International Journal of Community Medicine and Public Health
AlQarni NS et al. Int J Community Med Public Health. 2018 Jul;5(7):2632-2636
http://www.ijcmph.com
pISSN 2394-6032 | eISSN 2394-6040

DOI: http://dx.doi.org/10.18203/2394-6040.ijcmph20182492

Review Article

Effectiveness of influenza vaccine in children

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Received: 25 May 2018
Accepted: 11 June 2018

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ABSTRACT

Oseltamivir delivers modest clinical advantages to children with influenza when started within 48 hours of symptom beginning. Nevertheless, effectiveness and safety stay controversial. We conducted the current meta-analysis using a comprehensive search of EMBASE, MEDLINE, PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials till 15 February 2018 for randomized controlled trials of oseltamivir therapy in children. Four studies met the search criteria. Overall, oseltamivir treatment significantly reduced the duration of illness in the ITTI population (RMST difference, -18.2 hours; 95% CI, −32.2 to −0.6 hours). In trials that enrolled patients without asthma, the difference was larger (RMST difference −26.7 hours; 95% CI, −49.8 to −6.1 hours).Risk of otitis media was 34% lower in the ITTI population. Vomiting was the only adverse event with a significantly higher risk in the treatment group. Regardless of considerable heterogeneity in pediatric trials, we found that treatment with oseltamivir treatment started within 24 hours of symptom onset provides substantial benefits to children with influenza infection and lowered the risk of developing otitis media.

Keywords: Oseltamivir, Influenza, Meta-Analysis, Infection, Children

INTRODUCTION

Influenza infection is extremely contagious, influencing individuals of all ages and all socioeconomic backgrounds, and has an especially significant impact on children. Community studies show that school-aged children have most noteworthy rates of influenza infection, with yearly rates as high as 42% in imminent observation studies.[1] Influenza places a great load of sickness on children, whether measured by yearly attack rates, hospitalizations, or outpatient visits.[2,3] The influence of influenza is not limited to the viral infection, since influenza regularly predisposes children to bacterial complications, such as acute otitis media.[4] However, vaccines remain the most effective way to prevent infections.[5] Therefore, prevention approaches must be

coupled with management of influenza virus infections to reduce the load of infection.

Oseltamivir remains the only recommended antiviral drug for treating influenza in children less than five years of age.[6] The indication for the effectiveness of oseltamivir in earlier healthy children of this age, in which treatment started within 48 hours of the onset of symptoms reduced the duration of illness by one and a half days and the incidence of influenza-associated acute otitis media by 44% in children from one to twelve years of age. Subsequent the practice with severe disease in young children during the 2009 pandemic, oseltamivir is now licensed for children as young as 2 weeks.[7]

Substantial decreases of severe results were established amongst hospitalized adults, but these effects were decreased and not significant amongst children. Oseltamivir residues debatable in some quarters for numerous explanations, comprising safety worries.[8] A current meta-analysis, utilizing singular-level information from all RCTs of convenient oseltamivir management in outpatients with simple influenza (less than two days from symptom onset), affirmed substantial decreases in duration of disease and complications in those randomized and infected, but not between the uninfected [9]. The aim of the current meta-analysis was to review the published randomized controlled trials in children to estimate the effectiveness of influenza vaccine in children.

METHODS

Data sources and searches

We conducted the current meta-analysis using a comprehensive search of EMBASE, MEDLINE, PubMed, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials till 15 February 2018 for randomized controlled trials of oseltamivir therapy in children. Both semiparametric and parametric methods were used. No language restrictions were imposed.

Selection criteria

Studies were included in this meta-analysis if they satisfied the following criteria: patients who received at least one dose of study drug and who had laboratory-confirmed influenza virus infection which involved both children with and without influenza virus infection, all of whom were randomized to receive treatment or placebo. the investigators reported relative risks (RRs) with 95% CI.

