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A change of colloid from hydroxyethyl starch to gelatin does not reduce rate of renal failure or mortality in surgical critical care patients: Results of a retrospective cohort study☆

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ABSTRACT

Purpose: Hydroxyethyl starch (HES) may compromise renal function in critically ill patients. As an alternative, gelatin (GEL) was suggested. This study investigated whether GEL (4%) may have advantages over HES (6%, 130/0.4) with respect to acute renal failure (ARF), length of intensive care unit /hospital stay, and 30-day mortality and evaluated dose-dependent effects.
Material and methods: We performed a retrospective cohort analysis of 1522 surgical intensive care patients in a single university hospital where HES was changed to GEL in June 2006. The year before, 515 patients received HES; the year after, 540 patients received GEL. Within both years, 497 patients received crystalloids (CRY) only. Fluid therapy was performed upon clinical judgment and did not follow a study protocol.
Results: There was no difference in ARF between HES and GEL ($P = .292$), but ARF was more frequent in both colloid cohorts compared with CRY (HES/GEL vs CRY, $P < .05$). Mortality and maximum daily dose of both HES ($r = 0.93$) and GEL ($r = 0.93$) were significantly correlated, but mortality and total amount of CRY or total fluid intake were not significantly correlated. Cumulative amounts of fluids given were significantly higher in both colloid groups compared with CRY only, and GEL was given in higher doses than HES. In both colloid cohorts, the need for renal replacement therapy and 30-day mortality were significantly higher, and intensive care unit and hospital stay was longer, compared with CRY.
Conclusions: A change of colloid from HES to GEL did not reduce the rate of ARF or mortality in surgical critical care patients. Both colloids appear to have dose-dependent effects on renal function.

1. Introduction

The debate on volume resuscitation for critically ill patients remains controversial. In the intensive care unit (ICU), crystalloid solutions are used for daily fluid and electrolyte substitution and as a first-line intervention in acute hypovolemia [1,2]. Until recently, the administration of colloidal solutions like hydroxyethyl starch (HES) or gelatin (GEL) was well accepted for the apparently rapid and lasting restoration of blood pressure for volume deficits. However, new evidence on the risk-benefit ratio and efficiency of colloids has led to an ongoing debate.

A Cochrane report on fluid resuscitation in critically ill patients identified 25 trials (>9000 patients) comparing HES with crystalloids and 11 studies (506 patients) that evaluated GEL [3]; the use of both colloids was not associated with a reduction of mortality, but no dose dependency was noted regarding renal function. A recent meta-analysis included 10 studies that analyzed the effect of HES vs crystalloids on renal function in critically ill patients with sepsis [4]. In this analysis, the administration of HES was associated with higher 90-day mortality, an increased risk for acute renal failure (ARF), and a higher need for renal replacement therapy (RRT) vs the control substance.

Based on the publications of controlled trials [5-7], the European Medicines Agency has recommended limiting the use of HES for therapy of acute hypovolemia. The utilization of HES in patients with sepsis or burn injury or in critically ill patients was rejected [8]. In consequence, a Royal College of Anaesthetists position statement suggested that GEL may be an alternative to HES, although data on GEL are considered weak in the same publication [9]. In a retrospective cohort analysis,

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use of colloids was associated with a dose-dependent reduction of renal function in critically ill patients for both HES and GEL [10]. A follow-up analysis showed benefits for patients with severe sepsis that were treated with crystalloids only [11]. However, there are insufficient data on the effect of GEL on renal function and mortality in ICU patients, and data on dose-dependency are rarely reported.

To shed more light on this issue and to analyze the value of GEL as an alternative for HES, this retrospective cohort study was performed to compare the effects of HES, GEL, and crystalloids with respect to renal function and 30-day survival in critically ill patients in a surgical university hospital ICU. Furthermore, we evaluated dose-dependent effects of both colloids on these parameters.

2. Material and methods

2.1. Setting, patients, and study groups

We retrospectively screened the data of all patients admitted to a 24-bed interdisciplinary surgical ICU at Saarland University Hospital within the period of June 2005 to June 2007. In accordance with German regulations, no ethical approval was necessary for this survey, as only anonymized data were collected and only epidemiological data were evaluated without an a priori study protocol (noninterventional study according to German Pharmaceutical Act §4 Abs. 23).

The fluid therapy regimen was changed within the last week of May 2006 from HES 6% (130/0.4) (Voluven; Fresenius Kabi, Bad Homburg, Germany) to GEL 4% (Gelafundin 4%; Braun Melsungen AG, Melsungen, Germany) based on safety considerations. Indications for fluid therapy and bolus colloid application were driven by the attending physician. Balanced acetated electrolyte solutions were used as the standard crystalloid for daily routine fluid therapy in all cohorts. For special indications, normal saline or glucose (5%) solutions were administered. Patients receiving both types of colloid during their stay on ICU were excluded from the study.

