REVIEW ARTICLE

Efficacy of *Lianhuaqingwen* Capsule Compared With Oseltamivir for Influenza A Virus Infection: A Meta-analysis of Randomized, Controlled Trials

Pan Zhao, MD, PhD; Hao-zhen Yang; Hong-yu Lv; Zhen-man Wei

ABSTRACT

In this meta-analysis, the authors review the results of studies on the efficacy of *lianhuaqingwen* capsule (LHQW-C) compared with oseltamivir in treating influenza A virus infection. The authors searched PubMed, Embase, Wanfang Data, and the China National Knowledge Infrastructure (CNKI) from the date of inception until December 31, 2012. The Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) were also searched. Five randomized, controlled trials were finally included and analyzed in this review. Compared with individuals treated with oseltamivir, this meta-analysis showed that participants treated with LHQW-C had a shorter duration of (1) fever, weighted mean difference (WMD) = -4.65 (95% CI, -8.91 to -0.38; $P = .030$); (2) cough, WMD = -9.79 (95% CI, -14.61 to -4.97; $P < .0001$); (3) sore throat, WMD = -13.01 (95% CI, -21.76 to -4.27; $P = .004$); and (4) body ache, WMD = -16.68 (95% CI, -32.33 to -1.03; $P = .040$). The review also found that the efficacy of the 2 treatments on viral shedding was similar with WMD = -0.24 (95% CI, -4.79 to 4.31; $P = .920$). The authors conclude that LHQW-C was superior to oseltamivir in improving the symptoms of influenza A virus infection. (*Altern Ther Health Med.* 2014;20(2):25-30.)

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Recently, a novel avian influenza virus, H7N9, has emerged in China, and it is much more transmissible to humans and much more difficult to track down than previous strains.[1] As this virus shows, the threat of pandemic influenza has remained a major, international public health concern.[2] Rapid antigenic evolution in an influenza virus increases the likelihood of emergence of novel strains.[3] Under the circumstances, if vaccines are not yet available, treatment plays a crucial role in control of the disease.

Oseltamivir, a neuraminidase inhibitor, has been widely used against influenza virus infection in the world, and it has exhibited potent efficacy in antiviral therapy.[4-6] In China, traditional Chinese materia medica with a history of thousands of years has been used to treat various diseases.[7-13] *Lianhuaqingwen* capsule (LHQW-C) is a traditional Chinese prescription composed of (1) *zhimahuang*—honey-fried herba ephedrae, (2) *xingren*—semen armeniacae amarum, (3) *lianqiao*—fructus forsythiae, (4) *bohe*—fructus forsythiae,

(5) *banlangen*—radix isatidis, (6) *yuxingcao*—herba houttuyniae, (7) *guanzhong*—dryopteris setosa, (8) *jinyinhua*—flos lonicera japonicae, (9) *shigao*—gypsum fibrosum, (10) *dahuang*—radix et rhizoma rhei, (11) *guanghuoxiang*—herba pogostemonis, (12) *hongjingtian*—herba rhodiolae, and (13) *gancao*—radix et rhizoma glycyrrhizae. The China State Food and Drug Administration approved LHQW-C in 2004.

In this meta-analysis, the authors have compared the efficacy and safety of LHQW-C and oseltamivir in treating influenza A virus infection.

METHODS

Search Strategy

The authors searched PubMed, Embase, Wanfang Data, and the China National Knowledge Infrastructure (CNKI) from the date of inception until December 31, 2012. The Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Database of Systematic Reviews (CDSR) were also searched. Of these databases, the Wanfang database and CNKI provided literature in Chinese. In this study, the search was designed using the following search terms: lianhuaqingwen capsule, oseltamivir, and influenza. Reference lists from retrieved documents were also searched.

Eligibility Criteria

This meta-analysis included studies on individuals older than 3 years who were hospitalized with a clinical or laboratory diagnosis of influenza infection. For inclusion, the study must have (1) been a randomized, controlled trial; (2) included an intervention group treated with LHQW-C and a control group treated with oseltamivir; and (3) involved human participants.

