltamivir	5	5	A, C	1
Liu et al[22] 2012	84	84	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	No	No	Modified Yinqiao Decoction	Oseltamivir	5	5	A	1
Tang et al[20] 2013	57	63	44/13	43/20	19.7 ± 0.2	20.6 ± 0.3	Yes	Unclear	No	No	No	Differential Treatment	Oseltamivir	5	5	A, B, and C	1
Zhang et al[24] 2011	30	30	17/13	16/14	22.77 ± 3.86	23.37 ± 3.99	Yes	Unclear	No	No	No	Prescription of TCM	Oseltamivir	5	5	A, B, and C	1
Zhang[25] 2011	40	40	26/14	25/15	32.1	31.1	Yes	Random-number tables	No	No	No	Lianhuaqingwen capsule + antiviral drug	Antiviral drug	Unclear	Unclear	A, B	2
Zhang et al[27] 2012	84	84	43/41	42/42	39.16 ± 12.18	37.25 ± 16.13	Yes	SAS ruanjian	No	No	No	Differential treatment	Oseltamivir	7	7	A, C	2
Zeng et al[11] 2011	59	55	31/28	25/30	18.52 ± 7.77	19.62 ± 5.58	Yes	Random-number tables	No	Lost 1 case	No	Maxinshigan soup	Oseltamivir	7	7	A, B, and C	3
Xiao et al[16] 2014	25	33	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	No	No	Tianlong compound preparation	Oseltamivir	3	3	A	1
Zhao et al[26] 2011	31	16	27/4	14/2	18.97 ± 2.88	20.06 ± 2.86	Yes	Unclear	No	No	No	Differential treatment	Oseltamivir	3	3	A and C	1
Zhao et al[17] 2011	26	24	22/4	21/3	21.35	21.77	Yes	Unclear	No	No	No	Tanreqing injection + oseltamivir	Oseltamivir	3–10	3–10	A	1
Zheng et al[21] 2010	52	51	35/17	33/18	17.17 ± 9.50	15.80 ± 9.04	Yes	Unclear	No	No	No	JuLa Qingdu decoction + oseltamivir	Oseltamivir			A, B, and C	1
Chen et al[12] 2011	31	55	18/13	30/25	20.06 ± 8.96	19.62 ± 5.58	Yes	Random number tables	No	Lost 2 case	No	Differential treatment	Oseltamivir	5	5	A an d B	3
Chen et al[8] 2010	31	22	18/13	9/13	19.87 ± 9.20	20.68 ± 6.97	Yes	Computer random number generator	No	Lost 2 cases	Single blind	Differential treatment	Oseltamivir	5	5	A an d B	5
Ma et al[19] 2010	133	147	87/46	84/63	22.8 ± 6.0	23.2 ± 8.3	Yes	Unclear	No	No	No	Differential Treatment	Oseltamivir	5	5–7	A and C	1
Han[18] 2011	144	65	80/64	37/28	Unclear	Unclear	Yes	Unclear	No	No	No	SangJuYin + Yanhuning	Oseltamivir	Unclear	Unclear	A	1