2.2. Variables and end points

Bolus fluid treatment was defined as the intravenous administration of HES, GEL, or crystalloids to treat a volume deficit. All fluids administered were included in the analysis of *daily fluid balance*, which was defined as the difference between total fluid intake (enteral and parenteral intake, blood products, and other documented intake) and output (urine, dialysis, drainages, secretions, and other documented losses). Fluid balance was defined as median in liters per day. Crystalloids and colloids are presented as maximum daily or ICU-stay cumulative amounts in liters per day or milliliters per kilogram body weight (BW).

The primary end point was defined as acute kidney injury according to the risk, injury, failure, loss of renal function, and end-stage kidney injury (RIFLE) criteria [12]. RIFLE-F was specified by a 3-fold increase of serum creatinine level compared with admission, a serum creatinine level of at least 4 mg/dL (352 μmol/L) accompanied by an acute elevation of at least 0.5 mg/dL (44 μmol/L), and/or a primary need for RRT. In patients with previous need for dialysis, RRT on ICU did not qualify for ARF. Continuous venovenous hemodialysis was the standard method for RRT. Indications were evaluated in accordance with a consultant from the department of nephrology and included ongoing and otherwise therapy-refractory hyperkalemia, hypervolemia, renal acidosis, and uremia. Further end points were length of ICU or hospital stay and 30-day mortality, as well as dose-dependent effects of both colloids and the crystalloid-colloid ratio.

2.3. Data acquisition

Data collection was based on paper and electronic patient records (Copra version 5; Copra System Inc, Sasbachwalden, Germany). Analyzed data were stored in a Microsoft Access 2007 database (Microsoft Corp, Redmond, WA). Non-ICU data and laboratory parameters were reviewed using SAP ERP software (version 6.0; SAP AG, Walldorf, Germany). The observed cohorts were compared with respect to demographic data, results of examination at ICU admission, as well as progression and follow-up parameters. Evaluation of disease and risk of death was stratified using the Acute Physiological and Chronic Health Evaluation II (APACHE II) score [13].

2.4. Statistical analysis

Sigmaplot 9.0/Sigmastat 3.1 (Systat Software, Inc, San Jose, CA) was used for statistical performance and graphical data presentation. Frequency of distribution with respect to analyzed parameters in observed cohorts was performed by χ^2 testing. Normal distribution of data was evaluated by Kolmogorov-Smirnov test. Parametric data were analyzed using 1-way analysis of variance; nonparametric data were analyzed by Kruskal-Wallis analysis of variance. Post hoc multiple comparisons were performed using the Dunn method. Continuous data are presented as median and 25th to 75th interquartile range. Log-rank test (Kaplan-Meier) was used to compare 30-day survival among the 3 patient groups. Comparison of 2 groups was performed using Student *t* test or Mann-Whitney *U* test. *P* values $< .05$ were regarded significant for all tests.

3. Results

3.1. Cohort characteristics

Within the study period of 2 years, 1552 patient charts were included; 515 patients were treated with HES, whereas 540 received GEL as colloid. In a third cohort of 497 patients, no colloidal solution was administered, and fluid substitution was implemented by crystalloids only (Table 1). There was no significant difference among groups concerning previous renal failure or creatinine levels on ICU admission, but in the HES group, less patients required dialysis before ICU admission. Evaluation of APACHE II revealed a higher score at admission for patients treated with HES compared with GEL or CRY; this was statistically significant. No significant difference was observed for an APACHE II score greater than 20 in the 3 cohorts.

3.2. Fluid balance and administration during ICU stay

Patients in colloid cohorts received significantly more total fluid per day and more crystalloids per day and stay, and were balanced more positive compared with the CRY cohort, but there was no significant difference between both GEL and HES cohorts with respect to fluid balance and crystalloid intake (Table 2). However, in the GEL cohort, significantly higher volumes of colloid were applied when compared with HES.

3.3. Acute renal failure

Acute renal failure was detected significantly more often in the HES and GEL cohorts compared with CRY during their stay on ICU, but there was no significant difference between both colloids (Table 3). The same results were obtained for newly diagnosed ARF, but for acute-on-chronic renal failure, no significant differences were seen between groups. Total need for RRT was significantly higher in the GEL group compared with the CRY cohort. After exclusion of previous need for dialysis, RRT was performed significantly more often in both GEL and HES cohorts compared with the CRY group, but there was no difference between both colloid groups.

Incidence of ARF was higher in patients that received higher maximum daily doses or cumulative doses of colloids (Fig. 1A-B); there was a good correlation between ARF and GEL or HES regarding ICU cumulative dose (HES $r = 0.74$, GEL $r = 0.70$), but this was not statistically significant. A significant correlation was found for ARF and maximum