Quality Control

Two investigators independently extracted data from each study using predefined forms, and disagreement was resolved by discussion among investigators and reference to the original article. When several publications pertaining to a single study were identified, the most complete publication was used. The quality of all selected articles was graded in accordance with the PRISMA Statement.[14]

Efficacy Measures

Efficacy was measured using the following criteria: (1) duration of fever, (2) duration of flu-like symptoms, and (3) duration of viral shedding. The safety of treatment was also assessed.

Data analysis

Data analysis was carried out using the Review Manager Software 4.2 (Cochrane Collaboration, Oxford, United Kingdom). The estimated effect measures for treatment and control means were weighted mean difference (WMD), reported with 95% confidence intervals (CIs). Significant heterogeneity was evaluated by the χ^2 and I^2 tests. In the absence of statistically significant heterogeneity, the fixed-effect method was used to combine the results. When heterogeneity was confirmed, the random-effect method was used. The overall effect was tested using z scores, with significance set at $P < .05$.

RESULTS

Study Selection and Characteristics

Searches resulted in 1963 unique articles. Only 5 randomized controlled trials (RCTs) met the inclusion criteria.[14-18] Figure 1 shows the flowchart of the selection process. The total number of participants involved was 620, of which 309 were in the LHQW-C group (treatment group) and 311 in the oseltamivir group (control group). Table 1 summarizes the main characteristics of the included RCTs.

Clinical Outcomes

Duration of Fever. The 5 included studies reported the effects of LHQW-C compared with oseltamivir in reducing fever (defervescence).[15-19] Shorter fever durations were shown for the LHQW-C groups compared with those for the oseltamivir groups, and the difference between the 2 groups was statistically significant with WMD = -4.65 (95% CI, -8.91 to -0.38; $P = .030$). Table 2 shows the effect of LHQW-C versus oseltamivir on the time to defervescence.

Duration of Flu-like Symptoms. The 5 included trials studied the effects of LHQW-C compared with oseltamivir on flu-like symptoms.[8] In these studies, 4 reported the time to cough alleviation, 4 reported the time to sore throat alleviation, and 3 reported the time to body ache alleviation. The treatment groups had shorter duration of (1) cough, WMD = -9.79 (95% CI, -14.61 to -4.97; $P < .0001$); (2) sore throat, WMD = -13.01 (95% CI, -21.76 to -4.27; $P = .004$); and (3) body ache, WMD = -16.68 (95% CI, -32.33 to -1.03; $P = .040$). Figure 2 shows the forest plot of effect comparison of LHQW-C versus oseltamivir on duration of flu-like symptoms.

Viral Shedding. The 5 included trials reported on the effects of LHQW-C compared with oseltamivir on viral shedding. No statistical differences existed between the 2 groups on duration from onset to negativity of viral ribonucleic acid (RNA), with WMD = -0.24 (95% CI, -4.79 to 4.31; $P = .920$). Table 3 shows the effect of LHQW-C versus oseltamivir on the duration from onset to negativity of viral RNA.

Safety. For the participants treated with LHQW-C and oseltamivir in the included studies, no significant, drug-related, serious adverse events were observed; for example, no neuropsychiatric events, including delirium or abnormal behavior, occurred.

