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Assessment of hemodynamic and gastric mucosal acidosis with modified fluid gelatin versus 6% hydroxyethyl starch: a prospective, randomized study

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Abstract *Objective*: To investigate the effect of 4% succinylated modified fluid gelatin (MFG) versus mean weight, highly substituted 6% hydroxyethyl starch (HES) on hemodynamic and gastric mucosal acidosis variables, in septic hypovolemic patients.
Design: Prospective, randomized, clinical investigation.
Setting: University hospital intensive care unit.
Patients: Thirty-four septic hypovolemic ventilated and hemodynamically controlled patients.
Interventions: Invasive hemodynamic and gastric tonometric measurements.
Measurements and results: Hemodynamic and tonometric parameters were recorded at baseline and 60 min after infusion of 500 ml of each colloid. In all patients central venous pressure, pulmonary artery occlusion pressure, cardiac index and mean arterial pressure increased significantly with both colloids, and hemoglobin concentration decreased by the same amount while oxygen delivery remained stable. Gastric intramucosal pH increased from 7.27 ± 0.08 to 7.31 ± 0.07 ($p < 0.001$) with MFG and decreased non-significantly from 7.26 ± 0.11 to 7.22 ± 0.08 (ns) with HES. Carbon dioxide gastric mucosal arterial gradient decreased from 18 ± 9 to 13 ± 9 mmHg ($p < 0.0005$) in the MFG group and rose non-significantly from 18 ± 11 to 21 ± 11 mmHg with HES.
Conclusions: Although MFG and 6% HES have the same hemodynamic effects, their physicochemical properties induce different responses on gastric mucosal acidosis in septic, hypovolemic and ventilated patients. These effects of MFG and HES on gastric mucosa need to be considered in patient management.

Key words Gastric mucosal acidosis · Hemodynamics · Colloid · Modified fluid gelatin · Hydroxyethyl starch · Sepsis

Introduction

Hypovolemia is a common clinical occurrence in intensive care medicine and results from several mechanisms such as water or blood losses, vasoplegia or capillary leak syndrome. This explains the fact that fluid replacement therapy is one of the key treatments in severe sepsis and septic shock.

Although there is no consensus concerning the ideal fluid replacement, colloids are efficient in this indication [1, 2, 3]. Modified fluid gelatins (MFG) are inexpensive and are widely used in European medical practice, but were said to be responsible for anaphylactic reactions. Hetastarch (HES), another widely used colloid which has the same efficiency as MFG, but at higher cost, is able to alter blood coagulation [4, 5], enhance blood losses [6] and possibly promote tubular necrosis in renal grafts [7].

Absolute and/or relative hypovolemia may lead to gut tissue hypoxia and promotes multiple organ failure

syndrome. Assessment of hypovolemia is difficult in intensive care for various reasons, but the measurement of intramucosal pH is reported to be a simple and useful method to detect the reduction of gastric mucosal blood flow in critical care patients [8]. Intramucosal pH monitoring in acute experimental hypovolemia is reliable [9, 10, 11], but it has not been fully assessed in hypovolemic septic patients.

We hypothesized that if hypovolemia is able to induce a gastric mucosal acidosis by reduction of gastric mucosal blood flow, correction of blood flow disturbances by a fluid challenge may increase intramucosal pH. Because of the lack of consensus concerning the ideal plasma expander, we prospectively compared the systemic hemodynamic and tonometric variables of two plasma expanders with different chemical properties in severe septic, hypovolemic and ventilated patients with controlled arterial pressure: modified fluid 4 % succinylated MFG versus mean weight 6 % HES.

Materials and methods

Inclusion criteria

Thirty-four septic, ventilated patients were included in the study (Servo 300, Siemens, Solna, Sweden). All patients had invasive monitoring for clinical purposes (pulmonary artery and arterial catheters) and fulfilled the following inclusion criteria: age over 16 years, systolic arterial pressure higher than 90 mmHg and hypovolemia defined by pulmonary artery occlusion pressure of 12 mmHg or less and intramucosal pH below 7.35 or PCO_2 gastric-artery gradient above 8 mmHg (gastric mucosal PCO_2 minus arterial PCO_2).

Patients with an overt hemodynamic, ventilatory or acid base status instability were excluded. Catecholamine infusions were not an exclusion criterion. Sepsis was identified by either positive bacterial blood cultures, bronchoalveolar lavage or clinical evidence of infection, coupled with at least three of the following signs: a) hyperthermia (rectal temperature > 38.2 °C) or hypothermia (rectal temperature < 35.5 °C), b) controlled ventilation, c) tachycardia (heart rate > 100 beats/min), d) abnormal white blood cell count (< 3,500/mm^3 or > 12,000/mm^3) or e) thrombocytopenia (< 100,000 platelets/mm^3). The study protocol was approved by the local ethics committee of our institution.

