

Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

Medwave 2015 Ago;15(Suppl 2):e6233 doi: 10.5867/medwave.2015.6233

What are the effects of hypertonic saline plus furosemide in acute heart failure?

Authors: Patricio Zepeda[1,3], Carmen Rain[1,3], Paola Sepúlveda[2,3]

Affiliation:

[1] Programa de Salud Basada en Evidencia, Pontificia Universidad Católica de Chile, Santiago, Chile

[2] Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile

[3] Proyecto Epistemonikos

E-mail: pasepulveda@med.puc.cl

Citation: Zepeda P, Rain C, Sepúlveda P. What are the effects of hypertonic saline plus furosemide in acute heart failure?. *Medwave* 2015 Ago;15(Suppl 2):e6233 doi: 10.5867/medwave.2015.6233

Publication date: 27/8/2015

Abstract

In search of new therapies to solve diuretic resistance in acute heart failure, the addition of hypertonic saline has been proposed. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified two systematic reviews including nine pertinent randomized controlled trials. We combined the evidence and generated a summary of findings following the GRADE approach. We concluded hypertonic saline associated with furosemide probably decrease mortality, length of hospital stay and hospital readmission in patients with acute decompensated heart failure.

Problem

Volume depletion is the mainstay of treatment for acute heart failure, mainly with loop diuretics such as furosemide. However, some patients develop resistance to diuretics. Among the alternatives that have arisen as a potential solution to this clinical problem is the use of hypertonic saline. The increase in plasma osmolarity allows mobilization of extracellular fluid into intravascular. As baroreceptors sense intravascular expansion, peripheral resistance decreases, improving ejection fraction, therefore increasing kidney and other organs blood flow, which improves response to diuretics. In addition, animal studies show hypertonic saline alone could improve myocardial contractility and reduce proinflammatory factors.

Methods

We used Epistemonikos database, which is maintained by screening more than 30 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

- Adding hypertonic saline to furosemide probably decreases mortality, length of hospital stay and hospital readmissions in patients with acute heart failure.

About the body of evidence for this question

<p>What is the evidence. See evidence matrix in Epistemonikos later</p>	<p>We found two systematic reviews [1],[2] including nine randomized controlled trials reported in 10 references [3],[4],[5],[6],[7],[8],[9],[10],[11],[12].</p>
<p>What types of patients were included</p>	<p>All studies included patients with heart failure; six of them had reduced ejection fraction as inclusion criteria: three with <45% [4],[6],[7], three with <40% [8],[11],[12] and one with <35% [9],[10]. Three studies required patients were refractory to standard treatment [4],[7],[9],[10]. Seven studies restricted inclusion to patients with preserved renal function: three of them set creatinine limit in 2 mg/dl and without previous consumption of non-steroidal anti-inflammatories [4],[7],[9],[10].</p>
<p>What types of interventions were included</p>	<p>Hypertonic saline in various concentrations, adjusted according sodium plasma level in five studies [4],[6],[8],[9],[10],[11], combined with intravenous furosemide in doses ranging from 250 to 2000 mg/day, administered either as bolus or continuous infusion. All studies compared with furosemide alone that was administered in the same way and dose as in the group intervened.</p>
<p>What types of outcomes were measured</p>	<p>All-cause mortality, mortality from heart failure, need for hospitalization, length of hospital stay, change in New York Heart Association (NYHA) classification, renal function, cardiac markers, body weight.</p>

Summary of findings

Information on the effects of adding hypertonic saline to the treatment with furosemide is based on nine randomized trials including 2566 patients. Only four studies reported overall mortality [4],[8],[10],[12], three studies reported readmissions [4],[8],[10], six studies reported length of hospital stay [4],[6],[7],[8],[10],[11] and seven studies reported change in creatinine serum level [3],[4],[6],[7],[8],[10],[12].

- Adding hypertonic saline to furosemide probably decreases mortality in patients with acute heart failure. The certainty of the evidence is moderate.
- Adding hypertonic saline to furosemide probably decreases length of hospital stay in patients with acute heart failure. The certainty of the evidence is moderate.
- Adding hypertonic saline to furosemide probably decreases hospital readmissions in patients with acute heart failure. The certainty of the evidence is moderate.