Study	Sample		Sex (male/female)		Age		Randomization	Random method	Sample size estimate	Lost and exit	blind	Interventions		Treatment time (d)		Outcomes	Jadad Scale
	E	C	E	C	E	C						E	C	E	C		
Liu et al[23] 2011	31	21	18/13	13/9	19.87 ± 9.20	20.09 ± 5.64	Yes	Random number tables	No	No	No	Differential treatment	Oseltamivir	5	5	A and B	2
Wang et al[28] 2011	103	103	65/38	58/45	19.6 ± 7.1	18.7 ± 5.3	Yes	Random number tables	Yes	Yes	Double blind	Maxingshigan−yinqiaosan	Oseltamivir	5	5	B	6
OuYang et al[9] 2010	116	58	59/57	31/27	19.23 ± 10.44	19.69 ± 9.91	Yes	Unclear	No	No	No	Lianhuaqingwen capsule	Oseltamivir	3−5	3−5	A	1
Wei and Luo[30] 2010	30	16	17/13	10/6	17.76 ± 2.68	16.25 ± 6.003	Yes	Unclear	No	No	No	Lianhuaqingwen capsule	Oseltamivir	5	5	B	1
Dou et al[29] 2010	63	36	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	No	No	Fixed prescription	Oseltamivir	3−5	3−5	B and C	1
Zhang et al[31] 2012	56	56	30/26	31/25	20 ± 10.30	22.30 ± 11.6	Yes	Random number tables	No	No	No	Lianhuaqingwen capsule	Oseltamivir	5	5	B and C	2
Weng et al[32] 2010	150	150	95/55	90/60	10.5	11.2	Yes	Unclear	No	No	No	Clear solution dampness soup	Oseltamivir	5	5	A	1
Geng and Yu[33] 2011	38	30	22/16	19/11	35.1	34.23	Yes	Unclear	No	No	No	Lianhuaqingwen capsule + antiviral drug	Oseltamivir	5	5	B	1
Tu et al[34] 2013	128	107	91/37	78/29	23.06 ± 6.22	25.11 ± 5.02	Yes	Unclear	No	No	No	Banlangen + oseltamivir	Oseltamivir	7	7	A	1
Tian et al[35] 2011	40	20	16/24	12/8	22.9 ± 4.3	22.9 ± 6.4	Yes	Unclear	No	No	No	QingKaiLing (oral)	Oseltamivir	5−7	5−7	A an d B	1
Qian et al[38] 2011	25	29	11/14	16/13	40.91 ± 19.81	41.22 ± 15.62	Yes	Unclear	No	No	No	Tanreqing injection + oseltamivir	Oseltamivir	5	5	A, B, and C	1
Li[36] 2010	55	55	28/27	32/23	31.35	30.77	Yes	Unclear	No	No	No	Tanreqing injection + oseltamivir	Oseltamivir	5	5	A	1
Chai et al[37] 2010	23	23	13/10	14/9	22.20 ± 2.38	21.5 ± 2.43	Yes	Unclear	No	No	No	Differential treatment + oseltamivir	Oseltamivir	7	7	A	1
Duan et al[10] 2011	122	122	64/58	63/59	21.5 ± 5.9	21.4 ± 3.9	Yes	Computer random number generator	Yes	Lost 12 cases	Double blind	Lianhuaqingwen capsule	Oseltamivir	7	7	B and C	6

A = effective rate; B = time to defervescence; C = duration of viral shedding; TCM = traditional Chinese medicine.

