Dilutional Acidosis following Hetastarch or Albumin in Healthy Volunteers

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Background: The intent of this study was to evaluate the impact of the commonly used colloids—hetastarch and albumin—on in vivo acid–base balance. From this evaluation, a better understanding of the mechanism of dilutional acidosis was expected.

Methods: In a prospective, randomized fashion, 11 healthy volunteers were administered 15 ml/kg hetastarch solution, 6%, or 15 ml/kg albumin, 5%, intravenously over 30 min. Four weeks later, the study subjects were administered the other colloid. Arterial blood gas and electrolyte parameters were measured at baseline and at 30, 60, 90, 120, 210, and 300 min after colloid administration. Pre- and postlaboratory values were compared within groups using a paired t test and a Wilcoxon signed rank test and between groups using repeated-measures analysis of variance and a Wilcoxon rank sum test.

Results: Thirty min after infusion, subjects who were administered hetastarch showed statistically significant changes ($P < 0.05$) in base excess (from 2.5 ± 0.9 mEq/l to 0.7 ± 1.1 mEq/l), HCO_3^- concentration (from 27 ± 1.0 mEq/l to 25 ± 1.3 mEq/l), Cl^- concentration (from 108 ± 2 mEq/l to 112 ± 2 mEq/l), albumin concentration (from 4.4 ± 0.2 g/dl to 3.5 ± 0.5 g/dl), and arterial carbon dioxide tension ($Paco_2$; from 40.8 ± 2.3 mmHg to 39.2 ± 3.2 mmHg), whereas only the albumin concentration (from 4.4 ± 0.2 g/dl to 4.8 ± 0.6 g/dl) changed significantly in the albumin-treated group.

Conclusions: Decreases in base excess were observed for 210 min after hetastarch administration but not after albumin. The mechanism for this difference is discussed. (Key words: Hyperchloremic acidosis; normal saline; volume expansion.)

IN the treatment of patients with volume depletion, colloid solutions, such as albumin and hetastarch, are administered commonly. Inadequate fluid resuscitation is well-recognized to result in lactic acidosis; however, the impact on acid–base balance of the colloid solutions have not been evaluated. Any acid–base change may be clinically important, especially in the treatment of patients with marked acid–base abnormalities. It was the intent of this study to evaluate acid–base changes after administration of the two most commonly used colloid solutions—hetastarch and albumin.

In addition to documenting acid–base changes related to colloid solution administration, a secondary goal of this study was to clarify the mechanism responsible for dilutional acidosis. Dilutional acidosis has been documented after administration of normal saline and is theorized to result from volume expansion and subsequent dilution of serum bicarbonate.[1–4] With these colloid solutions, volume expansion is expected also. If the mechanism for this acid–base change is valid, an acid–base change should be observed after administration of hetastarch and albumin.

Materials and Methods

After approval by the institutional review board and the Human Subjects Review Committee (University of California, Irvine Medical Center, Orange, CA), enlistment of healthy adult volunteers began. Volunteers were excluded if they had medical problems or were prescribed long-term medications, including nonsteroidal antiinflammatory drugs or birth control pills. Each volunteer was assigned randomly to receive either 15 ml/kg hetastarch solution, 6% (Hespan; DuPont Pharma, Wilmington, DE), or 15 ml/kg human albumin solution, 5% (Albumarc 5%; Baxter Healthcare Corp., Glendale, CA) over 30 min with use of an infusion pump. Each volunteer returned 4 weeks after administration of the first colloid and was administered the other colloid following the same protocol. Before colloid administration, an 18-gauge intravenous catheter and a 20-gauge radial artery catheter were placed. Arterial blood was drawn through the radial artery catheter before infusion (time 0), at the end of colloid infusion (time 30), and at 60, 90, 120, 210, and 300 min after the start of colloid infusion. Arterial blood gas parameters (NOVA Stat Profile 5; NOVA Biomedical, Waltham, MA) and Na^+, K^+, Cl^-, HCO_3^-, albumin, and lactate concentrations (Beckman CX-7; Beckman Labs, Brea, CA) were measured. The blood-gas machine was calibrated at the beginning of data collection, with a two-point calibration and a one-point calibration after each blood sample.

