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Jerry Johnson

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Author: Jerry Johnson PA-S

Advisor: Ryane Lester PA-C

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Abstract

Background: With the advent of newer and "safer" fluids there have been numerous trials and studies conducted to test the safety and validity of colloids. Are colloids more effective then crystalloid for emergent resuscitation? The purpose of this systematic literature review is to assess the claims on treatment success and explore safety to gain clarity on which fluid is the best treatment for the patient.

Methods: A systematic database search was conducted from 2006 to the present. The search utilized such sources as PubMed, UpToDate and ScienceDirect. This search included more than 70 journal articles, where 24 articles were selected for review for their credibility and usage within the medical community.

Results: Considering the reviewed articles, it seems that the benefits may not outweigh the risks inherent with colloids. In summary, using colloids as an alternative to crystalloids made little to no difference in the cause of mortality. However, there was evidence that colloids can increase the need for renal therapies overall.

Conclusion: Colloids were merely marginal, if at all, more effective than crystalloids in reducing the mortality rates, but with the added risk of renal dysfunction. There are instances where colloids might be selected, but those occurrences should be critically challenged. In the end, it appears to be left up to clinical judgement, provider experience, and accessibility on which fluid selection is optimal.

Introduction

Acute care settings are designed to treat the critically ill and injured. Providers in these settings rely on IV fluids for resuscitation of critically ill or injured patients. The goal of this paper is to evaluate the effectiveness of IV fluids to determine if colloids are more effective than crystalloids in the resuscitation of critically ill adults. The different fluids will be evaluated in the setting of sepsis, acute fluid resuscitation in the ICU, hypovolemia, to include hemorrhagic shock, and burns patients. The outcome measures will be mortality of these critically ill patients. Hemorrhage is responsible for 30–40% of trauma mortality with 33–56% of these deaths occurring during the prehospital period.[1] Patients that do reach critical care in time to receive treatment, mortality can be caused by continued hemorrhage, shock, sepsis, coagulopathy, and/or incomplete resuscitation. Altogether, the need for early resuscitation methods is critical. Treatment with blood products may not always be available or the right course of treatment for patients. Ensuring providers have all the necessary information when making treatment decisions is essential, and the reviewed trials provide insight on optimal care. Individual patient profiles were examined to determine the effectiveness of colloids. The discussion of what fluid is most suited for patient treatment has been controversial considering the main goal of IV fluids is to expand intravascular space. The main discussion that is occurring within the medical community is what is the safety and efficacy of fluids in resuscitation. Thus, comparing the long-term patient outcomes is essential in determining treatment plans. The fluids that are considered colloids are albumin, hydroxyethyl starch and gelatin. Lactated Ringer's and normal saline (sodium chloride) are considered crystalloids. These colloid and crystalloid fluids were given in the reviewed trials.

Function of Colloids and Crystalloids

Crystalloids have several different compositions and can respond differently within the body based on its biochemical structure. Crystalloids that contain sodium and chloride are water-soluble electrolytes and lack proteins that make the molecules insoluble within the body. Crystalloids containing sodium and chloride can be isotonic meaning the fluid can contain the same balance and number of electrolytes as the plasma, hypertonic meaning the fluid contains more electrolytes than the plasma, or hypotonic meaning the fluid contains less electrolytes than the plasma. Other compositions such as Ringer's lactate contain sodium chloride, along with sodium lactate, potassium chloride and calcium. Due to Ringer's lactate crystalloids having additional elemental components, Ringer's lactate crystalloids are used to replace the fluid and electrolytes with a patient that requires extra electrolyte composition. It should be noted, the most common isotonic fluids do not cause water to shift between the extracellular fluid and the intracellular fluid.[2] A major disadvantage of crystalloids is the limited time the fluid remains within the plasma. For example, when a patient is treated with a 1000mL bag of fluid, generally up to 200 mL of that fluid is maintained within the vascular system and the rest is shifted into the interstitial space.[2]

In contrast, colloids contain larger insoluble molecules than those of the crystalloid compositions, which can include proteins, complex polysaccharides, albumins, starches, and dextran. The larger molecules in colloids will not easily cross the capillary walls and remain within the intravascular space for a much longer period than crystalloids, which is where the benefit of colloid fluids are supposed to be derived.[2] The theory is larger molecules in colloids provide the ability to maintain a higher osmotic pressure for longer periods and are publicized as the main purpose of colloid fluids.

HES is a colloid composed of three hydroxy ethylated starches dispersed into a solution of water and salts. HES has two main different compositions HES 200/0.5 and HES 130/0.4, the first number represents the molecular weight and the second the ratio of substitution. The metabolism of HES is through endogenous amylase, which will break down the starch molecules (Figure 1). Next, the broken-down starch molecules will be filtered within the glomerulus and excreted into the urine. Considering the substitution ratio of the fluid being applied is extremely important. The substitution ratio is the determination of how slow or fast the molecules will degrade within the vascular system. The higher the substitution ratio is the longer the molecules will remain in the bloodstream, which in turn should require less fluids needing to be given to patients over the time of resuscitation. The usage of colloids has been tested in patients suffering from sepsis and will be discussed.

Colloid Usage in Sepsis

"Despite more than 20 years of intense therapeutic investigation, mortality from septic shock has remained at approximately 40-50%."[1] Utilizing fluid resuscitation is a mainstay in the management of severe sepsis and septic shock. "Inadequate initial treatment and delayed hemodynamic stabilization may be associated with increased risk of death in patients with severe sepsis."[3] Overall early fluid resuscitation is a major step in the management of severe sepsis and leads to improved prognosis. "Optimized management in the first 6 hours has been reported to significantly reduce mortality in patients with severe sepsis and septic shock."[3] Choosing the right fluid might be the deciding factor to shift the balance in the patient's favor. Providers must weigh the risk and benefits of all the fluids, including risks of acute kidney injury, increased bleeding, and allergic reaction/anaphylaxis. The main question that needs to be answered is what fluid is best in the treatment of sepsis and septic shock? This is a question that has been

researched over several clinical trials over the past few years. The reviewed studies provide insight into patient management and assist providers in selecting the proper fluid given the patient profile. Relevant studies involving sepsis and fluid management examined below as part of the overall review.

Assessment of Hemodynamic efficacy and safety of 6% Hydroxyethyl starch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study was double-blind, randomized, controlled multicenter study conducted throughout 24 different medical centers in France and three medical centers within Germany. One hundred patients were randomized to be treated with Hydroxyethyl starch (HES) and 96 patients were randomized to a control group with NaCl. When selecting patients, the origin of sepsis was noted and can be found within Table 1. Most patients selected had a prevalence of sepsis within the lungs and abdomen. "There were no significant differences between treatment groups in demographic and baseline characteristics."[4] The Simplified Acute Physiology Score II was used to evaluate patients estimated mortality within the ICU. The authors found that there was no significant difference in vital signs or hemodynamics within the two study groups. Patients within the study received a maximum of 50 ml/kg/day on the first day and 25 ml/kg/day from the second to the fourth day. The same formulary was used within both the HES and NaCl groups. It was noted that if any fluid was required beyond the four-day time it was intravenous crystalloids with no upper volume limit. Patients were followed for a total of 28 days and monitored for all-cause mortality. To control for provider bias, the fluids were identical in appearance and packaging. The study adequately controlled for biases and ensured the most thorough evaluation of fluids was conducted. The study used well established protocols and was found to meet safety standards by the French Independent Ethics Committee.

The authors found in order to reach the desired hemodynamic stability significantly less HES was used than NaCl (1,379 ± 886 ml in the HES group and 1,709 ± 1,164 ml in the NaCl group [Mean difference = -331 ± 1,033, 95% CI -640 to -21], P = 0.0185).[4] The time to reach hemodynamic stability was an average of 2.5 hours shorter within the HES group, however these findings were not found to be statistically significant (Table 2). The usage of HES during this study did not induce AKI and the tubular or glomerular function was not affected (Table 3). Urinary biomarkers of AKI were used as a ratio to urinary creatinine. "The study concluded that there was no statistically significant effect on mortality when comparing HES and NaCl treatment groups."[4] Therefore, the study found no major differences in mortality when contrasting HES to NaCl.

In short, this study was one of two trials reviewed that found no major difference between the need for renal replacement therapy when using HES over crystalloid for emergent resuscitation. This is the only trial that found no difference between the need for renal replacement with HES over crystalloid in sepsis. However, this has not been confirmed in larger trials. In fact, the opposite was found in larger trials and HES and other colloids should not be used within septic patients.

The next study evaluated is the *Scandinavian Starch for Severe Sepsis / Septic Shock (6S) trial*, which was a large study conducted in 2009- 2022 throughout Denmark, Norway, Finland, and Iceland. The trial was a blinded, parallel group with randomized patients (Table 4). A total of 1211 patients were evaluated with 407 being excluded for the following reasons: 138 underwent renal-replacement therapy, 152 received >1000 ml of synthetic colloids, 51 consent could not be obtained and 25 were already in another ICU trial. Consequently, 804 total patients underwent randomization, where another 4 were excluded from the trial.[5] Nonetheless, 400 were

assigned to receive HES 130/0.42 and 400 were assigned to receive Ringer's Lactate. The trial

patients all fit criteria for severe sepsis according to the Society of Critical Care Medicine and

American College of Chest Physicians. "The composite outcome measure of 90-day mortality or

end-stage kidney disease defined as dialysis-dependency 90 days after randomization will be the

primary outcome measure, and these two outcome measures will also be analyzed separately."[5]

Patients were followed up with at 6 month and 1 -year re-evaluation periods to assess for all-

cause mortality. The need for renal replacement therapy was followed for 90 days after

randomization. The fluids were visually identical and were given in 500 ml "flex bag" plastic

bottles, which were put into black plastic bags to control for provider bias.

