Is acyclovir effective for the treatment of varicella in children and adolescents?

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Abstract

Introduction

Varicella (chickenpox) is a frequent and highly contagious infectious disease, caused by the Varicella zoster virus. Traditionally, it has been recommended to focus on the management of symptoms, since there is controversy about the role of antivirals, particularly in children and adolescents.

Methods

To answer this question we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach.

Results and conclusions

We identified three systematic reviews including three studies overall, all of them corresponding to randomized trials. We concluded the use of acyclovir might not decrease the associated complications, and it is not clear whether it reduces lesions or itching because the certainty of the evidence is very low.

Problem

Varicella is an infectious disease caused by the Varicella zoster virus. Most cases occur before the age of fourteen, determining school absenteeism and generating significant expenses.Traditionally, the management of this condition relies on symptomatic treatment only. However, 5 to 10% suffer skin, respiratory or central nervous system complications.

Acyclovir is an antiviral of virostatic action with a structure analogous to guanosine, which acts by inhibiting replication of Varicella zoster virus. However, its actual efficacy for the treatment of varicella remains unclear.

Key messages

- It is not clear if acyclovir reduces lesions or pruritus in patients with varicella because the certainty of the evidence is very low.
- Acyclovir might not reduce the complications associated with varicella, but the certainty of the evidence is low.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found three systematic reviews[1,2,3] that included three primary studies[4,5,6], all corresponding to randomized trials.
What types of patients were included*	All trials considered only immunocompetent patients, with less than 24 hours from the beginning of symptoms. Two trials[4,6] required laboratory confirmation, and one only a clinical diagnosis[5]. All trials included patients under 18 years of age. One trial included patients between 5 and 16[4]; one trial between 2 and 12[5] and one trial only included adolescents between 13 and 18 years[6]. Exclusion criteria were: participants over 18 years old, immunocompromised patients or who had received varicella vaccine[4,5,6]. All trials were performed on an outpatient basis[4,5,6].
What types of interventions were included*	All trials used acyclovir as an intervention and compared it against placebo. One trial[4] adjusted the dose according to age: 20 mg/kg for those between 5 and 7, 15 mg/kg for patients between 7 and 12, and 10 mg/kg for adolescents between 12 and 16 years. One trial[5] administered 800 mg and one trial[6] adjusted the dose by body weight. All trials used acyclovir for 5 days in 4 daily doses, initiated within the first 24 hours.
What types of outcomes were measured	The trials measured multiple outcomes, which were pooled by the identified systematic reviews as follows: • Days of appearance of new lesions. • Total number of lesions.- Duration of fever (37.8 ° C). • Duration of pruritus. • Skin complications: Bacterial superinfection. • Complications of the central nervous system: Ataxia, meningoencephalitis. • Respiratory complications: Acute pneumonia, otitis media, pharyngitis and bronchitis. The follow-up was 28 days in two trials[5,6] and up to 1 year in one trial[4].

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information, we generated a structured summary denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos) using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies when it is possible, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Summary of Findings

The information on the effects of acyclovir is based on three randomized trials including 988 patients. All trials reported time of appearance of new lesions, total number of lesions, and time until resolution of fever and skin complications (988 patients). Two trials[4,5] also measured time to resolution of pruritus, and central nervous system and respiratory complications (826 patients).

- The summary of findings is as follows:
- It is not clear if acyclovir decreases the days of appearance of new lesions, because the certainty of the evidence is very low.
- It is not clear if acyclovir decreases the total number of lesions because the certainty of the evidence is very low.
- Acyclovir probably decreases the duration of fever. The certainty of the evidence is moderate.
- It is not clear if acyclovir reduces the duration of itching because the certainty of the evidence is very low.
- Acyclovir might have minimal or no impact on varicella-associated skin complications, but the certainty of the evidence is low.
- Acyclovir might have minimal or no impact on central nervous system complications associated with varicella, but the certainty of the evidence is low.
- Acyclovir might have minimal or no impact on respiratory complications associated with varicella, but the certainty of the evidence is low.

Acyclovir for varicella				
Patients	Varicella			
Intervention	Acyclovir			
Comparison	Placebo			
Outcome	Absolute effect*		Relative effect (95% CI)	Certainty of evidence (GRADE)
	WITHOUT acyclovir	WITH acyclovir		
	Difference: patients per 1000			
Days of appearance of new lesions	3.19 days	2.4 days	--	⨁◯◯◯[1,2,3] Very low
	MD: 0.79 days less (Margin of error: 1.59 less to 0.02 more)			
Total number of lesions	422	345	--	⨁◯◯◯[1,2,3] Very low
	MD: 77 lesions less (Margin of error: 8 to 145 less)			
Duration of fever	2.37 days	1.28 days	--	⨁⨁⨁◯[1] Moderate
	MD: 1.09 days less (Margin of error: 0.94 to 1.25 less)			
Duration of itching	2.86 days	2.4 days	--	⨁◯◯◯[1,2,3] Very low
	MD: 0.46 days less (Margin of error: 1.26 less to 0.34 more)			
Skin complications	23 per 1000	12 per 1000	RR 0.52 (0.19 to 1.47)	⨁⨁◯◯[1,3] Low
	Difference: 11 patients less (Margin of error: 19 less to 11 more)			
Central nervous system complications	5 per 1000	2 per 1000	RR 0.33 (0.04 to 3.16)	⨁⨁◯◯[1,3] Low
	Difference: 3 patients less (Margin of error: 5 less to 11 more)			
Respiratory complications	15 por 1000	15 por 1000	RR 0.99 (0.33 to 3.06)	⨁⨁◯◯[1,3] Low
	Difference: 0 patients (Margin of error: 11 less to 33 more)			

Margin of error: 95% confidence interval (CI).
RR: Risk ratio.
MD: Mean difference.
GRADE: Evidence grades of the GRADE Working Group (see later).