Hemoglobin and hematocrit concentrations were measured (Sysmex NE8000; TOA Medical Electronics Co., Los Alamitos, CA) at 0, 30, 60, 120, 210, and 300 min. Using these measurements, percentage changes in plasma volume were calculated.[5]

This article is accompanied by an Editorial View. Please see: Prough DS: Acidosis associated with perioperative saline administration: Dilution or delusion? ANESTHESIOLOGY 2000; 93:1167–9.

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Table 1. Blood Gas and Electrolyte Data before and Immediately after Infusion (30 min)

	Hetastarch		5% Albumin	
	Before	After	Before	After
pH	7.42 ± 0.02	7.41 ± 0.03*	7.42 ± 0.02	7.43 ± 0.02
P_{CO_2} (mm Hg)	40.8 ± 2.3	39.2 ± 3.2*	40.3 ± 3.5	40.1 ± 2.8
Na^+ (mEq/l)	143 ± 2	143 ± 1	143 ± 2	143 ± 2
K^+ (mEq/l)†	4.0 ± 0.2	3.9 ± 0.2*	4.2 ± 0.2	3.8 ± 0.2*
Cl^- (mEq/l)†	108 ± 2	112 ± 2*	108 ± 3	107 ± 2
Albumin (gms/dl)†	4.4 ± 0.2	3.5 ± 0.5*	4.4 ± 0.2	4.8 ± 0.6*
HCO_3^- (mEq/l)†	27 ± 1.0	25 ± 1.3*	26 ± 1.4	26 ± 1.4
BE_b (mEq/l)†	2.5 ± 0.9	0.7 ± 1.1*	2.2 ± 1.2	2.4 ± 1.3
Lactate (mEq/l)	1.4 ± 0.6	0.9 ± 0.8	1.0 ± 0.7	1.1 ± 0.6
Hct (%)	45.9 ± 4.0	39.4 ± 3.3	45.7 ± 3.7	41.0 ± 3.6
SID (mEq/l)†	43.0 ± 3.1	37.7 ± 3.4*	42.6 ± 2.7	43.1 ± 2.4

* $P < 0.005$ for the percent difference from baseline for the individual fluid. † $P < 0.005$ for both paired t test and Wilcoxon signed rank test when the (hetastarch − albumin) percent difference from baseline was tested.

P_{CO_2} = partial pressure of carbon dioxide; Na^+ = sodium; K^+ = potassium; Cl^- = chloride; HCO_3^- = bicarbonate; BE_b = base excess of blood; hct = hematocrit; SID = strong ion difference, which is the difference in charge between the cations Na^+ and K^+ and the anions Cl^- and lactate.

Statistical Analysis

Within Treatment Groups. Change from baseline and percent change from baseline were calculated. Paired t tests and Wilcoxon signed rank tests were used to test whether these changes were different from time 0 within the treatment group.

Difference between Treatments. The difference between hetastarch percent difference in change and albumin percent difference in change (hetastarch %difference − albumin %difference) was calculated for each time point and was compared using the Wilcoxon rank sum test. These same values were tested with use of a repeated-measures analysis of variance.

A P value less than 0.05 was considered statistically significant. Parameters are reported as mean ± standard deviation.

Results

Ten men and one woman were included in the study. One man was excluded from the study after an allergic response during initiation of albumin infusion. Average age was 26 ± 4 yr. The mean weight of the subjects when albumin was administered was 72.8 ± 8.0 kg, and they were administered a mean albumin volume of 1,094 ± 120 ml. The mean weight of the subjects when they were administered hetastarch was 73.7 ± 8.8 kg, with a mean hetastarch volume of 1,095 ± 118 ml.