"The primary outcome, death or dependence on dialysis at 90 days after randomization,

occurred in 202 patients (51%) in the starch group as compared with 173 patients (43%) in the

Ringer's acetate group (relative risk, 1.17; 95% CI, 1.01 to 1.36; P = 0.03)."[5] The P-value is

statistically significant and leads the researchers to conclude that patients with severe sepsis

receiving fluid resuscitation with HES had a higher risk of death at 90 days (Table 5). The

evaluated probability of survival using Kaplan-Meier analysis, which is a statistical tool that

measures the fraction of patients living after treatment, showed the survival time did not

significantly differ between the two groups (P=.07)(Figure 2). The patients within the colloid

group were more likely to have a need for renal-replacement therapy. The study found that 87

patients treated with HES required renal-replacement therapy, while only 65 patients treated with

Ringer's Acetate required renal-replacement therapy (relative risk, 1.35, 95% CI, 1.01-1.80;

P=.04. In short, this shows a statistically significant value when evaluating the relative risk.

Incidences of acute kidney injuries were found to have more than three points within the

Sequential Organ Failure Assessment score (SOFA), which means the patients would have a

higher need for dialysis. The need for renal-replacement therapy, lengthens the time a patient will require to stay within a healthcare facility; defined within the article as days alive outside of the medical facility (Table 5). The mean days alive outside of the hospital was 29 with HES and 34 with Ringer's Acetate, which also increases a patient's risk profile. Patients being hospitalized for a longer time can increase their mortality risk, due to iatrogenic causes. Within this study it was found that less overall fluid would be required for a patient to return to hemodynamic stability. The issues lie with the risk of using colloid fluids within the environment of severe sepsis. Consequently, the data in the clinical trial argues that patients with severe sepsis should not be treated with HES due to the increased mortality risk and dependency of renal replacement.

Colloid Usage in Treatment in Intensive Care Patients

The usage of intravenous fluids to increase intravascular volume is essential in treatment of patients within intensive care units and emergency departments in saving lives around the world. Globally, 0.9% sodium chloride (saline) is the most used fluid, although colloids were administered almost as often as crystalloids with intensive care patients. HES is the most frequently used colloid. Initially, colloid usage showed promise since colloids can safely and efficiently provide fluid resuscitation. However, there is an increased risk of kidney injury when using colloids.

Hydroxyethyl Starch for Fluid Resuscitation in Intensive Care (Chest) is a clinical trial that was conducted from December 2009 through January 2012. The authors released a paper on statistical analysis.[6] Similarly, this trial was modeled after the Saline versus Albumin Fluid Evaluation (SAFE) trial. The primary outcome was assessed from a standardized X_2 test demonstrating the statistical significance of the treatment and monitored for 90-day all-cause mortality. Cox proportional hazard model was utilized to obtain P-values and hazard ratio and

was conducted by blinding the study-groups assignments within medical-surgical ICUs in Australia and New Zealand. 7000 patients were enrolled through 32 different medical centers. 3500 patients were to receive 6% HES and 3500 were to receive 0.9% normal saline. The patient eligibility can be seen in Table 6 in the appendix. Indistinguishable Free flex 500-ml bags were used, which assisted in the blinding ensuring to reduce the provider bias. The study used a maximum of 50 ml per kilogram dosage of 6% HES (130/0.4). "Independent analysis of the concentration and degree of molar substitution of HES and the concentration of saline was obtained for a random sample of 20 bags with the use of gravimetric analysis and nuclear magnetic resonance spectroscopy (Chemical Analysis)."[6] The analysis of fluids allowed the authors to ensure the fluids were properly prepared and uniform for use within the trial. Controlling for the fluids was essential to ensure the removal of any additional variables from the trial. Such as different fluid levels within the study fluids. "Study treatments were randomly assigned over an encrypted Web-based randomization system with the use of a minimization algorithm stratified according to institution and an admission diagnosis of trauma."[6] If the patients required more than the prescribed fluid amount, within the first 24-hour period, the patients would be given 0.9% normal saline. All other aspects of care for the patients were conducted at the discretion of the treating clinicians.

"In the HES group, 597 of 3315 patients (18.0%) died within 90 days after randomization, as compared with 566 of 3336 patients (17.0%) in the saline group (relative risk in the HES group, 1.06; 95% confidence interval [CI], 0.96 to 1.18; P = 0.26)."[6] Therefore, there was no significant difference in the primary outcomes of the study and there is no difference with 90-day mortality when comparing HES to normal saline. Despite the lack of difference in survivability between HES and normal saline is a surprising result that has been replicated in

subsequent trials. Even in the situation that HES was developed for, it did not have any effect on overall survival. "In conclusion, our study does not provide evidence that resuscitation with 6% HES (130/0.4), as compared with saline, in the ICU provides any clinical benefit to the patient."[6]

Once again, the issue with utilizing HES comes from the risk of acute kidney injuries to the patients. "Renal-replacement therapy was administered to 235 of 3352 patients (7.0%) in the HES group and 196 of 3375 patients (5.8%) in the saline group (relative risk, 1.21; 95% CI, 1.00 to 1.45; P = 0.04)."[6] Analysis was conducted to show that serum creatinine levels were significantly increased within the HES groups. This increase in creatinine was seen initially and grew exponentially over day one to three (Figure 3), while the urine output was slightly decreased (Figure 4). The relative risk of the creatinine and urine-output components were analyzed using RIFLE criteria. Both met criteria for kidney dysfunction (RIFLE-R) or within the kidney injury (RIFLE-I). The use of HES led to an overall increased need for renal-replacement therapy and was found to be statistically significant.

Additionally, the study noted an increased need for blood products with the patients treated with HES and patients had a decreased rate of new cardiovascular failure. The Sequential Organ Failure Assessment (SOFA) score was used to analyze results, which demonstrated a reduced need for vasopressors in patients that were treated with HES. The decreased need for vasopressors was attributed to the increased intravascular expansion of HES fluid resuscitation. However, patients treated with HES showed an increase of treatment-related adverse events, such as pruritus and skin rash. The adverse skin events occurred at a rate of 1.8 times higher within the HES subgroups, with 169 patients having one of these adverse events. The normal saline group only had adverse skin events occur within 87 patients. The findings of adverse skin events are significant statistical findings with a P value of .006 (Figure 5). A possible cause of

increased adverse skin events with HES groups could be caused by an accumulation in tissue, specifically the reticuloendothelial system, which is manifested by pruritus with the potential of leading to AKI and hepatic injuries.

In contrast to HES, the study *A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit (SAFE)* compared albumin to saline. The primary outcome of trials was all-cause mortality at 28 days after inclusion into the trial. Also noting if patients had any new organ failure. The study was double blinded, randomized and conducted from 2001 to 2003 in 16 intensive care units across Australia and New Zealand. SOFA scores at baseline were utilized and any higher scores were reported every day for seven days, followed by tests every third day until discharged from the ICU or until the 28-day marker was reached. Importantly, the need for mechanical ventilation, need of renal-replacement therapy, and length of ICUs admissions were additionally noted.[6] Of the 6997 patients selected for the trial, 3497 were assigned to receive albumin and 3500 to receive normal saline. Exclusion criteria for the study included patients that underwent cardiac surgery, liver transplants and those undergoing treatment for burns.[6] The exact breakdown of patient characteristics upon admission into the clinical trial can be seen in Table 7 in the appendix. Dissemination within the study consisted of the colloid group receiving four percent albumin and crystalloid group receiving normal saline. The study was blinded and used identical masked cartons, however, the fluid amount and rates were determined by the treating providers and not chosen by the study investigators. The study investigators utilized George Institute for International Health at the University of Sydney, a secondary independent agency to assess the data analysis and manage the data collected.

When comparing the primary outcomes, there were 726 deaths in the albumin group and 729 in the saline group. (relative risk, 0.99; 95% CI, .097 to 1.09; P = 0.87).[6] When assessing for

new organ failure using the SOFA scores there was no significant difference. A Fischer's exact test was utilized to reach a P-value of 0.85. The need for renal-replacement therapy was statistically non-significant (relative risk, 0.09; 95% CI, 0.0 to .19; P = 0.41), meaning there was no difference in the need for renal-replacement therapy between the two groups.

Conversely, the results from this clinical trial refute findings from a previous clinical trial, Crystalloids vs. colloids in fluid resuscitation: a systematic review and was conducted in 1999, which reports patients that were treated with albumin in the ICU had a higher all-cause mortality.[6] Conversely, the results from this clinical trial refute findings from a previous clinical trial that reports patients that were treated with albumin in the ICU had a higher all-cause mortality. This previous study was *Crystalloids vs. colloids in fluid resuscitation: a systematic review* and was conducted in 1999.[6] Additionally, the results refute the evidence put forth by the Cochrane Injuries Group Albumin Reviewers' meta-analysis, which suggested that there would be an increase in mortality if patients were treated with albumin during resuscitation.[15] However, the trial did show evidence in patients that were suffering sepsis having a lower all-cause mortality when treated with albumin, but this was not a specific outcome within the study (Table 7). Nonetheless, the results showing lower all-cause mortality with albumin treatment could be a result of chance, so further studies into the specifics would be needed to confirm outcome causation.