Hypertonic saline with furosemide in acute heart failure				
Patients	Acute heart failure			
Intervention	Hypertonic saline with furosemide			
Comparison	Furosemide alone			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT hypertonic saline	WITH hypertonic saline		
	Difference: patients per 1000			
All cause mortality	265 per 1000	122 per 1000	RR 0.46 (0.36 to 0.59)	⊕⊕⊕○ [†] Moderate
	Difference: 143 patients less per 1000 (Margin of error: 109 to 170 less)			
Hospital readmission	364 por 1000	193 por 1000	RR 0.53 (0.45 to 0.61)	⊕⊕⊕○ [†] Moderate
	Difference: 171 patients less per 1000 (Margin of error: 142 to 200 less)			
Length of hospital stay	5.5 days	3.42 days	MD -2.08 (-2.16 to -1.99)	⊕⊕⊕○ [†] Moderate
	Difference: 2.08 days less (Margin of error: 1.99 to 2.16 less)			
RR: Risk ratio. MD: Mean difference. Margin of error = 95% confidence interval (CI). GRADE: evidence grades of the GRADE Working Group (see later in this article). * The risk WITHOUT hypertonic saline is based on the risk in the control group of the trials. The risk WITH hypertonic saline (and its margin of error) is calculated from relative effect (and its margin of error). † There is moderate risk of bias because most studies do not describe withdrawals and lost to follow-up.				

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 studies coincide on including patients with decompensated heart failure from any cause with decreased ejection fraction (EF <45%) with serum creatinine lower than 2 mg/dl, so the main population to apply this treatment are patients with these characteristics .
 - While studies excluded patients with creatinine greater than 2, it is reasonable to extrapolate this evidence to patients with severe renal dysfunction as pathophysiology would suggest a similar or greater effect.
-

About the outcomes included in this summary

- The outcomes presented in this summary are those considered critical for decision making by the authors of this summary, and coincide with those used in major clinical guidelines [13],[14],[15],[16].
-

Balance between benefits and risks, and certainty of the evidence

- The use of hypertonic saline with furosemide is a low-cost therapy that could decrease the use of inotropic therapy, mortality, hospital readmission, length of hospital stay and plasma creatinine (creatinine decreased in 0.56 mg/dl in the hypertonic saline group).
-

Resource considerations

- Regarding resources, it is considered a low-cost intervention, so the cost/benefit ratio is favorable.
-

Differences between this summary and other sources

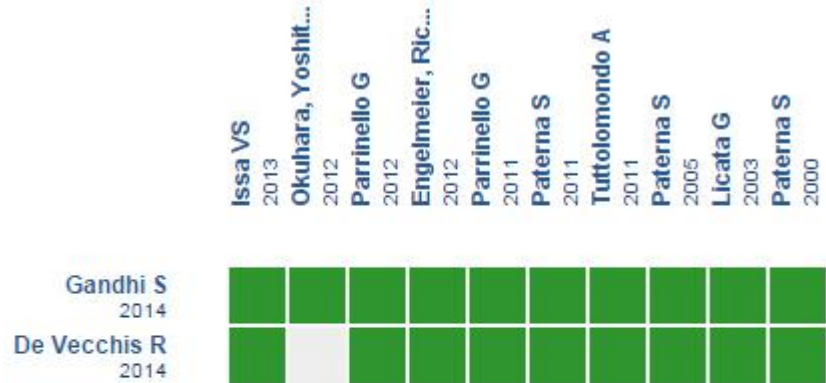
- Our conclusions are consistent with those of the systematic reviews [1],[2] in terms of mortality reduction, readmission, length of hospital stay and decreased plasma creatinine.
 - None of the main clinical guidelines [13],[14],[15],[16] mentioned the addition of hypertonic saline to furosemide, although it is important to state the systematic reviews were published later than most guidelines.
-

Could this evidence change in the future?

- The likelihood that future evidence change the information presented in this summary is low due to the certainty of the evidence.
 - We did not identify additional ongoing studies, so it is unlikely that new relevant information to this question appears.
-

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**: [Hypertonic saline plus furosemide for acute heart failure](#)

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.

