MEDwave

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
Medwave 2016; 16(Suppl5):e6801 doi: 10.5867/medwave.2016.6801

What is the role of recombinant activated protein C in the management of sepsis?

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Citation: Alvarado J, Castro R. What is the role of recombinant activated protein C in the management of sepsis?. *Medwave* 2016; 16(Suppl5):e6801 doi: 10.5867/medwave.2016.6801
Publication date: 20/12/2016

Abstract

During an episode of sepsis, systemic inflammatory response phenomenon triggers a series of procoagulant mechanisms. It has been suggested that the use of activated protein C could play a role in the management of this pathology, but there is no consensus. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified seven systematic reviews covering 35 primary studies addressing the question of this article, including six randomized trials. We extracted data, combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded activated protein C in sepsis probably does not decrease the mortality rate and increases the rate of hemorrhagic events.

Problem

Sepsis continues leading the causes of morbidity and mortality in intensive care units. Its incidence has been increasing, with greater complications and with more resistant infectious agents. While there has been some tendency to decreased mortality through some interventions, effective therapeutic tools remain limited.

Human protein C is a vitamin K dependent glycoprotein, structurally similar to other proteins that affect blood clotting, such as prothrombin, Factor VII, Factor IX and Factor X. It is thought that it would play an important role by regulating the anticoagulation, inflammation, cell death and maintaining the permeability of the walls of blood vessels. The pharmaceutical company that produced this drug withdrew it from the market in 2011.

Methods

We used Epistemonikos database, which is maintained by screening multiple 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
- The use of activated protein C in patients with sepsis probably does not decrease mortality.
- The use of activated protein C in patients with sepsis increases the risk of severe bleeding.
- Activated protein C is a high-cost therapy with clinically important adverse effects. For this reason it was withdrawn from the market.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found seven systematic reviews [1],[2],[3],[4],[5],[6],[7], including 35 primary studies [8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22] [23],[24], [25],[26], [27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38],[39],[40],[41],[42], six of which correspond to randomized controlled trials relevant to the question in this summary [8],[9],[10],[11],[12],[13]. This table and the summary in general are based on the latter.
What types of patients were included	Regarding the types of patients, it should be noted that the six trials were carried out after 1991, the year that the first consensus definition for sepsis and septic shock was performed, so that the definition and graduation of the severity of sepsis is homogenous between trials.
What types of interventions were included	In four of six trials, the type of activated protein C used was drotrecogin alpha-activated [8],[11],[12],[13] and in two was activated human C protein (rhAPC) [9],[10]. The route of administration was intravenous in all trials. Regarding the dose, five used a standard dose of 24 µg/kg/hour for a total of 96 hours [8],[10],[11],[12],[13]. One trial used variable doses and different time than 96 hours [9]. All trials compared against placebo or standard treatment.
What types of outcomes were measured	The different systematic reviews identified grouped the outcomes as follows: • Total mortality at 28 days of administration • 28-days mortality according to the age of the patients enrolled • 28-days mortality according to the duration of treatment • 28-days mortality according to protocol PROWESS (24 µg/kg/ hour of drotrecogin alpha for 96 hours) • 28-days mortality with treatment of more days than PROWESS • 28-days mortality according to APACHE II score • 28-days mortality according to levels of plasma protein C before infusion • 28-days mortality according to the number of organs affected • In-hospital overall mortality • Rate of massive bleeding during the first 28 days • Massive bleeding rate during administration of activated protein C • Overall hemorrhagic stroke rate during treatment

Summary of findings

The information on the effects of activated protein C on sepsis is based on six randomized trials including 6,781 patients. All trials measured the outcome mortality at 28 days and severe bleeding. The summary of findings is as follows:

- The use of activated protein C in patients with sepsis probably does not decrease the mortality rate. The certainty of the evidence is moderate.
- The use of activated protein C in patients with sepsis increases the rate of severe bleeding during hospitalization. The certainty of the evidence is high.