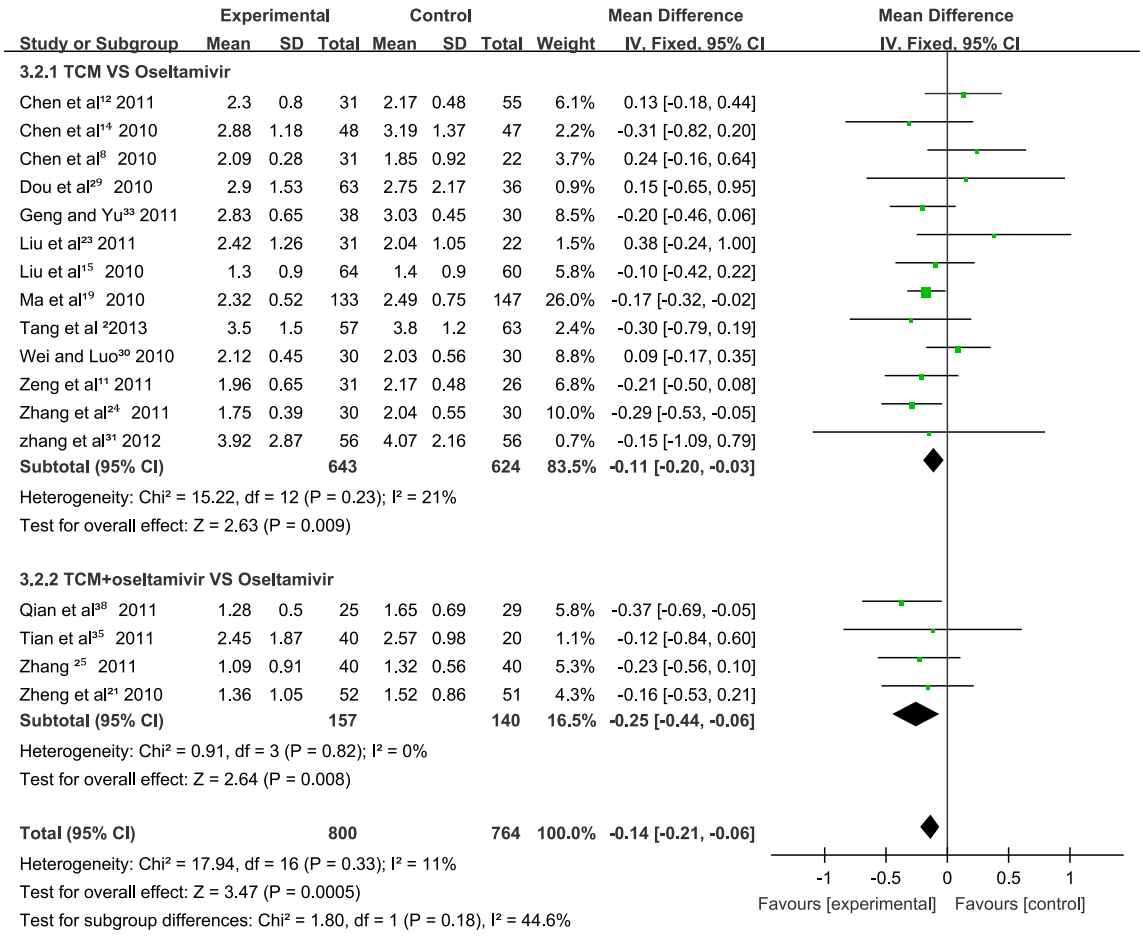

Fig. 1. Meta-analysis of time to defervescence: TCM versus control group. CI = confidence interval; IV = Inverse Variance methods; SD = standard deviation; TCM = traditional Chinese medicine.

and the random effects model was applied. When MD = −0.52, statistic $Z = 2.36$, and $p = 0.02$, the difference between the two groups was statistically significant, indicating that the duration of viral shedding was less for the integrated Chinese and Western medicine subgroups Influenza A (H1N1) than the control group. The combined subgroups used the random effects model, with statistics after the merger utilizing hypothesis testing, and the difference being not statistically significant ($p = 0.77$). The current evidence does not indicate that the difference in the duration of influenza A (H1N1) shedding between the two groups was not statistically significant (Fig. 2).

3.4. Effective rate analysis

In our review, 26 studies noted an effective rate, which included three of the high- and medium-quality studies.[8,11,12] We first analyzed the high- and medium-quality studies. After the test for heterogeneity ($p = 0.48$, $I^2 = 0\%$), a lower heterogeneity was noted using a fixed effects model (RR = 1, $p = 0.8$), and the difference between the two groups was not statistically significant. The total sample size in these 26 studies was 3148 cases. Statistical analyses on 18 TCM studies and eight integrated Chinese and Western medicine studies were performed using RR. After a test for heterogeneity ($p = 0.007$, $I^2 = 35\%$), a higher heterogeneity was noted in Subgroup 1 using a random effects model analysis [RR = 1.01 (95% CI: 0.99−1.03), statistic $Z = 1.32$, $p = 0.19$), and there was no statistical difference between the groups. After a test for heterogeneity ($p = 0.1$, $I^2 = 42\%$), random effects model analysis indicated heterogeneity in Subgroup 2 [RR = 1.00 (95% CI: 0.98−103), statistic $Z = 0.25$, $p = 0.80$], and the difference between the two groups was not statistically significant. The combined subgroups used the random effects model, with statistics after the merger utilizing hypothesis testing, and the difference being not statistically significant ($p = 0.23$). The current evidence did not indicate that the effective rate between the two groups was statistically significant (Fig. 3).