Data extraction

The final data were abstracted from each study using standardized form: the first author's name, year of publication, number of patients, age, study location, follow-up duration, and duration of illness. These factors were chosen because they represent the most important variables for assessing patient risk and treatment of patients. Flow diagram showing the selection criteria of assessed studies.[10]

Statistical analysis

The present meta-analysis utilized Stata version 12.0 software for statistical analysis. Mean Difference (MD) were calculated for continuous variables. Pooled odds ratios (OR) were calculated for discrete variables. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified using the I^2 inconsistency test with a significance set at the P-value <0.10 or I^2 score >50%.[11] DerSimonian-Laird random-effect meta-analysis was adopted when obvious heterogeneity existed.[12]

RESULTS

We recognized 102 citations using the search strategy. Of these, we excluded 64 after examining the title and abstract including removal of duplicates. We retrieved and evaluated 12 articles in more detail, of which 8 articles were excluded, leaving 4 studies that were eligible for inclusion (Figure 1). Main characteristics of included studies have been summarized in Table 1.

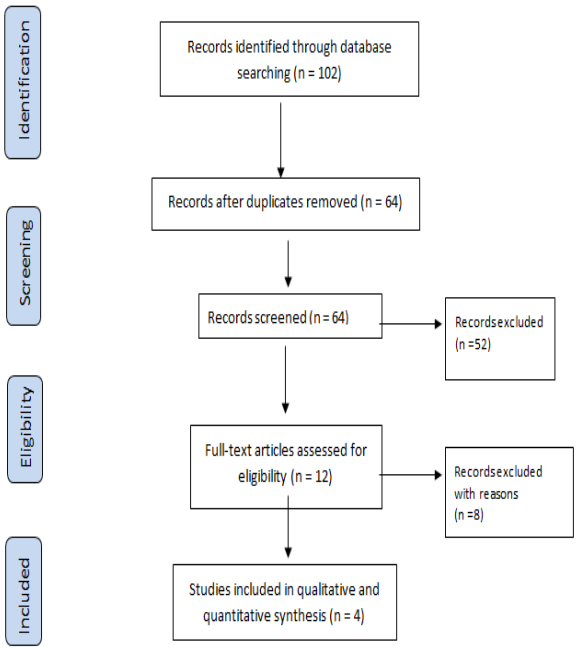

Figure 1: Flow diagram showing the selection criteria of assessed studies.

Generally, there was a significant reduction in the duration of illness among those who received timely oseltamivir treatment (RMST difference, -18.2 hours;

95% CI, −32.2 to −0.6 hours). An indicator for enrolling only asthma patients was significant in the meta-regression for the ITTI population (P = 0.02), representing heterogeneity among asthma-only and combined populations. The influence of treatment was larger in trials that enrolled children notwithstanding of asthma status (RMST difference −26.7 hours; 95% CI, −49.8 to −6.1 hours). For trials that enrolled only patients with asthma, there was no effect of treatment (Table 2).

Table 1: Main characteristics of included studies.

Study	Year	Country	N	N infected	Description	Duration of illness definition
Johnston[13]	2005	Worldwide	334	179	Children with asthma (≥6 y–≤12 y)	Time from illness onset to presence of mild or no cough, nasal congestion/runny nose, afebrile, return to normal activity
Whitley[14]	2001	USA	695	452	Otherwise healthy children (1–12 y)	Time from illness onset to presence of mild or no cough, nasal congestion/runny nose, afebrile, return to normal activity
Heinonen[15]	2010	Finland	408	98	Children (1–3 y), early treatment (≤24 h of symptom onset)	Time from illness onset to presence of mild or absent cough and rhinitis, afebrile, return to normal activities
Fry[16]	2014	Bangladesh	796	796	Age +1y, no upper age limit (89%	Time from illness onset to resolution of major symptoms (fever, tachypnea, difficult/ noisy breathing, cough, and any danger sign)

Table 2: Efficacy of oseltamivir treatment in reducing duration of illness.

Study	Time ratio 95% CI	Restricted mean survival time 95% CI
Johnston[13]	1.02 (0.70, 1.49)	0.9 (-31.4, 33.3)
Whitley[14]	0.73 (0.64, 0.84)	-31.8 (-47.4, -16.2)
Heinonen[15]	0.67 (0.47, 0.96)	-46.8 (-81.9, -11.7)
Fry[16]	0.87 (0.77, 0.98)	-10.5 (-20.9, -0.1)
Random effects model		-18.2 (-32.2, -0.6)

Table 3: Results adverse event outcomes.

