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Is iloprost effective in secondary Raynaud's phenomenon?

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Abstract

Patients with systemic sclerosis frequently have Raynaud's phenomenon and digital ischemic ulcers. Iloprost, a synthetic prostacyclin analogue, may be effective in these cases. Searching in Epistemonikos database, which is maintained by screening 20 databases, we identified three systematic reviews including seven randomized trials. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded iloprost may lead to little or no difference in the frequency or severity of secondary Raynaud, and it is associated to adverse effects and important costs.

Resumen

Los pacientes con esclerodermia presentan con frecuencia fenómeno de Raynaud asociado y úlceras digitales isquémicas. El iloprost, un análogo sintético de prostaciclina, podría ser efectivo en estos casos. Utilizando la base de datos Epistemonikos, la cual es mantenida mediante búsquedas en 20 bases de datos, identificamos tres revisiones sistemáticas que en conjunto incluyen siete estudios aleatorizados. Realizamos un metanálisis y tablas de resumen de los resultados utilizando el método GRADE. Concluimos que iloprost podría disminuir poco o nada la frecuencia y gravedad de los episodios de Raynaud secundario, y se asocia a efectos adversos y costos importantes.

Problem

Systemic sclerosis is a connective tissue disease characterized by fibrosis and vascular phenomena that frequently affect the skin and other organs. About 90% of patients with systemic sclerosis suffer from secondary Raynaud's phenomenon, which is usually more severe and it is accompanied by digital ischemic ulcers that carry the risk of infection, gangrene, osteomyelitis and amputation. Iloprost, a synthetic prostacyclin analogue with vasodilatory effect, has been proposed as a treatment for Raynaud's phenomenon associated to systemic sclerosis.

Methods

We used Epistemonikos database, which is maintained by screening more than 20 databases, to identify systematic reviews and their included primary studies.

With this information we generated a structured summary 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, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- Iloprost may lead to little or no difference in the frequency or severity of secondary Raynaud, and it is associated to adverse effects.
- It is not known if iloprost affects digital ulcer healing because the certainty of the evidence was estimated as very low.
- It is not known what is the benefit/risk ratio, and the benefit/cost is probably not favorable.

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] including seven randomized controlled studies comparing iloprost vs placebo [4],[5],[6],[7],[8],[9],[10]. One of the studies did not report usable data for our analysis, so it is not considered in this table or in the summary of findings [5].
What types of patients were included.	All studies included patients with systemic sclerosis exclusively, except one that also included patients with severe primary Raynaud's [6], but presented data in a way that allowed to separate the information of the systemic sclerosis group. Patients included in the studies presented a mean of 18 to 28 attacks per week [4],[7],[9],[10]. Two studies included patients with more than 12 episodes per week [6], but did not report average baseline frequency, and one study did not report any data on this regard [8].
What types of interventions were included.	Two studies evaluated oral iloprost [4],[7], and the rest administered it intravenously. The duration of treatment was variable, from three days to six weeks in the different studies.
What types of outcomes were measured.	Frequency, severity and duration of attacks; global evaluation of the impact of Raynaud's phenomenon made by patients or physicians; digital ulcer healing; Raynaud's score, etc.

Summary of findings

This information is based on six of seven randomized studies identified, including 595 patients. Five studies reported frequency [4],[6],[7],[9],[10], and four severity of attacks [4],[6],[8],[9]. Three studies measured digital ulcer healing [6],[8],[9], but only two reported data adequately [8],[9]. Adverse effects were reported in four studies [4],[7],[8],[9].

- Iloprost may lead to little or no difference in the frequency or severity of secondary Raynaud.
- It is not known if iloprost affects digital ulcer healing because the certainty of the evidence was estimated as very low.

Iloprost for secondary Raynaud's phenomenon

Patients Raynaud's phenomenon secondary to systemic sclerosis
Intervention Iloprost
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT Iloprost	WITH Iloprost		
	Difference: patients per 1000			
Frequency of attacks	The frequency of attacks decreased 11.2% (Margin of error: 24.52% less to 2.18% more)		MD -11.17 (-24.52 to 2.18)	⊕⊕◯◯ [1,2,3] Low
Severity of attacks	The severity of attacks decreased 2.3% (Margin of error: 6.27% less to 1.63% more)		MD -2.32 (-6.27 to 1.63)	⊕⊕◯◯ [1,2,3] Low
Digital ulcer healing	190 per 1000	322 per 1000	RR 1.69 (0.81 to 3.51)	⊕◯◯◯ [2,3] Very low
	Difference: 132 patients more per 1000 (Margin of error: 36 less to 478 more)			
Associated adverse effects	205 por 1000	440 por 1000	RR 2.15 (1.72 to 2.68)	⊕⊕⊕⊕ High
	Difference: 235 patients more per 1000 (Margin of error: 137 to 344 more)			