Colloid Usage in Hypovolemia

Hemorrhage accounts for up to 40% of trauma-related deaths.[7] Restoring end-organ perfusion and tissue oxygenation must be attained within a short time to reduce mortality. Most of the mortality occurs within 6 hours after injury and this critical time is where selecting the right fluid becomes essential.[7] Colloid usage within hypovolemic patients has not been nearly as

controversial. Colloids are regularly utilized within the United States and abroad for volume resuscitation.

Effects of fluid resuscitation with colloids vs. crystalloids on mortality in critically ill patients presenting with hypovolemic shock (CRISTAL), was a study conducted in February 2003 to August of 2012. Patients were selected from 57 different ICUs in France, Belgium, Canada, Algeria, and Tunisia. Initially, 6498 patients were assessed for eligibility, while only 2857 were selected due to exclusion criteria. Patients were randomized into a colloid group and a crystalloid group, 1414 to colloids and 1443 into crystalloid groups, respectively.[8] To be included in the CRISTAL study the patient must meet the following criteria for hypovolemia.

…require fluid resuscitation for acute hypovolemia as defined by the combination of (1) hypotension: systolic arterial pressure of less than 90 mm Hg, mean arterial pressure of less than 60 mm HG, orthostatic hypotension (i.e., a decrease in systolic arterial pressure of at least 20 mm Hg form the supine to the semi recumbent position), or a delta pulse pressure of 13% or higher; (2) evidence for low filling pressures and low cardiac index as assessed either invasively or noninvasively; and (3) signs of tissue hypoperfusion or hypoxia, including at least 2 of the following clinical symptoms: a Glasgow Coma score of less than 12, mottled skin, urinary output of less than 25 mL/h or capillary refilling time of 3 seconds or longer; and arterial lactate levels higher than 2 mmol/L, blood urea nitrogen higher than 56 mg/dL, or a fraction excretion of sodium of less than 1%.[8]

The patients were not supposed to receive any fluids prior to admission into the clinical trial, most patients excluded were due to receiving fluids prior to admission. The other exclusion criteria encompassed anesthesia related hypotension, chronic liver disease, chronic renal failure,

or acute anaphylactic reaction.8 A computer-generalized list was utilized with a fixed-block permutation, which randomized patients into a 1 to 1 ratio. The crystalloid group could use any hypertonic saline, isotonic solution, and buffered solutions.

The study allowed for usage of several different colloids, to include hypo-oncontics such as gelatins and albumins and hyperoncotics such as dextrans, hydroxyethyl starch and 20% or 25% albumins. The different treatment groups could select whatever fluid that was available within the facilities with the only restriction set within the colloid group to limit the dosage of hydroxyethyl starch to no more than 30ml/kg of body weight. Moreover, the providers were required to follow any local regulations set for usage of these fluids. Unlike previous studies discussed above, the study advisors did not deem it possible to blind the clinicians to the fluid interventions. Due to the interventions lasting throughout a patient's time within the ICU, it would not be possible to provide enough masked fluids solutions for adequate resuscitation and completion of the study. Instead, the investigators, sponsors, and members of the monitoring board were blinded when statistical analysis was conducted. The primary outcomes of this study were mortality at 28-days.

Importantly, the median fluid administered for the first week was 2000 mL of fluids with the patients in the colloid group and 3000 mL of fluids in the crystalloid group. When assessing the primary outcome of mortality at 28-days, the study concluded that there was no significant difference. There were 359 deaths in the colloid group and 390 deaths within the crystalloids group (RR, 0.96 [95% CI, 0.88-1.04], P=0.26).1 Surprisingly, this study showed there was no difference in the need for renal replacement therapy when comparing the two different types of fluids of colloids and crystalloids.

During the study there were 156 patients in the colloid group and 181 patients in the crystalloid group that identified a need for renal replacement, which was not found to be statistically significant.8 The discrepancy in renal replacement needed compared to other studies could be due to other studies focused more on HES than multiple different colloids and the fact that the dosage of starches never exceeded the dose recommended by regulatory agencies.8 Be that as it may, there was a significant difference in the mortality at 90-days for colloids vs crystalloids, showing 434 deaths in the colloid groups and 493 deaths in the crystalloid groups(RR 0.92 [95% CI,0.86 -0.99], P=.03).8 Conversely, there was a significant difference in mortality noted within the colloid and crystalloid study groups, which need further exploration to reach a conclusion of efficacy. Furthermore, resuscitation with colloids can be associated with faster removal of life-support, which was exhibited by the mean number of days being alive without mechanical ventilation within the colloid group being significantly lower. (Mean difference, 1.10 [95% CI, 0.14-2.06], P=0.01). The results from this clinical study were limited, due to the study outcomes and short timeframe of patients being tracked. Consequently, a statistically significant difference was found between the average base excess serum after fluid therapy (Figure 6) with a P-value of .001.8

Comparison of the Effectiveness of Hydroxyethyl Starch (Voluven) Solution With Normal Saline in Hemorrhagic Shock Treatment in Trauma (VOLUVEN Trial) was conducted in 2016 at Imam Khomeini Hospital in Ahvaz, Iran consisting of 100 initial participants. A total of 12 patients were excluded due to death, blood transfusion, or transference to an operating room. The colloid group received .5 L of colloid solution with 1.5 L of normal saline and the crystalloid group received 2 L of normal saline. This study's approach was unique in the fact that the study utilized a calculation of base excess status when comparing crystalloid vs colloids. The primary

outcome of the clinical trial was established by measuring the base excesses before and after

fluid therapy by drawing of ABG samples, 1 hour after administration.[9] Outcomes were

calculated by utilizing covariance analysis and linear methods.[9] This study's approach was

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Colloid Usage in Burn Resuscitation

To treat burns in an acute setting requires a large amount of fluid resuscitation. Fluid

resuscitation in burn patients is essential to effectively reduce mortality and lead to improved

outcomes. The inflammatory response that occurs during burns can surpass that seen with trauma

and sepsis patients.[10] Large fluid shifts that occur in severely burned patients with delaying, or

inadequate resuscitation can cause hypovolemia, tissue hypoperfusion, shock and organ failure.

Currently the fluid of choice for resuscitation is Lactated Ringers. The current Parkland

formulary can underestimate the actual fluid required for resuscitation.[10] However, the Parkland

formula excludes the usage of colloids within the first 24 hours of fluid resuscitation. The initial

assumption is if colloids were used within fluid resuscitation the colloid would leak across

capillaries and exert osmotic pull, which could draw more fluid into the interstitial spacing.

Nevertheless, the fear of colloid leakage is unsubstantiated and is reviewed in *Comparison of the*

Effectiveness of Hydroxyethyl Starch (Voluven) Solution With Normal Saline in Hemorrhagic

Shock Treatment in Trauma. The increase in fluid resuscitation can correlate with an increased

intra-abdominal pressure and abdominal compartment syndrome. Colloid usage has shown to

help limit the overall volume needed to reach hemodynamic stability and reviewed in

Hydroxyethyl starch supplementation in burn resuscitation—A prospective randomized controlled trial.

The clinical trial *Hydroxyethyl starch supplementation in burn resuscitation—A prospective randomized controlled trial* was conducted May 2004 to May 2006 at University Hospital Birmingham Burns Centre in the United Kingdom. Patient inclusion criteria constituted having burns exceeding 15% of total body surface area (TBSA) excluding those that had a 80% TBSA, were pregnant, or had a delay of transfer greater than 6 hours from the time of injury.[11] The Lund & Browder chart was employed for estimation of body surface area burned, this was confirmed by two members of the staff.[11] A block randomization was chosen to distribute the patient allocation incoherently in the trial. The study began with 43 patients and only concluded with 26 patients that completed the fluid trial and used for data analysis. The crystalloid group was given Hartmann's solution according to the Parkland formula, which is the normal practice for local hospitals. Meanwhile, patients selected for the colloid group received two-thirds resuscitation of Hartmann's solution and one-third of the fluid replaced with 6% HES, with max dosing of HES of 33ml/kg for 24 hours. However, the maximum dose given would not allow for the full one-third to be replaced with HES. Instead the maximum allowed volume of HES was infused at a regular rate and halved at 8 hours post-injury.[11] "The expansive value of 6% HES is in the region of 1:1.5, which means the blood volume expansion is achieved is 1.5 times the volume of HES infused. The total 6% HES hourly volume allowance was translated into its crystalloid equivalent, by multiplying it by 1.5. The resulting volume was subtracted from the predicted crystalloid requirement for the hour which provided the hourly Hartmann's volume to be infused."[11] Fluid resuscitation was titrated by the following criteria: Urine output of .5-1ml/kg/h in uncomplicated burns and 1-2 ml/kg/h in inhalation injury with mean arterial pressure

>70 mm HG and heart rate <120bpm.[11] The tracking of Albumin-creatinine ratio (ACR) was used to indicate endothelial dysfunction between the two groups and was used to determine the primary outcome for the clinical trial. ACR was utilized as a marker for capillary leakage and overall edema within the patients. Out of the 43 originally selected patients 26 were allowed into the trial (Table 10). The mean TBSA for the study was 27%.