DISCUSSION

It has been demonstrated that oseltamivir can prevent the release of progeny viral particles from infected host cells, shorten the duration of influenza, and decrease the development of serious complications.[20,21] However, a major shortcoming of oseltamivir is the emergence of viral

Figure 1. Flowchart of the Study's Selection Process

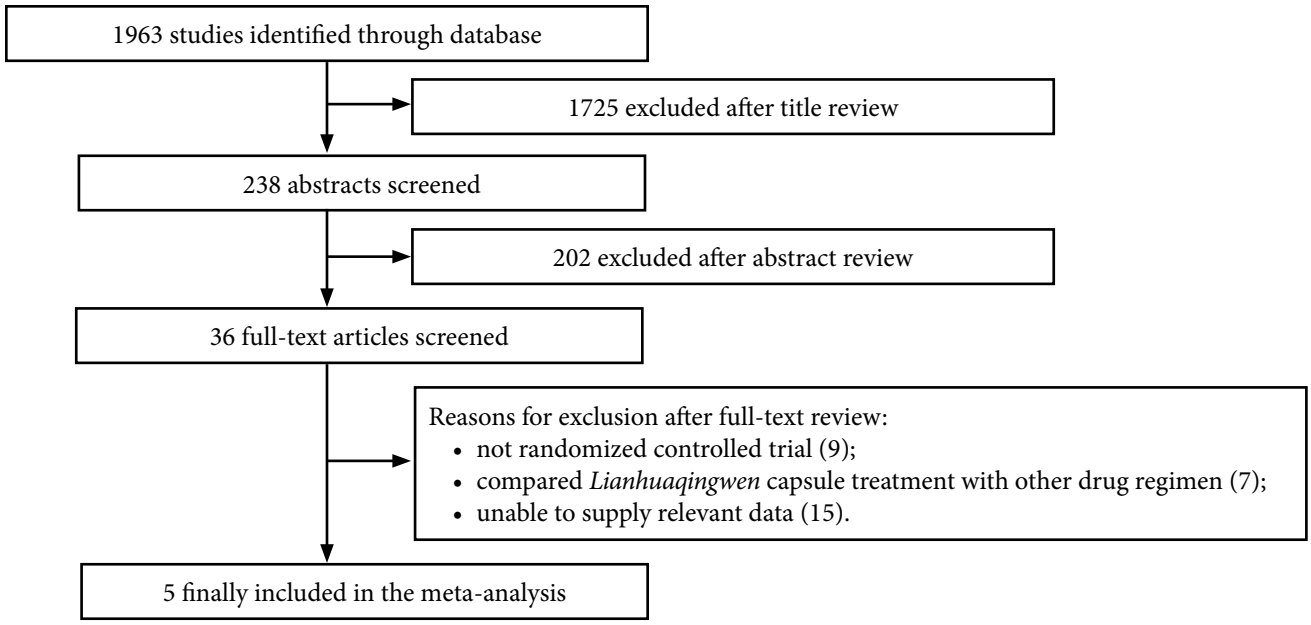


Table 1. Main Characteristics of the Included Trials

Literature	Sample and Intervention		Study Design	Grade
	Group Treated With LHQW-C (n = 309)	Group Treated With Oseltamivir (n = 311)		
Duan et al[14]	122 cases	122 cases	RCT, double-blind	A
Ma et al[15]	60 cases	74 cases	RCT, blinding not known	B
Liu et al[16]	64 cases	60 cases	RCT, blinding not known	B
Li et al[17]	25 cases	25 cases	RCT, blinding not confirmed	B
Geng et al[18]	38 cases	30 cases	RCT, blinding not known	B

Abbreviations: LHQW-C = lianhuaqingwen capsule; RCT = randomized, controlled trial.

Table 2. Effect of LHQW-C Versus Oseltamivir on the Time to Defervescence

Literature	Mean (SD) in LHQW-C	Mean (SD) in Oseltamivir	WMD	95% Confidence Interval
Duan et al[14]	17.00 (14.00)	23.00 (17.00)	-6.00	-9.91 to -2.09
Geng et al[18]	21.21 (6.56)	31.32 (4.54)	-10.11	-12.75 to -7.47
Li et al[17]	31.70 (16.70)	30.90 (12.60)	0.80	-7.40 to 9.00
Liu et al[16]	31.20 (21.60)	33.60 (21.60)	-2.40	-10.01 to 5.21
Ma et al [15]	61.20 (16.32)	62.16 (18.00)	-0.96	-7.08 to 5.16
Total			-4.65	-8.91 to -0.38