Pre- and postinfusion (times 0 and 30 min) blood gas and electrolyte values are shown in table 1. Of significance are the changes in Cl^- and the changes in base excess of blood (BE_b) or HCO_3^-. The Cl^- level increased 4 mEq/l in the hetastarch group, whereas no change was seen in the albumin group. The BE_b and HCO_3^- level changed in an acidotic direction for the hetastarch group but not for the albumin group. Progresssive changes for BE and Cl^- are shown in figures 1 and 2, respectively. Additionally, the albumin concentration was diluted by
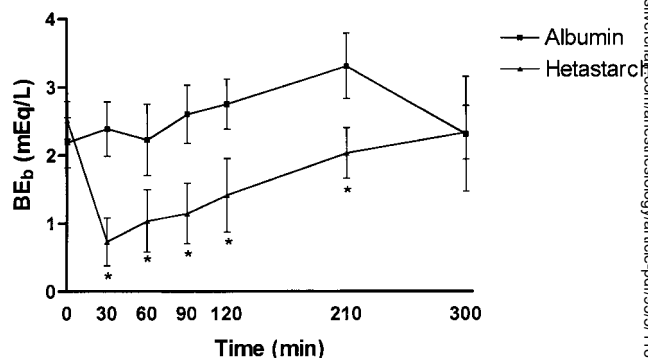
Fig. 1. Base excess of blood (BE_b) decreased in the hetastarch group, with return to baseline after 300 min. No significant change was seen in the albumin group. *$P < 0.05$ when compared with baseline.

the hetastarch, whereas the albumin concentration increased after its administration.

Change in plasma volume from baseline is shown in figure 3. The percent plasma volume changes after administration (time 0 to time 30 min) were 24 ± 7% and 28 ± 8% for albumin and hetastarch, respectively. No statistical difference between albumin and hetastarch in plasma volume change was seen.
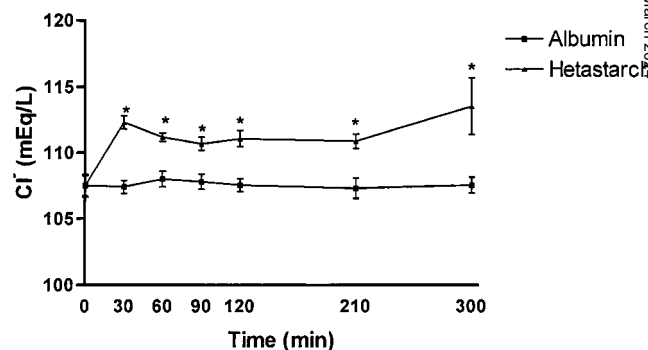
Fig. 2. Chloride levels increased significantly from baseline after hetastarch administration but were unchanged after albumin administration. *$P < 0.05$ when compared with baseline.
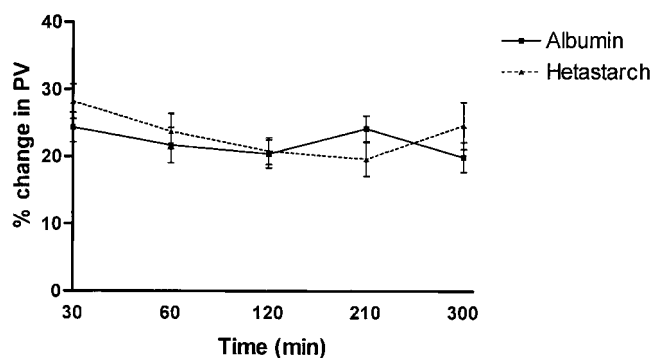
Fig. 3. Plasma volume (PV) change as calculated from changes in hematocrit and hemoglobin concentrations. There were no significant differences in volume expansion between the two groups.

Discussion

In these awake, spontaneously breathing subjects, no significant change in pH occurred after administration of either colloid; however, a significant negative change in BE occurred after hetastarch administration. Changes in BE and partial pressure of carbon dioxide (P_{CO_2}) are considered to be independent variables that describe the nonrespiratory and respiratory states of the patient's extracellular fluid. pH is the result of their interaction.[6] Therefore, the statistically significant change in BE represents a disturbance in the nonrespiratory acid–base state of these subjects.

