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How safe is gelatin? A systematic review and meta-analysis of gelatin-containing plasma expanders vs crystalloids and albumin☆,☆☆,★

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ABSTRACT

Gelatin is a widely used synthetic colloid resuscitation fluid. We undertook a systematic review and meta-analysis of adverse effects in randomized and nonrandomized studies comparing gelatin with crystalloid or albumin for treatment of hypovolemia. Multiple databases were searched systematically without language restrictions until August 2015. We assessed risk of bias of individual studies and certainty in evidence assessment by the Grading of Recommendations Assessment, Development, and Evaluation approach. Sixty studies were eligible, including 30 randomized controlled trials, 8 nonrandomized studies, and 22 animal studies. After gelatin administration, the risk ratios were 1.15 (95% confidence interval, 0.96-1.38) for mortality, 1.10 (0.86-1.41) for requiring allogeneic blood transfusion, 1.35 (0.58-3.14) for acute kidney injury, and 3.01 (1.27-7.14) for anaphylaxis. Well-performed nonrandomized trials found increased rates of hospital mortality and acute kidney injury or renal replacement therapy in the gelatin intervention periods. Between 17% and 31% of administered gelatin was taken up extravascularly. The mean crystalloid-to-colloid ratio was 1.4. Gelatin solutions increase the risk of anaphylaxis and may be harmful by increasing mortality, renal failure, and bleeding possibly due to extravascular uptake and coagulation impairment. Until well-designed randomized controlled trials show that gelatin is safe, we caution against the use of gelatins because cheaper and safer fluid alternatives are available.

1. Introduction

Gelatin is a colloid plasma substitute approved for the treatment and prevention of hypovolemia and listed by the World Health Organization as an essential medicine. As of 2010, gelatin was used in 25% of global resuscitation episodes [1]. Despite the lack of valid trial data, clinicians may have switched to gelatin after hydroxyethyl starch (HES), another class of colloid plasma expander, was restricted by the European Medicines Agency in 2013. [2] This was seen in German cardiac surgical intensive care units (ICUs) [3] and in the sales of gelatin units which doubled those of HES in 2013 in Europe [4]; furthermore, gelatin sales increased or continue unchanged in India, China, Korea, and Japan [4].

The risk profile of gelatin may be similar to that of HES, but previous meta-analyses of randomized controlled trials (RCT) within the acute care and perioperative setting have not found differences in the risk of death [5–7] or the occurrence of adverse effects [7] after gelatin administration. However, gelatin may prolong bleeding [8,9], and the US Food and Drug Administration withdrew gelatin in 1978 because of concerns [10]. Acute kidney injury (AKI) was observed to occur more frequently in patients receiving gelatin based on observations in several cohorts of septic and surgical patients [11–13]. Gelatins also increased the risk of anaphylactoid reactions several-fold in comparison to human albumin [14]. Finally, synthetic colloids may accumulate in the body. Between 26% and 42% of administered starch is initially taken up in the extravascular compartment [15], and repeated administration led to foamy macrophages in spleen, liver, kidney, and bone marrow with worsening of organ function [16,17]. In contrast, surprisingly little is known regarding the extravascular uptake and degradation of gelatin

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Table 1
Randomized controlled trials and reported outcomes