References

1. Gandhi S, Mosleh W, Myers RB. Hypertonic saline with furosemide for the treatment of acute congestive heart failure: a systematic review and meta-analysis. *Int J Cardiol.* 2014 May 1;173(2):139-45. | [CrossRef](#) | [PubMed](#) |
2. De Vecchis R, Esposito C, Ariano C, Cantatrione S. Hypertonic saline plus i.v. furosemide improve renal safety profile and clinical outcomes in acute decompensated heart failure: A meta-analysis of the literature. *Herz.* 2015 May;40(3):423-35. | [CrossRef](#) | [PubMed](#) |
3. Engelmeier RS, Le TT, Kamalay SE, Utecht KN, Nikstad TP, Kaliebe JW, et al. Randomized trial of high dose furosemide-hypertonic Saline in acute decompensated heart Failure with advanced renal disease. *Journal Am Coll Cardiol.* 2012;59(13s1):E958-E958. | [Link](#) |
4. Licata G, Di Pasquale P, Parrinello G, Cardinale A, Scandurra A, Follone G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-

- term effects. *Am Heart J.* 2003 Mar;145(3):459-66. | [PubMed](#) |
5. Okuhara Y, Hirotsu S, Naito Y, Iwasaku T, Eguchi A, Sawada H, et al. Impact of concomitant administration hypertonic saline solution and daily use furosemide in treatment of acute decompensated heart failure: Abstract 12149. *Cardiology.* 2012;126(21 Supplement). | [Link](#) |
 6. Parrinello G, Di Pasquale P, Torres D, Cardillo M, Schimmenti C, Lupo U, et al. Troponin I release after intravenous treatment with high furosemide doses plus hypertonic saline solution in decompensated heart failure trial (Tra-HSS-Fur). *Am Heart J.* 2012 Sep;164(3):351-7. | [CrossRef](#) | [PubMed](#) |
 7. Parrinello G, Paterna S, Di Pasquale P, Torres D, Mezzero M, Cardillo M, et al. Changes in estimating echocardiography pulmonary capillary wedge pressure after hypersaline plus furosemide versus furosemide alone in decompensated heart failure. *J Card Fail.* 2011 Apr;17(4):331-9. | [CrossRef](#) | [PubMed](#) |
 8. Paterna S, Fasullo S, Parrinello G, Cannizzaro S, Basile I, Vitrano G, et al. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York Heart Association class III (Class C) (SMAC-HF Study). *Am J Med Sci.* 2011 Jul;342(1):27-37. | [CrossRef](#) | [PubMed](#) |
 9. Paterna S, Di Pasquale P, Parrinello G, Amato P, Cardinale A, Follone G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. *Eur J Heart Fail.* 2000 Sep;2(3):305-13. | [PubMed](#) |
 10. Paterna S, Di Pasquale P, Parrinello G, Fornaciari E, Di Gaudio F, Fasullo S, et al. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide alone in refractory congestive heart failure: a double-blind study. *J Am Coll Cardiol.* 2005 Jun 21;45(12):1997-2003. | [PubMed](#) |
 11. Tuttolomondo A, Pinto A, Di Raimondo D, Corrao S, Di Sciacca R, Scaglione R, et al. Changes in natriuretic peptide and cytokine plasma levels in patients with heart failure, after treatment with high dose of furosemide plus hypertonic saline solution (HSS) and after a saline loading. *Nutr Metab Cardiovasc Dis.* 2011 May;21(5):372-9. | [CrossRef](#) | [PubMed](#) |
 12. Issa VS, Andrade L, Ayub-Ferreira SM, Bacal F, de Bragança AC, Guimarães GV, et al. Hypertonic saline solution for prevention of renal dysfunction in patients with decompensated heart failure. *Int J Cardiol.* 2013 Jul 15;167(1):34-40. | [CrossRef](#) | [PubMed](#) |
 13. Lindenfeld J, Albert NM, Boehmer JP, Collins SP, Ezekowitz JA, Givertz MM, et al. HFSA 2010 Comprehensive Heart Failure Practice Guideline. *J Card Fail* [Internet]. 2010 Jun;16(6):e1-194. | [Link](#) |
 14. Moe GW, Ezekowitz JA, O'Meara E, Lepage S, Howlett JG, Fremes S, et al. The 2014 Canadian Cardiovascular Society Heart Failure Management Guidelines Focus Update: anemia, biomarkers, and recent therapeutic trial implications. *Can J Cardiol.* Elsevier; 2015 Jan 1;31(1):3-16. | [Link](#) |
 15. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* 2013 Oct 15;128(16):e240-327. | [Link](#) |
 16. McMurray JJ V, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart. *Eur Heart J.* 2012 Jul;33(14):1787-847. | [Link](#) |

Author address:

[1] Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63
Santiago Centro
Chile



Esta obra de Medwave está bajo una licencia Creative Commons Atribución-No Comercial 3.0 Unported. Esta licencia permite el uso, distribución y reproducción del artículo en cualquier medio, siempre y cuando se otorgue el crédito correspondiente al autor del artículo y al medio en que se publica, en este caso, Medwave.