

## **Hypertonic is the solution? – a systematic review and meta-analysis**

Pedro O. Corda<sup>1\*</sup>(BSc), Daniel Resende<sup>1\*</sup>(BSc), Maria Cristina Mautempo Coelho<sup>2</sup>(MSc), José Mesquita Bastos<sup>2,3</sup> (MD, PhD) and Vera Afreixo<sup>4</sup> (PhD)

Correspondence email: pedrocorda@ua.pt

\*Both authors contributed equally in this work

1 Institute for Research in Biomedicine, Medical Sciences Department, University of Aveiro, Aveiro, Portugal.

2 Centro Hospitalar do Baixo Vouga, EPE, Aveiro, Portugal

3 School of Health, University of Aveiro, Aveiro, Portugal

4 Department of Mathematics & CIDMA, University of Aveiro, Portugal

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**Introduction:** Shock is broadly defined as an expression of circulatory failure resulting in decreased oxygen transport and nutrients and consequent cellular and tissue hypoxemia. Although reversible in its early phase, it can pose as a life-threatening condition and as such, constitutes a priority to treat (1). Four types of shock can be described: hypovolemic, cardiogenic, obstructive, and distributive (2). Hypovolemic shock constitutes one of the most common complications of blood loss that usually follows episodes of severe trauma (such as car accidents), post-operation haemorrhages or massive gastrointestinal bleeding (3). Currently, the isotonic solution of NaCl (0,9%) represents the hallmark solution to address this problem. However, its applicability is limited since in situations of severe volume losses it is necessary to apply a large quantity of isotonic solutions, which may cause several systemic complications (such as heart failure). Due to the limitation of volume transport and the adverse conditions that are felt in war-ravaged scenarios, a better alternative for the treatment of hypovolemic shock was needed. Hypertonic solutions (concentration of NaCl bigger than 0,9%) arise as a good candidate, allowing the restoration of vascular volume through a low volume of administration. Moreover, these solutions were very stable in the war conditions. However, because of its high concentration of NaCl, these solutions may have some adverse effects such as neuronal, renal and cardiovascular dysfunction. In recent years, a widespread group of alternatives are rising to more effectively resolve hypovolemic shocks, such as gelatines and colloids. Similar to hypertonic solutions, colloid solutions can be administered in small volumes and are stable over adverse conditions. Nevertheless, these

types of solutions are expensive and in the last years some of them have been reported as a cause of dead and renal complications (4). With the aim to try to find some alternatives some meta-analyses have been published in the last two years reassessing the potential of hypertonic solutions. These meta-analyses compare the isotonic and hypertonic solution, however, there is a flaw in comparison with colloids. Our study has the major goal of to compare the effectiveness of hypertonic solutions against the effectiveness of colloids solutions through an indirect meta-analysis approach.

**Methods:** To achieve the goal of this paper, the approach began initially by splitting data into two different groups: (i) articles that compare hypertonic and isotonic solutions and (ii) articles that compare colloids with isotonic solutions. Two direct meta-analyses were found and used as the start point for this work: (a) the first one compares hypertonic and isotonic solutions (5); (b) the second compares colloids and isotonic solutions (6). In both meta-analyses, the data was selected from situations of hypovolemic shock. After analysing data from both papers, an update on the current state of the art was considered, which was executed through a search in major electronic databases (PubMed, OVID, Embase and Central). For that purpose, the predefined mesh terms in each meta-analysis were used. In order to standardize the type of articles that would be included in the final analysis, a set of inclusion and exclusion criteria were defined based on the start point meta-analysis. These criteria were applied either in the papers included in both meta-analysis and in the update made. Data collection was done specifically for each group (i or ii). Major outcomes were considered: global mortality, mortality in the first 28 days, survival at discharge and systemic complications (neuronal, renal and cardiac dysfunctions). Data synthesis and analysis was conducted using a random and a fixed-effects model for two direct meta-analyses. The heterogeneity was evaluated by the Cochrane Chi-Square and the  $I^2$  statistic and the potential risk of bias was assessed through Egger's test. Transitivity assumption was used to perform the indirect meta-analysis and the effect estimates were produced by using the Bucher method. The meta-analysis was performed using MetaXL 5.3.

**Results:** Twelve and forty papers were retrieved from Thomas-Rueddel *et al.*, 2012 and Wu *et al.*, 2017, respectively. With the mesh terms from Thomas-Rueddel *et al.*, 2012 and Wu *et al.*, 2017, a total of 2053 citations were found among the databases already mentioned. 1678 citations were excluded based solely on the title and abstract analysis. Simultaneously, 6 citations were found to further analysis based on reference lists and other databases (i.e. Science Direct), totalling in 381 papers. Furthermore, this list was shortened for the following reasons: animal models (97); unavailable (6); not relevant (49); no hypovolemia (82);

uncontrolled (35); language (14); comparator not suitable or duplicated (58). After considering all criteria in the above-mentioned papers, a total of twenty-four articles were included with a total of 3523 individuals. For the mortality outcome, there are no significant differences between any treatment pair under analysis (see Table 1).

**Table 1:** All pairwise comparisons results obtained by Bucher method. Alb: Albumin; ISO: isotonic solution; Col: Colloid; HS: Hypertonic solution; HS D: Hypertonic solution with Dextran; RR: Relative Risk; LCI: Lower confidence interval; HCI: Higher confidence interval

Treatment 1	Treatment 2	RR	LCI 95%	HCI 95%
Alb	ISO	1.898495	0.677042	5.323574
Alb	HS	3.103392	0.342237	28.14143
Alb	HS D	2.780265	0.307045	25.17508
Alb	Col	1.019002	0.718252	1.445683
ISO	HS	1.016841	0.883099	1.170838
ISO	HS D	0.939066	0.825538	1.068206
ISO	Col	0.536742	0.19838	1.452224
HS	HS D	0.923513	0.788381	1.081808
HS	Col	0.583375	0.189413	1.796742
HS D	Col	0.651175	0.212024	1.999907

**Conclusion:** As previous reports described, no increase in mortality is significant when treatment with hypertonic solutions is applied, showing no relation between the outcomes analysed and the type of fluid used in treatment in either direct or indirect meta-analysis. However, hypertonic solutions seem to be an alternative in some emergency settings, requiring further studies to better elucidate this problem and effectively solve what is the best solution to treat hypovolemic shock in specific scenarios.

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ACCEPTED EXTENDED ABSTRACT