The primary outcome was concluded that in supplementation of HES in burn patients, HES allowed for smaller fluid volume requirement (Table 10) and less tissue edema within the first 24 hours (Table 11). The fluid requirement was corrected for the TBSA of each patient suffering burns. The results of lower median serum CRP at 48 hours is statistically significant with a P-value of .0001 within the treatment group of colloids. The ACR measurement at 12 hours when factoring in TBSA with a P-value of .0310 was found to be significant, within the treatment group of colloids. This reduction in serum CRP allowed the investigators to draw the conclusion that with treatment addition of colloids to burn regiments, patients with burns can benefit from treatment within the first 24 hours.[11] Withal, none of the patients within the clinical trial required renal-replacement therapy, which can be related to the reduced dosage of HES that was highlighted above.

A Prospective, Randomized Evaluation of Intra-abdominal Pressures with Crystalloid and Colloid Resuscitation in Burn Patients was conducted at burns center in California and Pennsylvania in 2002 and published in 2005. To meet inclusion criteria, patients had to have at least 25% TBSA with smoke inhalations or greater than 40% TBSA if no inhalation injury was present. Patient randomization was conducted by predetermined order produced in groups of 10. Patients assigned in the crystalloid group applied the Parkland formula for volume resuscitation. Utilization of Lactated Ringer's at a rate of 4 mL/ kg/%TBSA, first half over initial 8 hrs.[12]

Patients assigned to the colloid group were given plasma and crystalloid combination. The patients in the colloid group were initiated on a 24-hour goal of 2,000 mL of Lactated Ringer's and 75 mL/kg of fresh frozen plasma (FFP).[12] The FFP was titrated to maintain urine output between 0.5 and 1.0 mL/kg/h[12]. The primary outcome was a measure of intra-abdominal pressure (IAP) measured in mmHg, which is an indication of the threshold for intra-abdominal hypertension.

Conditions where fluids given were substituted with colloids such as FFP, a reduction could be observed in the overall amount of fluids required for resuscitation and reduce the overall occurrence of abdominal compartment syndrome with inevitably serious complications. There was a statistically significant rise within both groups in measured IAP. The crystalloid group had a rise to a mean IAP of 32.5mm Hg, which showed an increase of 26.5 mm Hg.[12] The colloid group had a rise to a mean IAP of 16.4 mm Hg, which only increased by 10.6 mm Hg.[12] Altogether, the IAP increase of the crystalloid and colloid groups had a statistically significant P-value of .0001. The patients within the plasma group were given less fluids overall throughout study, averaging only .561 L/kg. This clinical trial showed a direct relationship in the amount of fluid given to a patient and overall IAP.

A mere 31 patients reached the end of the trail, creating a major confinement for overall data analysis. To fully test these numbers with a power of 80%, with a 10% difference in survival, expecting a P-value of .05 would require an inclusion rate of over 900.[12] The investigator deemed full analysis unattainable, even if utilizing a large multi-institutional study.[12] Without a study of significant magnitude being conducted, the outcomes could not be directly confirmed.

Methods

PubMed, Science Direct and UpToDate were specifically searched to find articles that conducted trials on colloids, and additionally explored articles that conducted trials where providers compared colloids to crystalloids directly. The keywords utilized within the search were "colloid, crystalloids, emergency, resuscitation, burns, mortality, shock, burns and sepsis". Search criteria included peer-reviewed articles and clinical trials within the past 16 years. Of the 70 articles and clinical trials reviewed, 7 clinical trials and 13 articles were selected. These were selected for their relevance to the topic, timing of clinical trials conducted and impact on regulations for colloid usage. Several of the articles were selected for their direct reference in FDA and European guidelines.

Discussion

Providers utilizing IV fluids for resuscitation to critically ill patients want to provide the treatment with the best possible outcomes. The goal of this paper is to address if colloids usage would allow for improved outcomes. Several conclusions can be drawn from the research and will be discussed in each of the critically ill settings: including sepsis, hypovolemia, and burns. Additionally, the studies reviewed have limitations that are addressed.

Patients suffering from sepsis or septic shock were reviewed within the CRYSTMAS and 6S clinical trial. These trials show conclusive evidence against the usage of colloids within patients suffering sepsis. Both studies used HES in place of the colloid. The CRYSTMAS study chose to utilize normal saline, while the 6S chose to give Lactated Ringer's. This difference in crystalloid selection had very little to no impact on the outcomes of the clinical trial. In the CRYSTMAS and 6S clinical trial found no difference in mortality in septic patients. However,

there was a difference in the two trials when comparing the need for renal replacement therapy. In the CRYSTMAS trial the investigators found no statistically significant difference in the need for renal replacement when comparing colloid vs crystalloids. The 6S clinical trial found a statistically significant difference in the need for renal replacement when comparing colloids to crystalloids. These differences could be due to the limitation within the CRYSTMAS study. The CRYSTMAS study had a small patient population. This limited population size can lead to unreliable findings and not provide a full picture when comparing the two fluids. The main limitation within the CRYSTMAS study was the overall purpose of the study was not assessing the mortality, but focused on which IV fluid would allow a patient to reach hemodynamic stability fastest. One factor that could have affected the findings in the 6S clinical trial was the inclusion of patients that had AKI prior to application of the fluids. The inclusion of patients suffering from AKI could have affected the data and patient need for renal replacement therapy. As these patients suffering from AKI already have kidney dysfunction and could have led to the increased need for renal replacement therapy. Even with these limitations, there is no difference in mortality when treating patients with colloids vs crystalloid. Colloids have the increased risk of acute kidney injury in sepsis making the fluid benefit not worth the risk.

Hypovolemia and hypovolemic shock were tested within the CRISTAL and the VOLUVEN clinical trials. The outcomes of the CRISTAL study were tracking mortality and the need for renal replacement. Within the VOLUVEN clinical trial the outcome was not following mortality but calculating the base excess status when comparing crystalloids vs colloids. The findings of this clinical trial indicated that colloids are superior to crystalloids if properly administered to patients in hypovolemia and hypovolemic shock. This is most apparent in the

CRISTAL trial where the authors found a significant difference in mortality supporting colloids vs crystalloids.

There was some limitation within both clinical trials. The CRISTAL clinical trial was running over a period of 9 years. This is a long time to run a study and could prove difficult to maintain consistency in treatment protocols within the medical facilities. There was no mention if the trials controlled for these changes. There was no blinding of fluids within either the CRISTAL or VOLUVEN trials. These trials noted that it was not feasible to blind the fluids. The CRISTAL trial did note a chance of bias, but the authors refuted the claim by stating, "this would have likely resulted in an increased use of renal replacement therapy in patients treated with colloid."[8] The CRISTAL trial showed no significant difference in the need for renal replacement therapy when comparing crystalloid and colloids. Within the VOLUVEN clinical trial there was a much smaller patient cohort. Without adequate data points it can lead invalid data overall. The authors did not track mortality, but instead collected data on base excess status when comparing crystalloids to colloids. Other crucial sepsis indicators such as lactate were not collected.

Burn treatment with colloids was tested within clinical trials *A Prospective, Randomized Evaluation of Intra-abdominal Pressures with Crystalloid and Colloid Resuscitation in Burn Patients* and *Hydroxyethyl starch supplementation in burn resuscitation—A prospective randomized controlled trial*. These clinical trials did show some compelling evidence for the usage of colloids within burn patients. There were several limitations within both clinical trials. The two clinical trials used completely different colloids. One utilizes FFP and the other used HES. This difference in types of colloids used could lead to changes in the results from each study. Both clinical trials were hindered by the number of patients within the cohort, which can lead to issues with validity in the outcomes of the clinical trials. Additionally, it is almost

impossible to completely control differences in full thickness burns between the control and study group. However, the investigators attempted to control for this by changing the fluid calculation and ACR. This was noted to be a valid control but having different thicknesses and locations of burns can affect the results.

Conclusion:

In emergent resuscitation, efforts in the setting of sepsis, hypovolemia and burns, a provider has the options of colloids or crystalloids. This paper evaluated the effectiveness of colloids and crystalloid fluids to compare the outcomes of mortality. In the setting of sepsis, there is not enough evidence to support the usage of colloids. Several studies conducted show no decrease in mortality. This includes the CRYSTMAS and 6S clinical trial that showed no decrease in mortality in patients presenting in severe sepsis. The amount of fluid resuscitation needed by patients in sepsis is massive. Confirmed by the CRYSTMAS and 6S, the need for patients to undergo renal replacement therapy after resuscitation with colloids is a definite risk if the patients are in severe sepsis or septic shock. Acceptedly, during the clinical trials reviewed, colloid usage should not be used within sepsis and septic shock. There is little debate on restricting colloid usage in terms of septic patients. The medical community and guidelines have been established within the United States and the European union. These guidelines have established treatment protocols that restrict the usage, and these are supported by the findings within the CRYSTMAS and 6S clinical trials.