3.5. Safety evaluation

There were 18 studies that described the adverse drug reactions.[8–12,14,15,19–21,23,26–28,30–32,34] Of those studies,

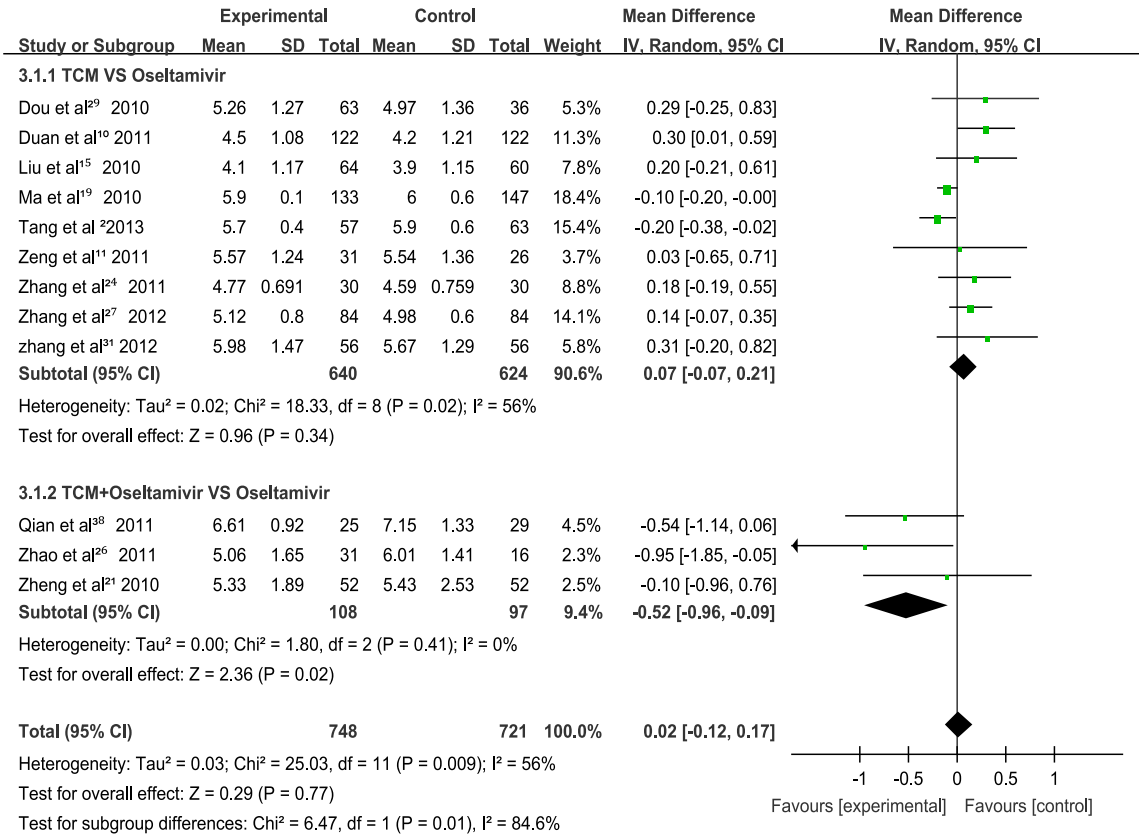

Fig. 2. Meta-analysis of viral shedding: TCM versus control group. CI = confidence interval; IV = Inverse Variance methods; SD = standard deviation; TCM = traditional Chinese medicine.

adverse reactions were not found in three studies[14,20,21]; 15 studies recorded 97 cases of adverse reactions (34 cases in the TCM group and 63 cases in the control group). The proportion of adverse reactions in the two groups was determined by Chi-square test, and the difference was statistically significant ($\chi^2 = 17.281$, $p < 0.001$). Nine of these studies[8,9,11,12,19,23,31,32,34] reported nausea/vomiting in 29 cases: the TCM group included two cases and 27 cases in the control group. Nine studies[8,12,23,26,27,30–32,34] reported diarrhea in 23 patients: 11 cases in the TCM group and 12 cases in the control group. There were five studies[8,11,12,23,34] that reported six cases of rash, all which occurred in the control group. One study reported that the TCM group had one case of watery stool and one case of arrhythmia; in that study, there was one case of chest pain in the control group.[14] One study reported that the participants in the TCM group experienced excessive sweating and diarrhea, whereas five patients in the control group had lower white blood cell count.[26] Another study reported that the TCM group had three patients who had secondary infection, and there was one control case of abdominal pain.[9] Two studies reported that neurological symptoms appeared in six cases (all in the control group).[30,31] In addition, one study reported only the number of adverse reactions, noting that the TCM group had 11 cases and the control group had seven, but did not state the specific nature of the adverse reactions.[36]