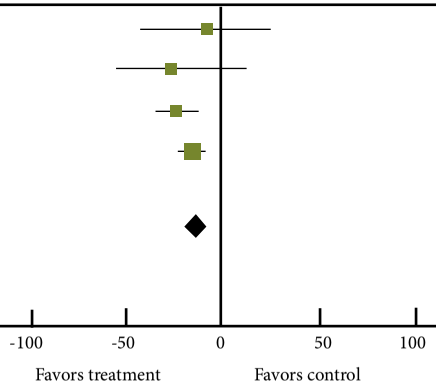
Note: Test for heterogeneity—$\chi^2 = 14.19$, $I^2 = 71.8\%$; test for overall effect—$z = 2.13$, $P = .030$.

Abbreviations: LHQW-C = lianhuaqingwen capsule; SD = standard deviation; WMD = weighted mean difference.

Figure 2. Forest Plot of Comparison Between LHQW-C Versus Oseltamivir on Duration of Flu-like Symptoms

Outcome: Time to cough alleviation (h)

Study or subcategory	n	Treatment mean (SD)	n	Control mean (DS)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Geng et al[18]	38	123.12 (49.12)	30	128.65 (68.45)		2.75	-5.53 (-34.58, 23.52)
Li et al[17]	25	108.80 (48.90)	25	127.20 (61.00)		2.47	-18.40 (-49.05, 12.25)
Liu et al[16]	44	98.40 (31.20)	48	117.60 (26.40)		16.50	-19.20 (-31.06, -7.34)
MA et al[15]	50	103.20 (16.32)	60	110.88 (12.00)		78.27	-7.68 (-13.13, -2.23)
Total (95% CI)	157		163			100.00	-9.79 (-14.61, -4.97)
Test for heterogeneity: $\chi^2 = 3.38$, $df = 3$ ($P = .34$), $I^2 = 11.2\%$							
Test for overall effect $z = 3.98$ ($P < .0001$)							



Outcome: Time to sore throat alleviation (h)

Study or subcategory	n	Treatment mean (SD)	n	Control mean (DS)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
Geng et al[18]	38	24.94 (6.67)	30	46.43 (9.20)		29.38	-21.49 (-25.41, -17.57)
Li et al[17]	25	38.20 (15.30)	25	48.60 (14.10)		24.55	-10.40 (-18.56, -2.24)
Liu et al[16]	36	67.20 (31.20)	40	79.20 (31.20)		17.28	-12.00 (-26.05, 2.05)
MA et al[15]	58	109.68 (14.64)	69	116.88 (10.80)		28.78	-7.20 (-11.75, -2.65)
Total (95% CI)	157		164			100.00	-13.01 (-21.76, -4.27)
Test for heterogeneity: $\chi^2 = 23.20$, $df = 3$ ($P = .0001$), $I^2 = 87.1\%$							
Test for overall effect $z = 2.92$ ($P < .004$)							

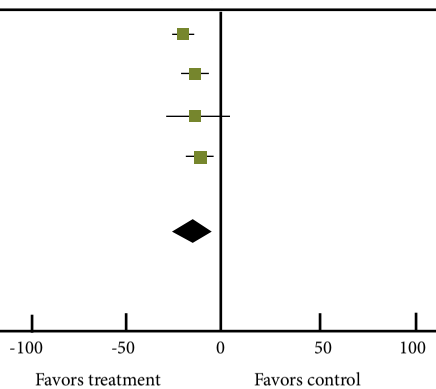


Figure 2. (continued)