Importantly, there is evidence to support the usage of colloids within hypovolemia, but some restrictions that must be placed on its usage. Several studies have come out to show that HES should not be used due to increased risk of AKI (CRYSTMAS and 6S). However, the trials were tested in a population with signs of sepsis and septic shock, so should not be considered as

direct results for treatment of hypovolemia. Albumin does seem to show promise if utilized appropriately with a combination of crystalloid. Demonstrated, the risk of renal-replacement therapy can be mitigated with lower doses of HES and colloids. During the larger CRISTAL trial, the results illustrated no increased need for renal replacement therapy and showed a reduction in all-cause mortality at 90 days. Authors noted an inherent need for more studies to be conducted to support finding of reduced renal replacement therapy need and reduction of mortality due to not being the direct outcome being tested. Altogether, the large-scale study allowed HES or other colloid usage to be recognized for faster patient recovery by manifesting a significantly lower mean number of days alive without mechanical ventilation within the colloid group. Nonetheless, the results of the clinical trials do not directly support the fear of using HES or other colloids in hypovolemic shock. More studies are required with restricted dosages to verify if HES does cause a need for renal-replacement therapy. Once additional study has been conducted on restricted HES dosages, there is potential for a shift within treatment protocols. As it currently stands, most treatment protocols forgo the usage of colloids, specifically HES in any circumstances. Even though HES may never become as utilized or as effective as initial claims, HES could have a purpose when used in a more restrictive and isolated environment.

Colloids usage within burns has not been extensively studied in larger multi-institutional studies in recent years. There is evidence that colloids can be effective within burn patients in the right circumstances. However, several smaller studies show promising results using either HES or plasma for substitution in fluid resuscitation. Results demonstrating colloid usage in burns can be seen within *Hydroxyethyl starch supplementation in burn resuscitation—A prospective randomized controlled trial* and *A Prospective, Randomized Evaluation of Intra-abdominal Pressures with Crystalloid and Colloid Resuscitation in Burn Patients*. Promise is shown with

colloid fluids, whether using references of IAP or measures of ACR for endothelial dysfunction. The ability for providers to reduce the amount of crystalloid usage by an addition of colloid could lessen the impact of resuscitation needed in burn patients. Even so, ensuring providers set clear goal directed recitation is essential. Within the article *Fluid resuscitation Management in patients with burns: update* discusses the following:

> Although there are reports of poorer outcomes in septic patients with the use of HES, the current scientific evidence does not suffice to support a specific contraindication for HES use in burn patients. As was the practice in many burn units, we formerly used HES after the first 24 h when it was needed and we did not have the impression that outcomes were worse in our patients, but this is a subjective evaluation.[13]

Several of the meta-analysis referenced that burn patients should not be given HES. In some of the larger studies burn patients were excluded from the studies. Then clinicians use these studies that excluded burn patients to draw conclusions that HES should not be given.

There needs to be a more in-depth clinical trial when utilizing colloids in early burn management as the studies *Hydroxyethyl starch supplementation in burn resuscitation—A prospective randomized controlled trial* and *A Prospective, Randomized Evaluation of Intra-abdominal Pressures with Crystalloid and Colloid Resuscitation in Burn Patients* show validity in colloid usage. The article *Fluid resuscitation Management in patients with burns: update* discusses the following:

> Multicenter randomized controlled trials on fluid resuscitation in major burns are still needed to define the best fluid therapy in this population. Data is lacking on the optimal end points for TTD, the difference between initial resuscitation with Ringer's lactate or

Ringer's acetate, the proper timing to initiate colloids, and the comparative performance of the different natural and synthetic colloids in burn patients.[13]

It has been concluded, healthcare providers should not use HES in patients in sepsis, kidney impairment, or in critically ill patients, and restricted use of HES is supported by the European Union of the Coordination Group for Mutual Recognition and Decentralized procedures- Human- and by the FDA in the United States. However, HES is supplied to EU only accredited hospitals for use, but specific training is required for the safe use of HES solutions. For safety, specific warnings on the packaging and the top of the product illustrate that HES medicines should not be used in patient profiles with sepsis, kidney impairment, or in critically ill patients.[14] An additional added contraindication included severe coagulopathy, which was not discussed within this paper and HES must be discontinued at the first sign of coagulopathy. Additionally, HES solutions for infusion are contraindicated in dehydrated patients, hyperhydrated patients, patients with intracranial or cerebral hemorrhage, burn injuries, severe hyperkalemia, hypernatremia, hyperchloremia, congestive heart failure, organ transplant patients and patients with impaired hepatic function.[14] However, some of the contraindications are not confirmed risks within clinical trials, such as burns.

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Appendix

Figure 1. Hydroxyethyl Starch molecule with the action of amylase
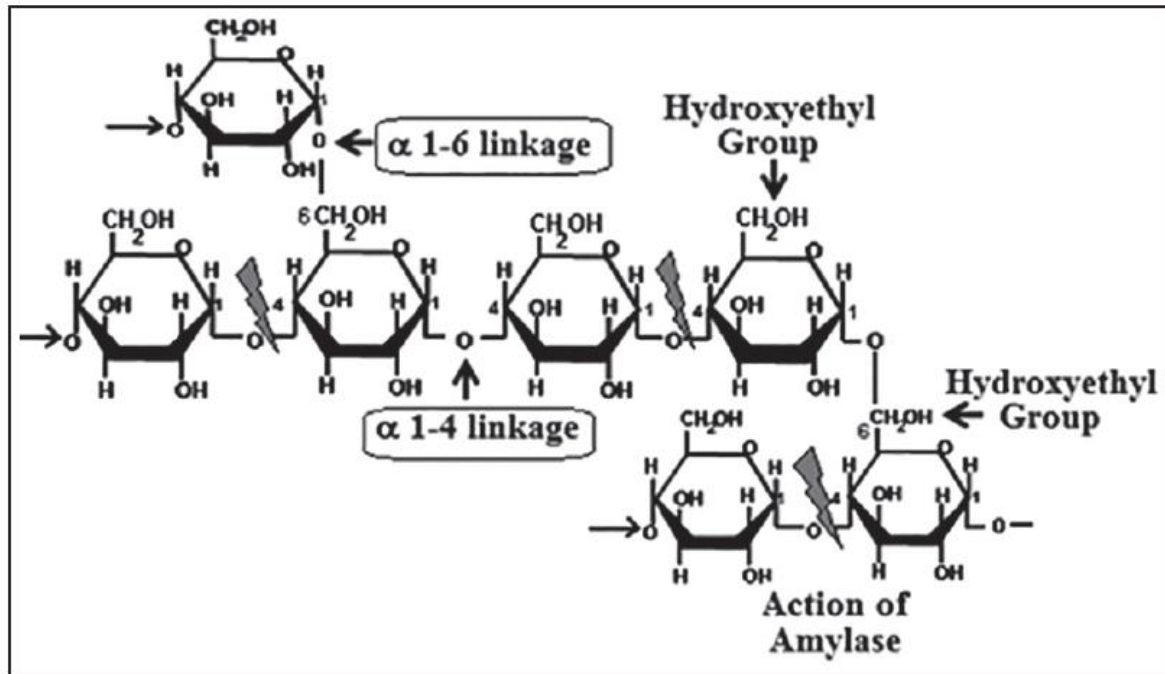
Table

1. Patient Demographics and baseline characteristics for patient in the CRYSTMAS study

	HES 130/0.4 (n = 100)	NaCl 0.9% (n = 96)
Gender, n (%)		
- Male	64 (64)	57 59)
- Female	36 (36)	39 (41)
Age, years, mean ± SD	65.8 ± 15.4	65.9 ± 14.7
Race, n (%)		
- Caucasian	96 (96)	93 97)
- Asian	1 (1)	1 (1)
- Black	1 (1)	1 (1)
- Other	2 (2)	1 (1)
Mean body mass index, kg/m2	26.2	26.0
Type of patient, n (%)		
- Medical	73 (73)	70 73)
- Surgical	27 (27)	26 (27)
Renal impairment prior to screening*, n (%)	62 (63.9)	65 (68.4)
SAPS II prior to randomization, mean	50	53
SOFA at screening, mean	7.9	9.1
Fluid input prior to randomization, ml/kg body weight, mean ± SD	35.5 ± 25.3	39.9 ± 28.6
Origin of sepsis, n (%)		
- Lungs	53 (53)	58 (60)
- Abdomen	24 (24)	18 (19)
- Urogenital	8 (8)	14 (15)
- Skin, bone and soft tissue	6 (6)	4 (4)
- Other	5 (5)	2 (2)
- Unknown	4 (4)	2 (2)
- Neurological system	3 (3)	2 (2)
- Ear nose and throat	2 (2)	0 (0)
Causative organism, n (%)		
- Gram-negative bacteria	35 (35)	41 (43)
- Gram-positive bacteria	25 (25)	27 (28)
- Other classes	40 (40)	32 (33)

Table 2: Efficacy outcomes during the CRYSTMAS study

	HES 130/0.4 (n = 88)	NaCl 0.9% (n = 86)	p
Mean volume of study drug used, ml (SD)	1,379 (886)	1,709 (1,164)	0.0185
Mean time to initial HDS, hours (SD)	11.8 (10.1)	14.3 (11.1)	NS
Number of patients prescribed intravenous catecholamines (%)	88 (88.0)	87 (90.6)	NS

HDS, hemodynamic stabilization; SD, standard deviation; HES, hydroxyethyl starch; NaCl, sodium chloride; NS, not significant.