4. Discussion

In this review, several Chinese herbal medicines demonstrated a potentially positive effect on the influenza A (H1N1) strain, especially on its time to defervescence, as in the studies analyzed, the mean time to defervescence in the TCM treatment group was less than that noted in the control group. Furthermore, the duration of influenza A (H1N1) shedding in the integrated Chinese and Western medicine subgroup was less than that noted in the control group, although existing evidence indicated that the difference in duration of viral shedding and effective rate between the two groups was statistically similar. The applicability of the included studies was limited, however, because their inclusion criteria, interventions, durations, and outcome measures were different. Consequently, more well-designed trials are required.

4.1. Quality of the evidence

We rated the quality of the evidence from the included studies as very low to low, and the reasons for this are as follows:

First, most of the retrieved studies did not provide adequate descriptions about the methodology used, which may have misled us (e.g., inclusion of nonrandomized trials and incorrect classification of the trials) if we had not clarified the

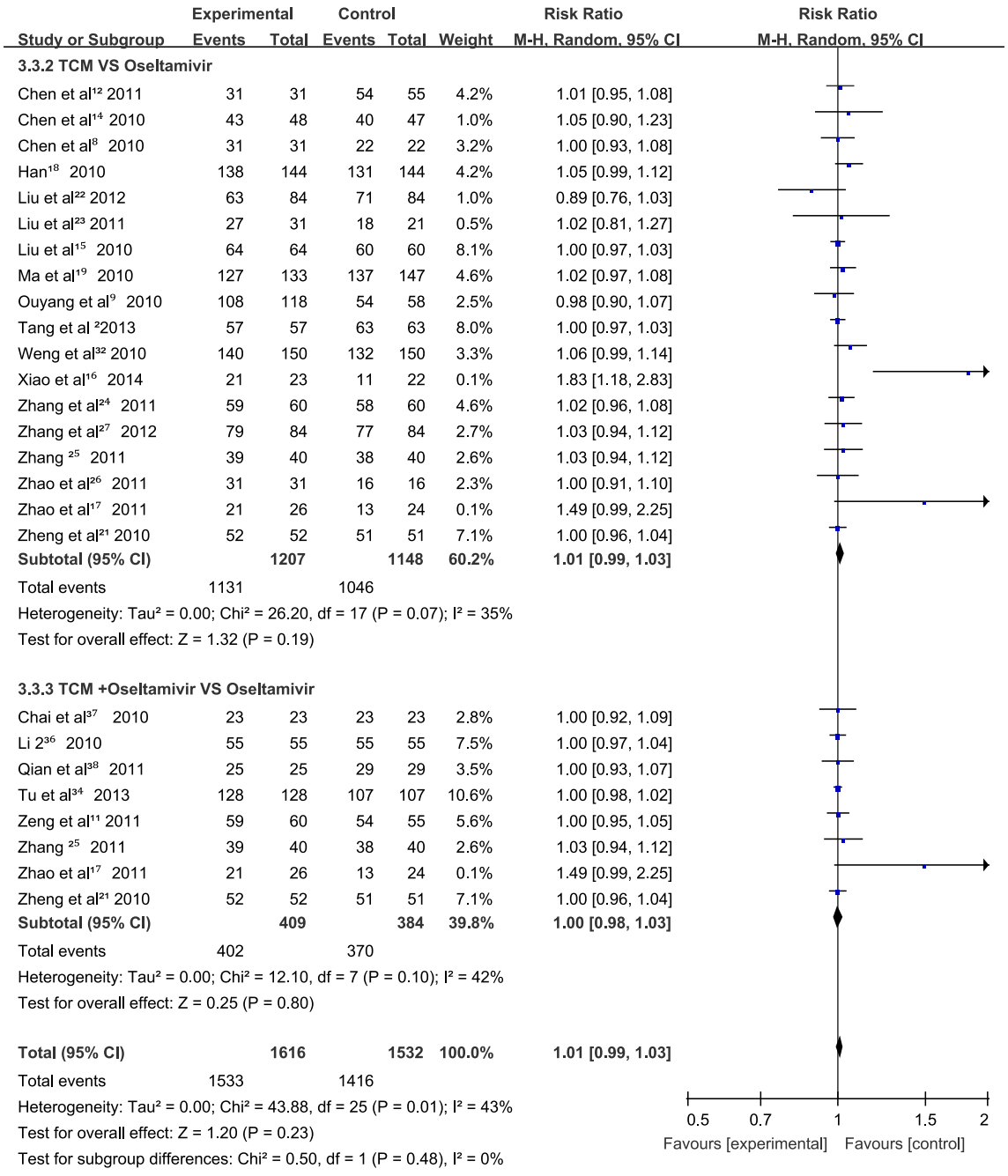

Fig. 3. Meta-analysis of effective rate: TCM versus control group. CI = confidence interval; M-H = Mantel-Haenszel methods; SD = standard deviation; TCM = traditional Chinese medicine.

details with the study authors. It was an exhausting but necessary process to interview every primary author of the trial before deciding whether to include the trials, when the methodological details were not reported. Contacting authors by telephone was more effective than corresponding by writing because of a higher response rate. However, even after confirmation of true randomization, we found that the methodological quality of the studies remained poor.

Allocation concealment is an important marker of trial quality. However, in our review, some articles failed to report or perform allocation concealment, and this leads to a high risk of selection and confounding bias.

Second, only 10 RCTs stated the randomization procedure used.[8,10–12,14,23,25,27,28,31] However, most of them provided insufficient information to judge whether the randomization process was conducted properly. For the balance of the trials, it was just mentioned that "the patients were randomized into two groups" and no further information was provided. Therefore, we could not exclude the possibility that some of these claimed RCTs were not real RCTs. This possibility came