Study	Diarrhea RR (95% CI)	Vomiting RR (95% CI)	Nausea RR (95% CI)
Johnston[13]	0.80 (0.36–1.81)	1.45 (0.83–2.53)	0.48 (0.13–1.50)
Whitley[14]	0.83 (0.52-1.31)	1.67 (1.08–2.56)	0.96 (0.45–2.02)
Heinonen[15]	0.96 (0.74–1.25)	1.54 (1.07–2.20)	-
Fry[16]	0.80 (0.53–1.21)	1.71 (0.90–3.25)	6.96 (0.86–56.3)
Overall	0.77 (0.68–1.30)	1.59 (1.05–2.42)	1.54 (0.43–3.21)

Table 3 shows that RR of vomiting was increased in the treatment group (RR, 1.59; 95% CI, 1.05, 2.42), but no indication of an increased risk of nausea, or diarrhea.

DISCUSSION

Oseltamivir selectively inhibits neuraminidase enzymes, which are glycoproteins found on the surface of influenza A and B. As neuraminidase is responsible for cleaving sialic and neuraminic acid, it is one of the key factors responsible for the influenza virion's entrance and exit from the host cell.[17] Inhibiting neuraminidase enzymes effectively halts the influenza virion's ability to spread to new human cells. In the present examination, we exhibited a diminishment in the duration of sickness of around 18 hours among kids who got convenient oseltamivir treatment contrasted with placebo treatment. Moreover, we found that treatment decreased the danger of otitis media and that there was little confirmation of safety issues, aside from vomiting. A current meta-analysis of all grown-up RCTs found a lessening in

duration of sickness in the intention-to-treat infected populace of 25 hours.[9]

The distinguished adult trials, comprising published and unpublished works, were directed around the period of licensure. The examination populaces differed in a few trials, yet all trials utilized a comparative endpoint. This endpoint was characterized as nonappearance of fever, however different indications could be either absent or mild. Conversely, there was considerably more variety in both investigation populace and endpoints in the pediatric examinations incorporated into this investigation. The biggest pediatric trial in urban Bangladesh, for instance, was led 10 years after licensure. This setting was evaluated the effectiveness of oseltamivir under conditions with abnormal amounts of swarming and poor sanitation. The essential result, period of clinical disease, was characterized by no indication of sickness, including fever, risk signs, or different signs that would require clinical referral.[16]

In children with influenza A, oseltamivir shortened the median time to resolution of illness from 6.5 to 3 days, a difference that most clinicians and parents might appreciate as being clinically significant. Moreover, early oseltamivir treatment provided a 3-day reduction in parental absence from work among children with influenza A. The efficacy of oseltamivir was most pronounced among unvaccinated children, which was primarily because of the longer duration of symptoms in unvaccinated placebo recipients, compared with the duration of symptoms in vaccinated placebo recipients. Furthermore, oseltamivir effectively prevented the development of acute otitis media as a complication of influenza when the treatment was started within 12 hours of symptom onset, but no efficacy could be demonstrated when the treatment was started within 24 hours.[18]

The real exceptions in this investigation were the trials that included just youngsters with asthma. The pooled gauge for the 3 trials that did not particularly select asthma patients was a lessening in disease span of 26.7 hours, which is nearer to that found in the adult study.[9] There is no unmistakable motivation to guess an alternate antiviral impact in asthmatic children contrasted with healthy ones. Relatively the distinction in viability might be clarified by the trouble in perceiving clinical ailment endpoints in those with basic respiratory conditions. Alternate endpoints such as enhancement in pulmonary function or the period of viral shedding might be more appropriate in future studies of asthmatic children. Molecular approaches to regulate respiratory viral burden have become standard since the original trials and can support distinct the role of viral replication and symptoms in these children.[19,20]

CONCLUSION

Regardless of considerable heterogeneity in pediatric trials, we found that treatment with oseltamivir treatment started within 24 hours of symptom onset provides substantial benefits to children with influenza infection and lowered the risk of developing otitis media. To confirm these results, further studies should be made to make a better understanding of the potential biological mechanisms. Large-scale and long-term randomized controlled trials in various populations must be carried out in future studies to deliver more significant evidence.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: AlQarni NS, Abdulla AM, Abdu RHA, Khan BFN, Alherz AHD, Waznah MAM, et al. Effectiveness of influenza vaccine in children. Int J Community Med Public Health 2018;5:2632-6.