Table 3: Urinary Biomarkers of AKI as a ratio to urinary creatine within the CRYSTMAS Study.

Treatment group	Baseline	Until HDSa	Day 1	Day 2	Day 3	Day 4	Day 8b	Lastc
				Mean (SD)				
Alpha-1-microglobulin/urinary creatinine, g/mmol								
HES 130/0.4	17.8 (21.0)	18.1 (14.8)	18.3 (16.0)	19.4 (20.3)	19.6 (20.5)	17.2 (14.4)	13.4 (14.9)	19.9 (22.7)
NaCl 0.9%	12.3 (12.9)	17.2 (18.0)	17.8 (17.1)	16.9 (15.0)	16.7 (14.9)	16.7 (13.8)	19.5 (23.9)	19.8 (23.3)
Beta-NAG/urinary creatinine, UI/mmol								
HES 130/0.4	4.9 (6.6)	4.1 (3.5)	5.0 (3.8)	7.9 (12.8)	8.1 (13.6)	5.5 (4.6)	4.5 (3.0)	6.7 (10.0)
NaCl 0.9%	4.1 (4.7)	4.2 (3.5)	6.0 (9.1)	4.7 (4.2)	4.5 (4.4)	4.2 (3.3)	5.8 (5.0)	5.7 (5.5)
NGAL/urinary creatinine, µg/mmol								
HES 130/0.4	283.0 (785.1)	352.8 (710.7)	229.9 (465.5)	325.9 (1,079.0)	432.9 (1458.2)	90.9 (203.4)	24.4 (71.5)	279.0 (884.8)
NaCl 0.9%	305.5 (833.9)	244.9 (452.4)	318.7 (644.8)	149.8 (303.2)	121.1 (306.1)	112.1 (373.7)	177.8 (551.5)	212.8 (604.8)

aFirst measurement until HDS visit (i.e., data recorded at day of withdrawal were assigned to the study visit corresponding to the actual time point of measurement); bdata recorded on Day 8; clast available post-baseline measurement; HES, hydroxyethyl starch; NaCl, sodium chloride; NAG, N-acetyl-β-D-glucosaminidase; NGAL, neutrophil gelatinase associated lipocalin; SD, standard deviation; HDS, hemodynamic stabilization.

Table 4: Patient selection for 6S clinical trials.
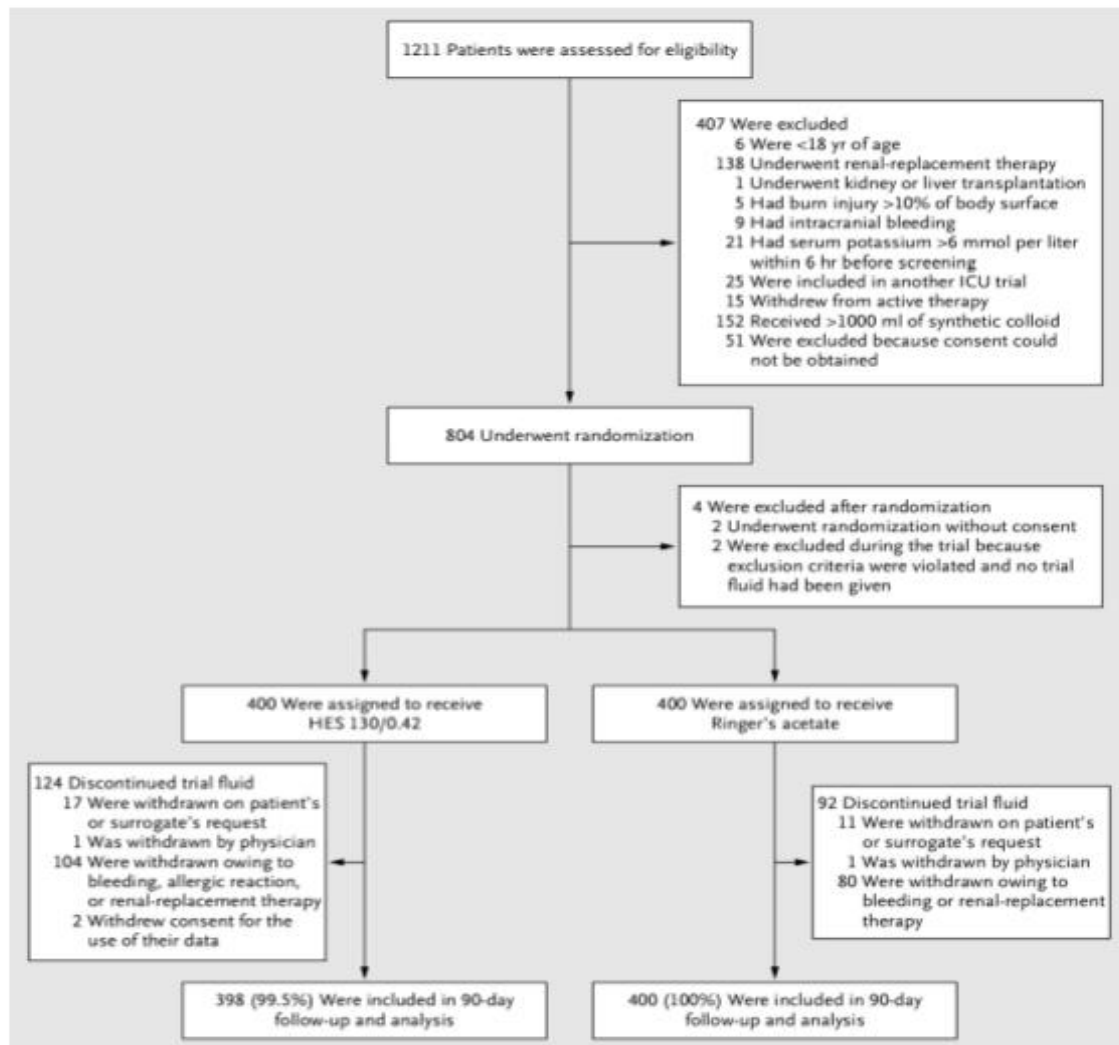
Table 5: Primary and secondary results from the 6S clinical trial

Outcome	HES 130/0.42 (N=398)	Ringer's Acetate (N=400)	Relative Risk (95% CI)	P Value
Primary outcome				
Dead or dependent on dialysis at day 90 — no. (%)	202 (51)	173 (43)	1.17 (1.01–1.36)	0.03
Dead at day 90 — no. (%)	201 (51)	172 (43)	1.17 (1.01–1.36)	0.03
Dependent on dialysis at day 90 — no. (%)	1 (0.25)	1 (0.25)	—	1.00
Secondary outcome measures				
Dead at day 28 — no. (%)	154 (39)	144 (36)	1.08 (0.90–1.28)	0.43
Severe bleeding — no. (%)†	38 (10)	25 (6)	1.52 (0.94–2.48)	0.09
Severe allergic reaction — no. (%)†	1 (0.25)	0	—	0.32
SOFA score at day 5 — median (interquartile range)	6 (2–11)	6 (0–10)	—	0.64
Use of renal-replacement therapy — no. (%)‡	87 (22)	65 (16)	1.35 (1.01–1.80)	0.04
Use of renal-replacement therapy or renal SOFA score ≥3 — no. (%)§	129 (32)	108 (27)	1.20 (0.97–1.48)	0.10
Doubling of plasma creatinine level — no. (%)†	148 (41)	127 (35)	1.18 (0.98–1.43)	0.08
Acidosis — no. (%)†¶	307 (77)	312 (78)	0.99 (0.92–1.06)	0.72
Alive without renal-replacement therapy — mean % of days‖	91	93	—	0.048
Use of mechanical ventilation — no. (%)†	325 (82)	321 (80)	1.02 (0.95–1.09)	0.61
Alive without mechanical ventilation — mean % of days‖	62	65	—	0.28
Alive and out of hospital — mean % of days‖	29	34	—	0.048

* For severe bleeding and severe allergic reaction, data were missing for 1 patient in the Ringer's acetate group. For doubling of the plasma creatinine level, data were missing for 38 patients in the HES 130/0.42 group and 34 patients in the Ringer's acetate group. For alive without mechanical ventilation, data were missing for 1 patient in the Ringer's acetate group. CI denotes confidence interval.

† Outcomes are for patients in the ICU during the 90-day trial period.

‡ Outcomes are for patients with any form of renal-replacement therapy during the 90-day trial period.

§ Outcomes are for patients with any form of renal-replacement therapy during the 90-day trial period or with a renal SOFA score of 3 or higher after the patient had a renal SOFA score of 2 or lower at randomization.

¶ Acidosis was defined as an arterial pH of less than 7.35.

‖ The mean percentage of days was calculated as the number of days without renal-replacement therapy or mechanical ventilation or the number of days out of the hospital divided by the number of days alive in the 90-day follow-up period.

Figure 2: Kaplan-Meier analysis for the patient's probability of survival within the 6S clinical trial.