Hemodynamic monitoring

All intravascular pressures were measured with the patient in the supine position using the midaxillary level as the zero reference and at end-expiratory time. Cardiac output was measured with a continuous thermodilution technique (Baxter Healthcare, Edwards Critical-Care Division, Irvine, Calif., USA). Arterial blood samples were collected for the immediate determination of PO_2, PCO_2, pH and bicarbonates (ABL 330, Radiometer, Copenhagen, Denmark) and hemoglobin saturation and concentration and arterial oxygen content using an oximeter (OSM 3, Radiometer, Copenhagen, Denmark). Hemodynamic and oxygen transport values were measured and calculated classically. Urinary output was monitored and expressed in milliliters per hour.

Gastric tonometry

Gastric intramucosal pH was indirectly determined using a gastrointestinal sump tonometer (TRIP tonometer, Tonometrics, Worcester, Mass., USA) according to the Fiddian-Green method [12]. The position in the stomach was confirmed radiologically. The tonometer balloon was filled with 2.5 ml of 0.9 % saline and allowed to equilibrate for 30 min. The first milliliter of aspirate was discarded and analysis was immediately performed (ABL 330, Radiometer, Copenhagen, Denmark) on the remaining 1.5 ml. We measured gastric PCO_2 in triplicate on the same sample and calculated the tonometered PCO_2 mean value. Arterial PCO_2 and bicarbonates were measured at the same time. The gastric pHi was calculated using the modified Henderson-Hasselbach equation:

$$pHi = 6.1 + Log_{10} (\text{arterial } HCO_3/F \times 0.03 \times \text{tonometered } PCO_2)$$

Where F is a time-dependent factor provided by the manufacturer for partially equilibrated samples at 30 min, 0.03 is the solubility coefficient of CO_2 in plasma at 37 °C and 6.1 is the pK of HCO_3/CO_2 system in plasma at 37 °C. The PCO_2 gap, expressed in millimeters of mercury, was calculated as gastric PCO_2 minus arterial PCO_2. All patients received H2 blocking agents (ranitidine 150 mg/day by continuous infusion) and enteral feeding was stopped for at least 2 h before the experiment.

Study protocol

The study design was a randomized unblinded trial. Patients were randomly allocated to receive either 500 ml of 6 % HES (weight average molecular weight: 200,000 daltons; number average molecular weight: 60,000; substitution ratio: 0.6; half life: 24-h; Elohès 6 %, Fresenius France Pharma, Louviers) or 500 ml of 4 % succinylated MFG (Weight average molecular weight: 35,000 daltons; number average molecular weight: 21,700; half life: 4-h; Gelofusin, Braun Medical, Boulogne, France). After baseline hemodynamic and tonometric measurements had been achieved, the colloid was infused within 30 min. Hemodynamic and tonometric measurements were repeated 60 min after the end of the colloid infusion. During protocol, no changes of ventilator settings or drug administration were allowed.

Statistical analysis

Statistical analysis was performed with SPSS software (SPSS, Chicago, Ill., USA). Values are presented as means ± SD. Paired data obtained before and after colloid infusion were compared using a non-parametric Wilcoxon signed rank test. Mann-Whitney test was used for comparison between the two colloid regimens. Qualitative data were analyzed using a χ^2 test. A p value less than 0.05 was considered significant.

Results

Study population

Thirty-four patients were included, 16 in the HES group and 18 in MFG. Two patients in HES group were excluded from the analysis because they experienced hemodynamic instability with an increase of the PCO_2

Table 1 Clinical features of the study population (*SAPS II* Simplifed Acute Physiology Score – calculated on the first day of hospitalization)

	Hetastarch	MFG
Number of patients	16	18
Age (years)	64 ± 13	65 ± 14
Weight (kg)	63 ± 17	64 ± 15
Sex (F/M)	4/12	4/14
SAPS II	52 ± 26	46 ± 19
Source of sepsis	Pulmonary: 9 Abdominal: 5 Cerebral: 2	Pulmonary: 10 Abdominal: 4 Soft tissue: 3 Cerebral: 1
Vasopressive drugs	8 patients Dobutamine: 8 patients (5–20 μg·kg·min) Norepinephrine: 2 patients (0.5–1.7 μg·kg·min) Epinephrine: 1 patient (0.3 μg·kg·min)	6 patients Dobutamine: 2 patients (10–25 μg·kg·min) Norepinephrine: 2 patients (0.3–0.5 μg·kg·min) Dopamine: 3 patients (8–10 μg·kg·min)
Fibrinogen (g/l)	5.7 ± 2.2	5.6 ± 1.9
White cell count (Giga/l)	18.9 ± 9.6	21.0 ± 8.9
Mortality (%)	62	68