*The risk WITHOUT acyclovir is based on the risk in the control group of the trials. The risk WITH acyclovir (and its margin of error) is calculated from relative effect (and its margin of error).

[1] The certainty of the evidence was downgraded in one level for risk of bias because the sequence of allocation was not concealed in the trials.
[2] The certainty of the evidence was downgraded in one level for inconsistency because I^2 was >80%.
[3] The certainty of the evidence was downgraded in one level due to imprecision since the confidence interval includes the possibility of a benefit or no effect.

Following the link to access the interactive version of this table (Interactive Summary of Findings – iSoF)

About the certainty of the evidence (GRADE)*

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.

† Substantially different = a large enough difference that it might affect a decision

Other considerations for decision-making

To whom this evidence does and does not apply

The evidence presented in this summary applies to children and adolescents who have varicella in an outpatient setting, and who receive treatment with acyclovir in the first 24 hours from the onset of symptoms.

It does not apply to patients with immunodeficiency, due to the direct exclusion of these in all the trials analysed.

About the outcomes included in this summary

The outcomes reported are those considered critical for decision-making, according to the opinion of the authors of this summary, and are in agreement with the ones selected by the main systematic reviews.

We considered the inclusion of the outcomes duration of lesions, hospitalizations and mortality; however, they were not reported. Considering the absence of effect in the other outcomes, there is no reason to expect an effect on the former.

Balance between benefits and risks, and certainty of the evidence

Although the intervention could reduce the duration of fever, this effect does not translate into a decrease in the complications associated with varicella. In summary, it could bring a marginal benefit in the acute course of the disease, decreasing the duration of fever.

Resource considerations

Considering that varicella is a self-limiting disease, that the trials used acyclovir in the first 24 hours of the rash, and that the economic cost of acyclovir is considerable, the clinical benefit of its use seems marginal in relation to its costs.

What would patients and their doctors think about this intervention

Considering there was no effect on the complications of varicella or a clinically relevant benefit for patients, most patients and their doctors should lean against the use in a population similar to the one evaluated in the trials. However, it is particularly important to inform patients and their caregivers about the existing uncertainty.

Differences between this summary and other sources

All the systematic reviews[1,2,3] excluded one trial[4] to estimate the benefits of acyclovir in terms of the total number of lesions and the days of appearance of new lesions, but this did not lead to different results to those obtained by this summary.

The effect of acyclovir in varicella was similar in children (2-12 years) and adolescents (12-18 years), which contrasts with the common belief that treatment would have a larger effect on adolescent population.

In the Varicella Zoster guideline of the Royal College of Physicians, symptomatic treatment is recommended acyclovir is not mentioned. This intervention is reserved for immunosuppressed or older adults[7].

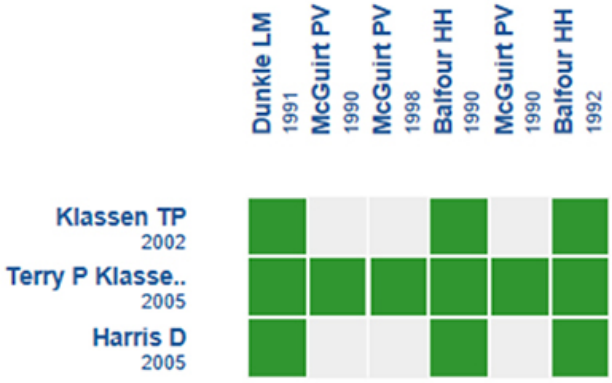
Could this evidence change in the future?

The probability of future evidence changing the conclusions of this summary is high, due to the existing uncertainty.

We did not identify ongoing trials addressing this question in the International Clinical Trials Registry Platform of the World Health Organization or systematic reviews in progress in the PROSPERO International prospective register of systematic reviews.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Una matriz de evidencia es una tabla que compara revisiones sistemáticas que responden una misma pregunta.
Las filas representan las revisiones sistemáticas, y las columnas muestran los estudios primarios.
Los recuadros en verde corresponden a estudios incluidos en las respectivas revisiones.
El sistema detecta automáticamente nuevas revisiones sistemáticas incluyendo cualquiera de los estudios primarios en la matriz, las cuales serán agregadas si efectivamente responden la misma pregunta.

Follow the link to access the **interactive version:** Acyclovir for varicella.

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier.

After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears.

This article is part of the Epistemonikos Evidence Synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and internal peer review process. Each of these articles corresponds to a summary, denominated FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question, with a friendly format to clinical professionals. Its main resources are based on the evidence matrix of Epistemonikos and analysis of results using GRADE methodology. Further details of the methods for developing this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997)

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database

www.epistemonikos.org.

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