Study ID	Patients	Study fluids	Gelatin dose (mL/kg)	Mortality	Transfusion exposure	Hemostasis	AKI	Anaphylaxis	Information on external study funding and authors' potential conflict of interest
Alavi 2012 [28]	92 Cardiac surgical patients	4% Gelatin, RL, 6% HES 130/0.4	100	24 h					
Akech 2006 [57]	88 Children with severe malaria	4% MFG, 4.5% HA	44	Hospital	Event rates			Event rates	Supported by Wellcome Trust, Wellcome Trust Senior Fellowship
Dung 1999 [67]	50 Children with dengue shock syndrome	% MFG, NS, RL, 6% dextran	30	Hospital				None occurred	Supported by the Wellcome Trust, GB and BBraun, Melsungen, Germany
Fries 2004 [29, 68]*	60 Adults with elective knee replacement surgery	4% MFG, RL, 6% HES 200/0.5	18		Event rates	TEG data			Supported by Fresenius GmbH Austria and B Braun, Melsungen, Germany
Gondos 2010 [69]	200 Critically ill patients	4% Gelatin, RL, 6% HES 130/0.4	10	ICU					Supported by Fresenius Kabi, Pulsion Medical Systems, MEDIAL Inc., HUMAN BioPlazma LLC, Hungary.
Haas 2007 [34]	42 Children scheduled for elective surgery	4% MFG, 5% HA, 6% HES 130/0.4	15			TEG data			
Himpe 1991 [70]	105 Cardiac surgical patients	3.5% ULG, 3% MFG, 20% HA	20	Hospital				None occurred	
Jin 2010 [35]	36 Patients undergoing gastrectomy for gastric cancer	4% MFG, RL, 6% HES 130/0.4	30			TEG data			Shanghai Science and Technology Development Fund, China.
Karoutsos 1999 [39]	42 Patients undergoing joint replacement	3.5% MFG, 5% HA, 6% HES 200/0.6	24			TEG data			
Karanko 1987 [71]	37 Patients with hypovolemia after CABG surgery	5.5% OPG, PPS, 6% dextran 70	10					None occurred	Supported by Turku University Foundation and the Academy of Finland
Kuitunen 2007 [36, 72]*	45 Cardiac surgical patients	4% MFG, 4% HA, 6% HES 200/0.5	15		Event rates	TEG data		None occurred	
Lamke 1976 [73]	83 Patients undergoing elective surgery	3.5% ULG, NS, 5% HA, 6% HES, 6% dextran 70	14					None occurred	
Lorenz 1994 [55]	231 Patients undergoing major surgery	3.5% ULG, RL	7					Event rates	Supported by Ciba-Geigy Zyma, Munich-Nyon; SK Beecham Pharma, Munich; Behringwerke AG, Marburg/Lahn.
Mittermayr 2007 [37]	61 Patients with major orthopedic surgery	4% MFG, RL, 6% HES 130/0.4	35		Event rates	TEG data			Supported by Fresenius, Pharma Austria GmbH, Graz, Austria, and B. Braun, Austria
Ngo 2001 [56]	222 Children with dengue shock syndrome	3% MFG, RL, NS, 6% dextran 70	20–40	Hospital				Event rates	Supported by The Wellcome Trust
NNNITG 1996 [74]	776 Preterm babies	4% MFG, dextrose 10% or dextrose saline	30	2 y					Supported by EC funds (concerted action)
Parker 2004 [75]	396 Patients with major orthopedic surgery	4% MFG, NS	7	30 d	Event rates				Supported by B. Braun Medical
Schramko 2010 [38]	45 Cardiac surgical patients	4% MFG, RA, 6% HES 130/0.4	28		Event rates	TEG data			Supported by government grant
Scott 1995 [76]	93 Cardiac surgical patients	3.5% ULG, Plasma-Lyte, 4.6% HA	13		Event rates				
Soares 2009 [30]	40 Patients with cardiac surgery without CPB	4% MFG, NS	12	30 d	Event rates		Event rates		
Stockwell 1992 [77]	475 Critically ill patients	3.5% ULG, 4.5% HA	44	ICU			Event rates		
Stoddart 1996 [78]	30 Neonates undergoing surgery	3.5% ULG, 4.5% HA	25					None occurred	
Tollofsrud 1995 [79]	40 Cardiac surgical patients	3.5% ULG, RA, 4% HA, 6% dextran 70	30	24 h					Supported by the Anders Jahre's Fund for the Promotion of Science
Topcu 2012 [80]	75 Patients with major orthopedic surgery	4% MFG, RL, 6% HES 130/0.4	36			TEG data			
Upadhyay 2005 [31]	60 Children with septic shock	3.5% ULG, NS	30	ICU			Event rates		
van der Heijden 2009 [33]	48 Critically ill patients	4% MFG, NS, 5% HA, 6% HES	20	ICU					Supported by B. Braun