Table 6: Patient eligibility for the CHEST clinical trial

19,475 Patients were assessed for eligibility

10,612 Were ineligible
 111 Were under 18 yr of age
 3324 Received fluid previously
 512 Received ≥1000 ml of 6% HES (130/0.4)
 4 Had known allergic reaction
 1193 Had nontraumatic intracranial hemorrhage
 1257 Received renal-replacement therapy
 256 Had serum creatinine level ≥350 μmol/liter
  (4.0 mg/dl)
 24 Had severe hypernatremia
 9 Had severe hyperchloremia
 575 Were pregnant or breast-feeding
 1127 Were admitted after cardiac surgery
 402 Received treatment for burns or after liver
  transplantation
 1011 Had limited life expectancy
 341 Had limitation of therapy
 165 Were previously enrolled in the study
 301 Were transferred from another ICU and
  received fluid

1863 Were eligible but were excluded
 735 Were overlooked for randomization
 547 Were withdrawn by clinician
 335 Did not provide consent
 235 Were excluded for other reasons
 11 Had problem accessing the Web

7000 Underwent randomization

3500 Were assigned to receive 6% hydroxyethyl starch (130/0.4)

3500 Were assigned to receive 0.9% saline

137 (3.9%) Withdrew consent

113 (3.2%) Withdrew consent

3323 Provided consent for all data
35 Provided consent for early data only
5 Provided consent for primary outcome data only

3340 Provided consent for all data
44 Provided consent for early data only
3 Provided consent for primary outcome data only

5 (0.1%) Were lost to follow-up

3 (0.1%) Were lost to follow-up

3358 (95.9%) Were included in the analysis

3384 (96.7%) Were included in the analysis

43 (1.2%) Were lost to follow-up at 90 days

48 (1.4%) Were lost to follow-up at 90 days

3315 (94.7%) Were included in the 90-day analysis

3336 (95.3%) Were included in the 90-day analysis

Figure 1. Assessment, Randomization, and Follow-up of the Patients.

Figure 3: Serum Creatine in patients during the CHEST clinical trial

A Serum Creatinine

No. at Risk								
HES	3260	2197	2899	2111	1576	1238	998	851
Saline	3283	2253	2916	2196	1614	1291	1026	857

Figure 4: Urine output in patients during the CHEST clinical trial

B Urine Output

No. at Risk								
HES	1417	3202	3076	2269	1702	1292	1071	894
Saline	1385	3237	3119	2341	1719	1348	1110	894

Figure 5: Patient outcomes and adverse events within the CHEST clinical trial

Table 2. Outcomes and Adverse Events.*

Variable	HES	Saline	Relative Risk (95% CI)	P Value
Outcome				
Primary outcome of death at day 90 — no./total no. (%)	597/3315 (18.0)	566/3336 (17.0)	1.06 (0.96 to 1.18)	0.26
Secondary outcomes — no./total no. (%)				
Renal outcomes				
RIFLE-R	1788/3309 (54.0)	1912/3335 (57.3)	0.94 (0.90 to 0.98)	0.007
RIFLE-I	1130/3265 (34.6)	1253/3300 (38.0)	0.91 (0.85 to 0.97)	0.005
RIFLE-F	336/3243 (10.4)	301/3263 (9.2)	1.12 (0.97 to 1.30)	0.12
Use of renal-replacement therapy	235/3352 (7.0)	196/3375 (5.8)	1.21 (1.00 to 1.45)	0.04
New organ failure†				
Respiratory	540/2062 (26.2)	524/2094 (25.0)	1.05 (0.94 to 1.16)	0.39
Cardiovascular	663/1815 (36.5)	722/1808 (39.9)	0.91 (0.84 to 0.99)	0.03
Coagulation	142/2987 (4.8)	119/3010 (4.0)	1.20 (0.95 to 1.53)	0.13
Hepatic	55/2830 (1.9)	36/2887 (1.2)	1.56 (1.03 to 2.36)	0.03
Tertiary outcomes — no./total no. (%)				
Death in ICU	364/3313 (11.0)	360/3331 (10.8)	1.02 (0.89 to 1.17)	0.81
Death within 28 days	458/3313 (13.8)	437/3331 (13.1)	1.05 (0.93 to 1.19)	0.40
Death in hospital	483/3307 (14.6)	456/3324 (13.7)	1.06 (0.95 to 1.20)	0.30
			Mean Difference (95% CI)	
Service utilization — no.				
Days in ICU	7.3±0.2	6.9±0.2	0.4 (0.0 to 0.9)	0.07
Days in hospital	19.3±0.3	19.1±0.3	0.2 (-0.8 to 1.1)	0.72
Days receiving mechanical ventilation‡	6.0±0.2	5.7±0.2	0.4 (-0.1 to 0.8)	0.12
Days receiving renal-replacement therapy‡	5.6±0.4	5.5±0.4	0.1 (-0.1 to 1.2)	0.86
Treatment-related adverse events§				
Any event — no./total no. (%)	180/3871 (4.6)	95/2879 (3.3)		0.006
Pruritus	137/3871 (3.5)	73/2879 (2.5)		
Skin rash	34/3871 (0.9)	16/2879 (0.6)		
Other	9/3871 (0.2)	6/2879 (0.2)		
Serious adverse events — no./total no. (%)¶	2/3871 (0.1)	2/2879 (0.1)		0.77

* Plus–minus values are means ±SE.
† New organ failure was defined as a Sequential Organ Failure Assessment (SOFA) score[12] of at least 3 for each category in patients who did not have such organ failure at baseline.
‡ Data are presented for the proportion of patients who received the intervention.
§ Adverse events in the HES group include those in patients who received HES both before and after randomization.
¶ Among the serious (nonfatal) treatment-related adverse events were one case each of anaphylactic shock and extravasation of fluid causing airway obstruction in the HES group and one case each of toxic epidermal necrolysis requiring unblinding of the study-group assignment and unexplained severe hypotension in the saline group.

**Table 7**: Baseline Characteristics of Patient within the SAFE clinical trial

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Albumin Group	Saline Group
Age — yr	58.6±19.1	58.5±18.7
Female sex — no. (%)	1424 (40.7)	1376 (39.3)
Reason for admission to ICU — no. (%)		
Surgical	1473 (43.0)	1465 (42.8)
Medical	1955 (57.0)	1958 (57.2)
Source of admission to ICU — no. (%)		
Emergency department	948 (27.7)	977 (28.5)
Hospital floor	614 (17.9)	573 (16.7)
Another ICU	63 (1.8)	66 (1.9)
Another hospital	323 (9.4)	341 (10.0)
Operating room (emergency surgery)	801 (23.4)	780 (22.8)
Operating room (elective surgery)	662 (19.3)	678 (19.8)
Same ICU (readmission)	17 (0.5)	8 (0.2)
Predefined subgroups — no. (%)		
Trauma	597 (17.4)	590 (17.2)
Severe sepsis	603 (18.1)	615 (18.4)
Acute respiratory distress syndrome	61 (1.8)	66 (1.9)
APACHE II score†	18.7±7.9	19.0±8.0
Physiological variables		
Heart rate — beats/min	91.4±23.5	92.3±23.5
Mean arterial pressure — mm Hg	77.8±16.4	78.2±16.3
Central venous pressure — mm Hg	9.0±4.7	8.6±4.6‡
Urine output — ml/hr	89.7±132.4	95.0±161.4
Serum albumin — g/liter	27.4±7.8	27.7±7.9
Organ failure— no. (%)§		
No failure	1962 (57.2)	1885 (55.1)
1 organ	1075 (31.4)	1148 (33.5)
2 organs	335 (9.8)	329 (9.6)
3 organs	50 (1.5)	57 (1.7)
4 organs	5 (0.1)	4 (0.1)
5 organs	1 (<0.1)	0
Mechanical ventilation — no. (%)	2186 (63.8)	2217 (64.8)
Renal-replacement therapy — no. (%)	45 (1.3)	41 (1.2)
Albumin in previous 72 hr — no. (%)	127 (3.7)	135 (3.9)

* Plus–minus values are means ±SD. Percentages were calculated according to the number of patients for whom data were available: for sex, 3497 in the albumin group and 3500 in the saline group; for severe sepsis, 3339 in the albumin group and 3338 in the saline group; and for all the other variables, 3428 in the albumin group and 3423 in the saline group. Because of rounding, not all percentages total 100. ICU denotes intensive care unit, and APACHE II Acute Physiology and Chronic Health Evaluation II.
† Higher scores on APACHE II indicate more severe illness.
‡ P=0.03 for the comparison with the value in the albumin group (without correction for multiple-hypothesis testing).
§ Organ failure was defined as a Sequential Organ-Failure Assessment score[18] of 3 or 4 for any individual organ system.