Activated protein C for sepsis				
Patients Intervention Comparison	Sepsis Activated protein C Placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT activated protein C	**WITH Activated protein C**		
	Difference: patients per 1000			
Mortality at 28 days	229 per 1000	226 per 1000	RR 0.98 (0.88 to 1.1)	⊕⊕⊕◯[1] Moderate
	Difference: 3 patients less per 1000 (Margin of error: 22 less to 17 more)			
Severe bleeding	22 per 1000	32 per 1000	RR 1.48 (1.1 to 2.0)	⊕⊕⊕⊕ High
	Difference: 10 patients more per 1000 (Margin of error: 2 to 21 more)			

RR= Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

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

[1] We downgraded the certainty of the evidence because of inconsistency of results among trials.

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 first consensus on the definition of sepsis was developed in 1991 where a definition of sepsis was made and the terms severe sepsis and septic shock were proposed. In the year 2016, the third consensus gave rise to the new definition of sepsis involving organic dysfunction, eliminating the concept of severe sepsis. All patients would fall into the last definition involving the concepts of sepsis and septic shock. So the evidence summarized in this article can be applied to patients with any type of sepsis and septic shock.

About the outcomes included in this summary

- This summary includes the two most important outcomes in deciding whether or not to use activated protein C, according to the opinion of the authors of this summary. These two outcomes are also those in which systematic reviews place greater emphasis. In addition, it would increase other adverse events not disaggregated in this article.

Balance between benefits and risks, and certainty of the evidence

- Activated protein C in patients with sepsis probably does not decrease the rate of 28-days mortality and, according to the analyses, produces an increase in the rate of massive hemorrhage within treated patients. The benefit/risk balance is unfavorable to the use of activated protein C.

What would patients and their doctors think about this intervention

- While Eli Lilly's drotrecogin alfa product generated high expectations for its promising results, in the light of all the existing evidence, all clinicians should give up their use.

Resource considerations

- It is an intervention that does not produce benefit and is associated to adverse effects, and that also carries a high cost.

Differences between this summary and other sources

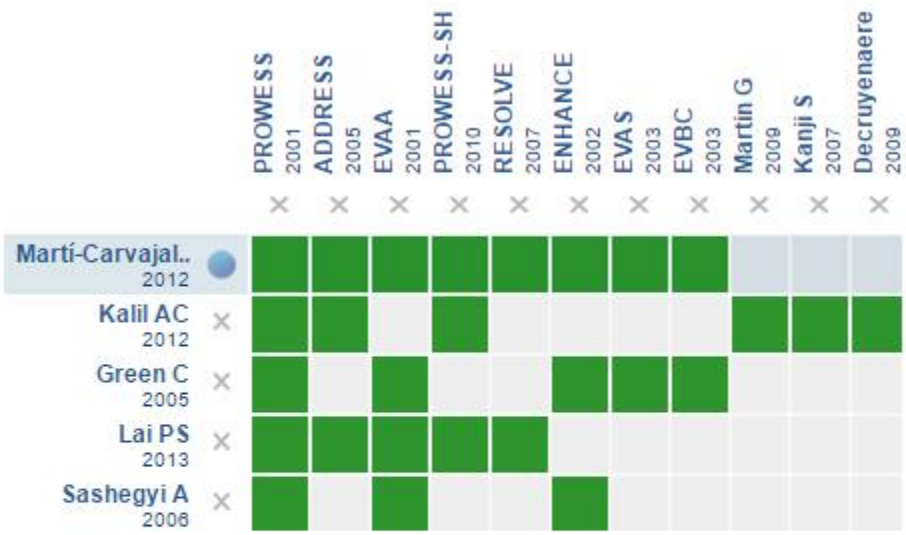
- Our summary is consistent with the conclusions of most identified systematic reviews. However, in three systematic reviews [1],[2],[6] the findings are different and support the use of activated C protein either in patients with septic shock [1],[2] or in any type of patient [6].
- Following the results found in one of the systematic reviews the drug was withdrawn from the market in several countries and the main guideline recommends against its use [43].

Could this evidence change in the future?

- The probability that the presented evidence changes in the future is very low due to the certainty of the existing evidence and the withdrawal of the drug from the market.

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 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**: Recombinant activated protein C for the treatment of sepsis

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.

The details about the methods used to produce these summaries 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).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

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