to the forefront in the trials conducted by Han 2011,[18] Zhang 2011,[25] and Li 2010.[36] These trials only have one credited author, and therefore, it would be impossible for an RCT to be done properly in terms of randomization procedure and allocation concealment. Only two trials claimed double blind.[10,28] We understood that it was difficult to perform double blinding because of certain features associated with Chinese herbs, such as aroma and appearance; however, blinding to the outcome assessors and data analyzer could be feasible. All the trials except two did not report presample size estimation,[10,28] and for a majority of the trials, the sample size was small. Therefore, we are not sure if they could provide sufficient statistical power to detect the difference between groups. It is well-known that poorly designed trials show larger differences between the experimental and control groups than those conducted rigorously,[39,40] and as such the small improvements in outcomes should be regarded with caution.

Third, there was lack of knowledge on placebo control in the included trials. Only one Chinese herbal injection was used in the review (*Tanreqing* injection),[17,19,30] and all demonstrated positive results in terms of defervescence and global symptoms improvement. However, no adequate placebo control was used to offset the effect of the injection alone. It is known that an injection alone has a strong potential placebo effect, and therefore, the overall effect of a Chinese herbal injection could not rule out the effect that the injection itself produced. These positive effects should also be interpreted conservatively.

Finally, among high-quality studies, we found that the data reported for time to defervescence were inconsistent. However, data on duration of viral shedding and effective rate in these studies were consistent, suggesting that study quality may affect the results of the analysis. Thus, there is a need to increase the quality of such studies for further evaluation.

4.2. Select interventions

In TCM practice, herbal preparations should match the type of syndrome differentiation, that is, *bianzheng*, a specific diagnosis in TCM. This approach is also known as "treatment based on individualized (tailored) syndrome pattern," and is thought to be one of the advantages of TCM. However, in this review, only eight trials provided information on patients' syndrome differentiation.[8,12,19,20,23,26,27,37] Chinese medicine practitioners believed that treating patients without syndrome differentiation will impair the advantages of Chinese herbs, and this might be another reason for the unsatisfactory therapeutic effect of Chinese herbs on H1N1 influenza in the review. Thus, there is a need to encourage authors to explain each "Bianzheng" using common medical terms in future trials, which would make their study more understandable for physicians and consumers.

The control group interventions (oseltamivir as a main therapeutic drug) were more reasonable, except for two studies. Oseltamivir (Tamiflu) is approved by the US FDA for use against Type A and Type B influenza infections.