Because hetastarch is mixed in normal saline, it is easy to assume that dilutional acidosis, resulting from the saline infusion, is the mechanism for this BE change. The mechanism thought to be responsible for dilutional acidosis relies on volume expansion as a primary feature.[7] Previous studies[8–10] have shown slightly greater increases in blood volume after administration of hetastarch as compared with albumin. In this study, plasma volume expansion was calculated from changes in hematocrit concentration. Maximum increases in plasma volume of 24 and 28% were seen after administration of albumin and hetastarch, respectively. This small difference was not significant. Despite subtle differences in volume expansion, significant volume expansion occurred with both fluids, but only hetastarch administration resulted in an acid–base change. Therefore, the lack of acid–base change after albumin administration does not confirm the concept of volume expansion as a primary mechanism for this acid–base change. Other factors must play a role.

A factor that could explain this discrepancy is the differing electrolyte concentrations of these fluids. Albumin is precipitated from human plasma. When first developed, this albumin precipitate was reconstituted in a hypertonic sodium chloride solution, with an Na^+ and Cl^- concentration of 300 mEq/l. This hypertonicity was necessary to achieve thermal stability. Subsequently, it was found that sodium acetyltryptophanate and sodium

caprylate could achieve similar goals without the high salt concentration. Thus was born "salt-poor" albumin.[11,12] Albumin is made from these constituents with normal saline added as needed to achieve an isotonic solution. In addition, the pH is adjusted to 6.4–7.4 with use of sodium carbonate, sodium bicarbonate, sodium hydroxide, or acetic acid. This creates a solution with a sodium concentration of 150 mEq/l, resulting from sodium acetyltryptophanate, sodium caprylate, sodium chloride, sodium carbonate, sodium bicarbonate, and sodium hydroxide.[13] On average, the chloride and bicarbonate concentrations are 93 mEq/l and < 0.05 M, respectively (oral and written communication, Roger Lundblad, Ph.D., Baxter Hyland Immuno, Glendale, CA, June 1997 and September 1999). Conversely, hetastarch is constituted in normal saline solution with sodium and chloride concentrations of 154 mEq/l.[14] Similar to albumin, hetastarch also is pH-adjusted. Therefore, a major dissimilarity between albumin and hetastarch is the chloride concentration.

Recently, Scheingraber *et al.*[15] demonstrated a dose-response relation between pH, BE, and chloride after normal saline infusion. In their study, P_{CO_2} was kept constant. Saline was administered throughout gynecologic surgery, which resulted in concurrent changes in pH. They concluded that these pH changes were caused by the Cl^-. In this study, volume expansion was created with solutions of a similar composition as Scheingraber *et al.*[15] This resulted in a BE change in the hetastarch group but not in the albumin group. These data, along with the data of Scheingraber *et al.*,[15] strongly suggest that dilutional acidosis is not related to volume expansion but rather to the chloride load.

A theoretical mechanism for this acid–base change can be proposed using the physicochemical acid–base theory.[16–18] It is this increase in $[Cl^-]$ that, according to this new approach, would be primarily responsible for the acid–base effect. According to the physicochemical theory, metabolic acid–base change is related to changes in two factors: the strong ion difference (SID) and the albumin concentration. The SID generally is defined as the difference in the strong cations (Na^+, K^+) and the strong anions (Cl^-, lactic acid). After hetastarch administration, the $[Cl^-]$ increases, which causes a change in SID and causes acidosis; however, in the albumin group no significant change in SID was seen.

The other component of metabolic derangement as defined by the physicochemical theory is the albumin concentration. The albumin also changed in concentration after administration of these colloids, but it did so most significantly in the hetastarch group. An albumin decrease results in an alkalotic shift. Therefore, in the hetastarch group, the decrease in albumin mitigated some of the change that resulted from the decreased SID. (For a more extensive discussion of the physicochemical approach, see the original text.[19])

The classic mechanism for dilutional acidosis based on volume expansion was developed around *in vitro* dog blood studies, which showed a correlation between the bicarbonate concentration and the volume expansion of the blood with normal saline.[20] The same relation also could have been established easily between the chloride load and the bicarbonate. In this study, volume expansion occurred with both fluids; however, acid–base change only occurred with the high-chloride–containing solution. This indicates a chloride mechanism, rather than volume expansion, as the factor that changes the acid–base state after normal saline administration.

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