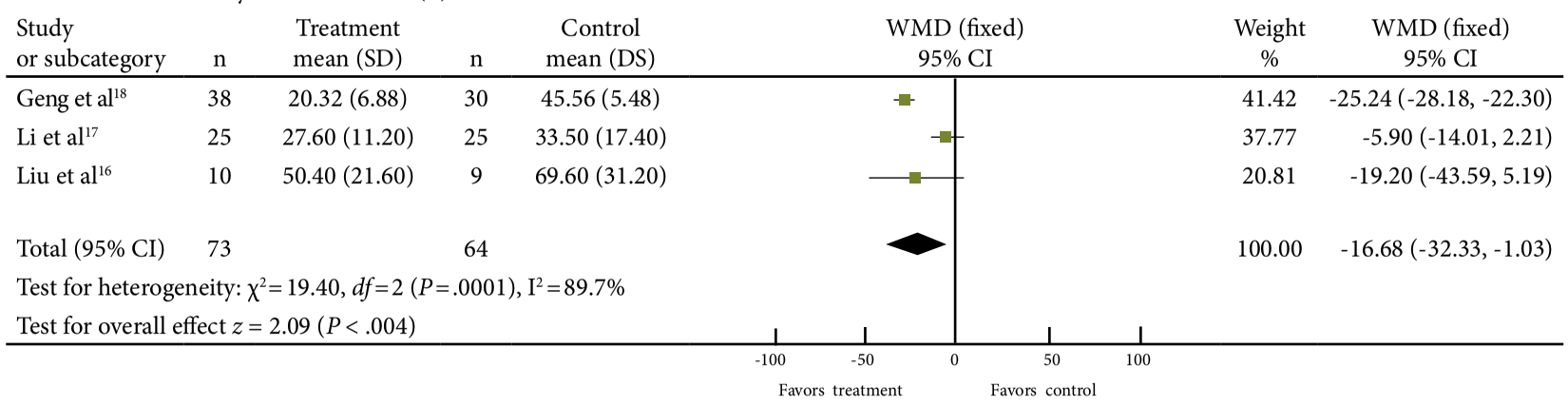


Table 3. Effect of LHQW-C Versus Oseltamivir on Duration From Onset to Negativity of Viral RNA

Literature	Mean (SD) in LHQW-C	Mean (SD) in Oseltamivir	WMD	95% Confidence Interval
Duan et al[14]	108.00 (36.00)	101.00 (34.00)	7.00	-1.79 to 15.79
Li et al[17]	108.00 (50.40)	98.40 (43.20)	9.60	-16.42 to 35.62
Liu et al[16]	98.40 (40.80)	93.60 (40.80)	4.80	-9.57 to 19.17
Ma et al[15]	139.20 (19.20)	144.00 (14.40)	-4.80	-10.66 to 1.06
Total			-0.24	-4.79 to 4.31

Note: Test for heterogeneity—$\chi^2 = 5.95$, $I^2 = 49.6\%$; test for overall effect—$z = 0.10$, $P = .920$.

Abbreviations: LHQW-C = lianhuaqingwen capsule; SD = standard deviation; WMD = weighted mean difference; RNA = ribonucleic acid.

resistance.[22] Therefore, it is of crucial importance to find an effective and safe alternative for treating influenza infection, especially in rural areas of China where the supply of oseltamivir is often insufficient.

As an alternative therapy, LHQW-C has been studied in recent years in China. However, because the mechanism of traditional Chinese medicine in the treatment of influenza is complex, it is difficult to determine which ingredient plays the main role in anti-influenza virus infection. In this meta-analysis, the outcomes showed that participants treated with LHQW-C had shorter durations of fever and flu-like symptoms than participants treated with oseltamivir and that the efficacy of the 2 treatments on viral shedding was similar. The included studies did not report any severe adverse events in either of the 2 groups.

CONCLUSION

LHQW-C can improve the symptoms that individuals experience with influenza A virus infection more significantly than oseltamivir and is similar to oseltamivir in viral shedding.

AUTHOR DISCLOSURE STATEMENT

Pan Zhao and Hao-zhen Yang contributed equally to this work. The research team received no financial support for this study and declare that they had no conflicts of interest.

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