4.3. Adverse drug reactions

Within our study, 18 studies reported adverse drug reactions.[8–12,14,15,23,26–28,30,31,34] The adverse reactions were shown in Table 2. Those studies recorded 97 cases of adverse reactions (34 in the treatment group and 63 in the control group). Given the proportion of adverse reactions in the

Table 2
Adverse reactions record.

Study	Sample		Adverse reactions	Adverse reactions record	
	E	C		E	C
Zhang et al[27] 2012	84	84	Yes	No	5 cases of diarrhea
Chen et al[14] 2010	48	47	Yes	1 case of watery and 1 case of arrhythmia	1 case of pneumonia and 1 case of chest pain
Liu et al[15] 2010	64	60	Yes	No	No
Tang et al[20] 2013	57	63	Yes	No	No
Zeng et al[11] 2011	59	55	Yes	No	2 cases of nausea and vomiting, 1 case of rash
Zhao et al[26] 2011	31	16	Yes	1 case of sweat and diarrhea	5 cases had lower white blood cell count
Zheng et al[21] 2010	52	51	Yes	No	No
Chen et al[12] 2011	31	55	Yes	1 case of diarrhea,	1 case of rash, 2 cases of vomiting
Chen et al[8] 2010	31	22	Yes	1 case of diarrhea	1 case of rash, 3 cases of nausea and vomiting
Ma et al[19] 2010	133	147	Yes	No	4 cases of nausea, loss of appetite
Liu et al[23] 2011	31	21	Yes	1 case of diarrhea	2 cases of rash, 2 cases of vomiting
Wang et al[28] 2011	103	103	Yes	No	1 case of nausea and vomiting
OuYang et al[9] 2010	116	58	Yes	3 cases of secondary infection	1 case of abdominal pain
Wei and Luo[30] 2010	30	16	Yes	2 cases of diarrhea	2 cases of diarrhea, 1 case of nausea, 1 case of neurological symptoms
Zhang et al[31] 2010	56	56	Yes	4 cases of diarrhea	6 cases of nausea, vomiting, 5 cases of neurological symptoms
Weng et al[32] 2010	150	150	Yes	No	6 cases of nausea, 3 cases of diarrhea
Tu et al[34] 2013	128	107	Yes	2 cases of nausea and vomiting, 1 case of diarrhea	2 cases of nausea and vomiting, 1 case of abdominal pain, 1 case of rash
Duan et al[10] 2011	122	122	Yes	11 cases	7 cases

C = control group; E = experimental group.

experimental group as opposed to the control group, our review found inadequate reporting on adverse events in the included trials. In fact, 11 trials did not mention whether they had monitored adverse effects at all. Ultimately, conclusions about the safety of herbal medicines cannot be drawn from this review due to the limited, inadequate recording and reporting of adverse events. Even for those trials that reported adverse events, the reports were very brief and provided limited information. In China, there is a general perception that it is safe to use herbal medicines for various conditions. However, with the increasing reports of liver toxicity and other adverse events associated with Chinese herbal medicines,[41,42] there should be more emphasis on the monitoring and reporting of adverse events to justify the safety of Chinese herbs in clinical trials in the future.

4.4. Agreements and disagreements with other studies or reviews

The results of well-designed RCTs with large sample sizes in the future may confirm or refute our conclusions. There is one known systematic review of TCM for influenza,[43] where the results indicated that most Chinese medical herbs in the included studies showed effects similar to antiviral drugs in preventing or treating influenza. Few were shown to be superior to antiviral drugs, and no obvious adverse events were reported in the included studies. In summary, previous studies showed that administration of some Chinese herbs may have beneficial immunomodulatory effects for rapid recovery from viral infections.[42,44] However, in this review, it would appear that compared with oseltamivir, Chinese herbs might have superior potential effects on fever resolution than viral shedding, which also suggests that most Chinese herbs may not have antiviral effects. In the era of evidence-based medicine, TCM is facing a substantial challenge because of the lack of rigorous evidence-based research. Our review attempted to bring a measure of elucidation into the clinical use and policy making of Chinese herbs for H1N1 influenza in China. However, considerable work needs to be done before the evidence-based practice of TCM can become a reality.

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