Table 8: Paitient enrollment within the CRISTAL clinical trial
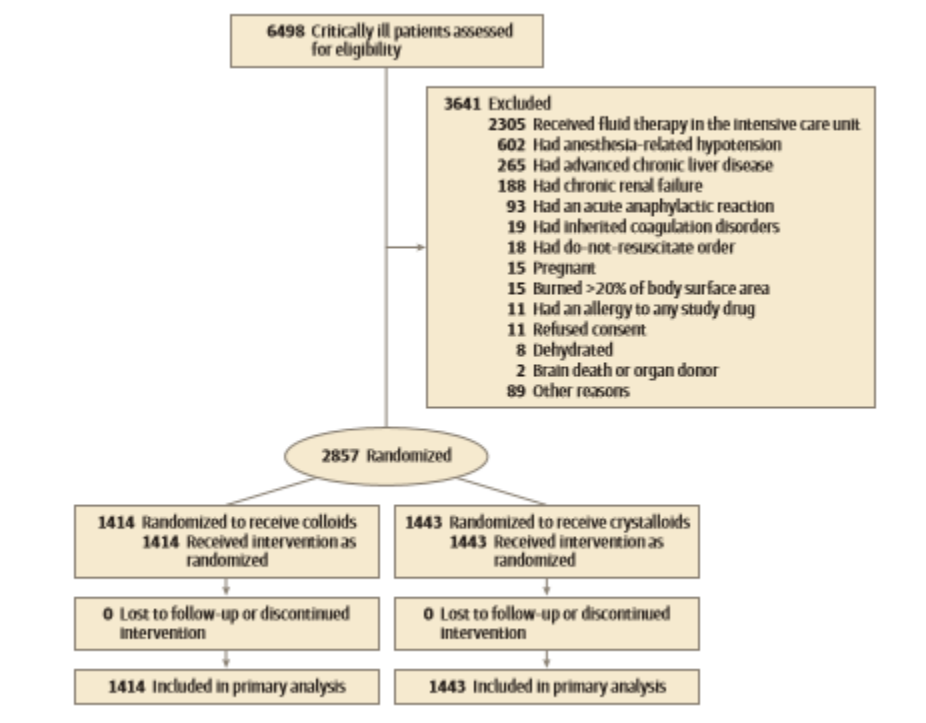
**Table 9**: Outcomes by treatment group CRISTAL clinical trial

	No. (%) of Patients			
	Colloids (n = 1414)	Crystalloids (n = 1443)	RR (95% CI)	P Value[a]
Death				
Within 28 d	359 (25.4)	390 (27.0)	0.96 (0.88 to 1.04)	.26
Within 90 d	434 (30.7)	493 (34.2)	0.92 (0.86 to 0.99)	.03
In ICU	355 (25.1)	405 (28.1)	0.92 (0.85 to 1.00)	.06
In hospital	426 (30.1)	471 (32.6)	0.94 (0.87 to 1.02)	.07
No. of days alive and without the following treatment or condition	Mean (SD)		Mean Difference (95% CI)	
Mechanical ventilation within the first 7 d	2.1 (2.4)	1.8 (2.3)	0.30 (0.09 to 0.48)	.01
Mechanical ventilation within the first 28 d	14.6 (11.4)	13.5 (11.5)	1.10 (0.14 to 2.06)	.01
Renal replacement therapy within the first 7 d	4.8 (2.9)	4.6 (2.9)	0.2 (−0.4 to 0.8)	.99
Renal replacement therapy within the first 28 d	13.9 (11.3)	13.1 (11.4)	0.8 (−1.6 to 3.3)	.90
Organ failure (SOFA score <6) within the first 7 d	6.2 (1.8)	6.1 (1.8)	0.06 (−0.10 to 0.20)	.31
Organ failure (SOFA score <6) within the first 28 d	21.4 (10.3)	20.9 (10.6)	0.6 (−0.4 to 1.5)	.16
Vasopressor therapy within the first 7 d	5.0 (3.0)	4.7 (3.1)	0.30 (−0.03 to 0.50)	.04
Vasopressor therapy within the first 28 d	16.2 (11.5)	15.2 (11.7)	1.04 (−0.04 to 2.10)	.03
ICU stay within the first 28 d	8.3 (9.0)	8.1 (9.2)	0.2 (−0.5 to 0.9)	.69
Hospital stay within the first 28 d	11.9 (11.1)	11.6 (11.4)	0.3 (−0.5 to 1.1)	.37

Abbreviations: ICU, intensive care unit; RR, relative risk; SOFA, Sequential Organ Failure Assessment.

[a] For mortality end points, the analysis was performed using the Mantel-Haenszel test stratified based on admission diagnosis (ie, sepsis, trauma, or other causes of hypovolemic shock). The number of days alive and not receiving mechanical ventilation, vasopressor therapy, and renal replacement therapy and days alive without organ system failure were compared between randomized groups using the nonparametric Wilcoxon rank sum test.

Figure 6: Base Excess changes *Comparison of the Effectiveness of Hydroxyethyl Starch (Voluven) Solution With Normal Saline in Hemorrhagic Shock Treatment in Trauma* clinical trial
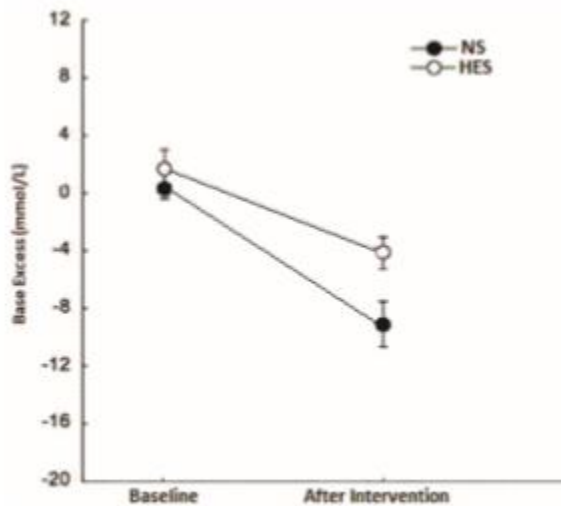
Figure 7: Patient recruitment for burns fluid resuscitation in *Hydroexyethylstarch supplementation in burn resucitation*
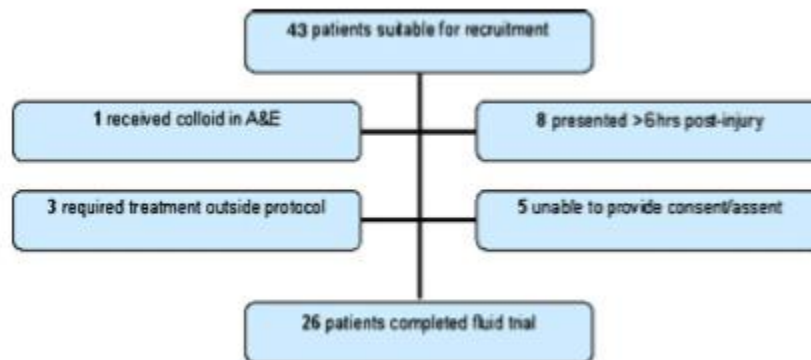
Table 10: Resucitation Fluid date for *Hydroexyethylstarch supplementation in burn resuscitation clinical trial*

	Crystalloid only n = 14	Colloid-supplemented n = 12	p
Median data for first 24 h post-burn			
Volume of fluid infused (ml)	8450	8650	0.9798
Volume infused/%TBSA (ml)	307	263	0.0234
Volume infused/%TBSA/patient weight (ml/kg)	4.2	3.8	0.2740
Volume infused – volume predicted (range)	+545 (−835 to +3175)	−391 (−1084 to +2210)	0.2972
Crystalloid volume (ml)	8450	7306	–
HES volume (ml)	0	1585	–
Weight gain (kg)	2.5	1.4	0.0039
Weight gain/%TBSA	0.078	0.046	0.0037
Weight gain/%FTB	0.2	0.1	0.0055

TBSA = total body surface area, FTB = full thickness burn.

Table 11: Inflammatory marker data for *Hydroxyethylstarch supplemetnation in burn resucitation clinical trial*

	Crystalloid only $n = 14$	Colloid-supplemented $n = 12$	p
Median (95%CI) serum CRP at 48 h (mg/L)	210 (167–257)	128 (74–145)	0.0001
ACR at 6 h (mg/mmol)	2 (0.4–6.4)	2.6 (0.5–24.5)	0.4319
ACR at 12 h (mg/mmol)	1.3	1	0.4025
12 h ACR/%TBSA	0.04	0.02	0.0310
12 h ACR/%FTB	0.14	0.05	0.0080

CI = confidence interval, CRP = C-reactive protein, ACR = albumin-creatinine ratio, TBSA = total body surface area, FTB = full thickness burn.

Table 12: Peak results and findings for *A Prospective, Randomized Evaluation of Intra-abdominal Pressures with Crystalloid and Colloid Resuscitation in Burn Patients*

	Crystalloid	Plasma	p Value
No.	15	16	
Peak IAP (mm Hg)	32.5 ± 9.5	16.4 ± 7.5	<0.0001
IAP increase (mm Hg)	26.5 ± 7.9	10.6 ± 6.4	<0.0001
Time of peak IAP (hr)	72.7 ± 4.1	68.3 ± 11.1	0.16
Resuscitation volume (L/kg)	0.561 ± 0.160	0.360 ± 0.170	0.0021
Weight gain (%)	40.7 ± 17.8	15.3 ± 10.0	<0.0001
Urine output (ml/kg/h)	0.54 ± 0.26	0.83 ± 0.32	0.0097
Peak creatinine (mg/dL)	1.9 ± 1.0	1.5 ± 0.9	0.23
Peak BUN (mg/dL)	30.2 ± 13.4	24.6 ± 15.7	0.29
Peak base excess/deficit	-1.7 ± 5.5	1.3 ± 3.2	0.07
Peak PAP (mm Hg)	40.6 ± 5.6	35.2 ± 5.4	0.01

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