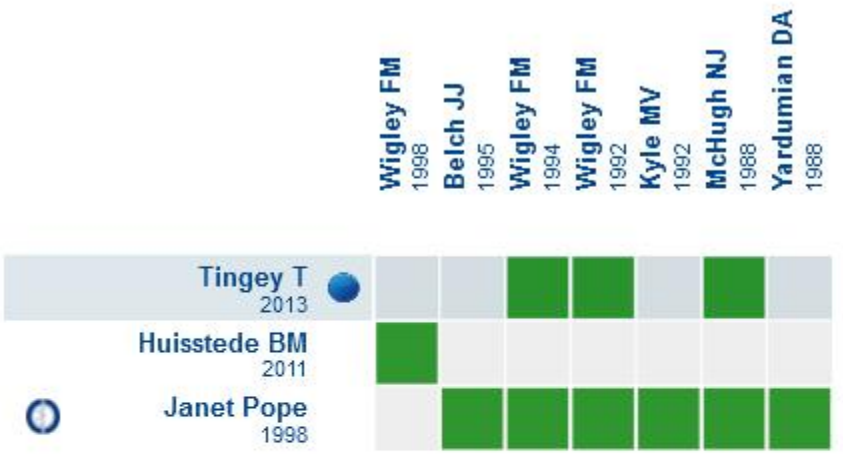
MD=Mean difference
RR: Risk ratio
Margin of error = 95% confidence interval.
GRADE: evidence grades of the GRADE Working Group (see last page)
* The risk in the group WITHOUT iloprost is based on the risk in the control group of the trials. The risk with iloprost (and its margin of error) is calculated from relative effect (and its margin of error)
**Adverse effects leading to treatment withdrawal.
[1]There is very important inconsistency in the studies. Some show big effect and some no effect. I^2 is 97% for frequency and 98% for severity.
[2] The effect estimate is not precise, including both benefit and risk. We downgraded two levels of certainty for digital ulcer healing, and one level for other outcomes.
[3] Even though we identified unpublished studies, these would probably support our conclusion, so we did not decrease the certainty of the evidence for this reason, except for digital ulcer healing.

Matrix of evidence: Iloprost vs placebo for secondary Raynaud's phenomenon

Other considerations for decision-making

To whom this evidence does and does not apply
• Studies have included patients with severe Raynaud's phenomenon secondary to systemic sclerosis. If the intervention has any benefit, this would be of less magnitude in less severe patients. • None of the studies evaluated patients with Raynaud's phenomenon secundary to other diseases, and only one study included a few patients with Primary Raunaud's, so evidence should be applied cautiously to these groups.
About the outcomes included in this summary
• Outcomes selected for this summary are those for which there is more information, and have been used in systematic reviews and guidelines. However, some research has shown the more important outcomes for patients might be others, insufficiently researched up to know [11],[12].
Balance between benefits and risks, and certainty of the evidence
• It is not possible to provide a risk/benefit ratio, since there is uncertainty about the latter. • The use of iloprost in these patients is not supported by evidence and it is associated to adverse effects and costs. However, in non-resource-constrained scenarios some patients might be inclined to use an unproven treatment. It is particularly important to inform the patient about the certainty of the evidence.
What would patients and their doctors think about this intervention
• This summary considers the outcomes more commonly used in guidelines. However, these migh not be the key outcomes for decision-making, so patients and clinicians will face substantial uncertainty.
Consideraciones de recursos
• Iloprost has high cost, and even though there is variability about the administration period in the studies, it is usually used for long periods in clinical practice. • Considering uncertainty about benefits, specially on the more important outcomes, it is not possible to provide an adequate cost/benefit analysis. However, given the scarce magnitude of benefits, if any, and the high cost, this balance is probably not favorable to using iloprost in these patients.
Differences between this summary and other sources
• This summary differs substantially from individual systematic reviews identified. The Cochrane review [2] is the more complete one, but did not include one study that evaluated more patients than all of the other studies combined [7]. Regarding the other reviews, one of them did not conduct meta-analysis of all of the studies, presenting the results of the Cochrane review and the newer study, but does not provide a pool estimate [1]. The third review is only focused on studies measuring digital ulcer healing outcomes [3]. • Our summary differs from the main guideline identified, which strongly recommends the intervention [13].
Could this evidence change in the future?
• Taking into account the current certainty of the evidence, the likelihood of new studies changing what we already know about the effects of iloprost on secundary Raynaud's phenomenon is high. • We identified at least four registered randomized studies evaluating this question that have not been published yet nor provided results in any other format up to now [14],[15],[16],[17]. So, a new systematic review might provide discordant information from the body of evidence evaluated in this summary.

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.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database (the review from which the matrix is built, appears highlighted).
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the interactive version [Iloprost vs placebo for secondary Raynaud's phenomenon]

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.

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 the website of Medwave or to contact the authors through email if they realize there is 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.

The details about the methods used to produce this summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organisation aiming to bring information closer to those making health decisions, through the use of technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

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