No different statistical baseline features between the two colloid groups

Table 2 Main hemodynamic and oxygen delivery parameters at baseline and at postinfusion time (*CVP* central venous pressure, *PAOP* pulmonary artery occlusion pressure, *MAP* mean arterial pressure, *CI* cardiac index, *SVRI* systemic vascular resistance index, DO_2 oxygen delivery, *ns* not significant)

	Baseline	Post infusion	*p* value
Hetastarch			
Heart rate (beats/min)	115 ± 17	119 ± 16	ns
CVP (mmHg)	6 ± 3	10 ± 4	0.002
PAOP (mmHg)	8 ± 2	12 ± 3	0.002
MAP (mmHg)	75 ± 15	84 ± 16	0.0009
CI (l·min·m^2)	3.7 ± 1.1	4.4 ± 0.9	0.012
SVR (dyne.sec/cm^5)	834 ± 297	873 ± 381	ns
DO_2 (ml·min·m^2)	481 ± 110	514 ± 133	ns
Hemoglobin (g/l)	104 ± 21	91 ± 18	0.001
Urine output (ml/h)	37 ± 44	53 ± 46	ns
MFG			
Heart rate (beats/min)	108 ± 22	107 ± 20	ns
CVP (mmHg)	7 ± 4	10 ± 4	0.003
PAOP (mmHg)	8 ± 2	11 ± 2	0.0028
MAP (mmHg)	76 ± 14	84 ± 13	0.0075
CI (l·min·m^2)	3.6 ± 1.1	4.4 ± 1.4	0.0057
SVR (dyne.sec/cm^5)	866 ± 332	884 ± 360	ns
DO2 (ml·min·m^2)	498 ± 140	531 ± 140	ns
Hemoglobin (g/l)	106 ± 14	96 ± 14	0.0003
Urine output (ml/h)	48 ± 22	95 ± 101	0.004

Table 3 Tonometric and blood gas data at baseline and at postinfusion time (PCO_2im intra-mucosal PCO_2, *pHim* intra-mucosal pH, PCO_2 *gap* mucosal arterial gradient of PCO_2, *ns* not significant at baseline between the two groups)

	Baseline	Postinfusion	*p* value
Hetastarch			
PCO_2im (mmHg)	55 ± 15	59 ± 14	ns
pHim	7.26 ± 0.11	7.22 ± 0.08	ns
PCO_2 gap (mmHg)	18 ± 11	21 ± 11	ns
Arterial pH	7.42 ± 0.07	7.41 ± 0.06	ns
Arterial PO_2 (mmHg)	110 ± 36	109 ± 34	ns
Arterial bicarbonates (mmol/l)	23.8 ± 3.4	23.7 ± 3.0	ns
Arterial PCO_2 (mmHg)	37 ± 7	37 ± 7	ns
MFG			
PCO_2im (mmHg)	55 ± 10	50 ± 6[a]	0.0006
pHim	7.27 ± 0.08	7.31 ± 0.07[b]	0.0007
PCO_2 gap (mmHg)	18 ± 9	13 ± 6[c]	0.0003
Arterial pH	7.44 ± 0.06	7.44 ± 0.07	ns
Arterial PO_2 (mmHg)	115 ± 46	107 ± 30	ns
Arterial bicarbonates (mmol/l)	24.9 ± 3.8	24.8 ± 3.4	ns
Arterial PCO_2 (mmHg)	37 ± 6	37 ± 5	ns

[a] $p < 0.04$ between the two groups at postinfusion time
[b] $p < 0.003$ between the two groups at postinfusion time
[c] $p < 0.02$ between the two groups at postinfusion time
To convert mmHg to kPa, multiply the value by 0.1333

gap. The final analysis was made on the 16 remaining patients in the HES group. Clinical features are summarized in Table 1. There were no differences at baseline between the two groups in the variables examined.

Table 2 summarizes the hemodynamics. As expected, there was a significant increase of central venous pressure, pulmonary artery occlusion pressure, mean arterial pressure and cardiac index in both groups without significant differences between the two colloids. Furthermore both plasma expanders induced a comparable decrease in hemoglobin concentration ($p < 0.0001$) while systemic vascular resistances remained unaltered. Oxygen delivery was not altered with respect to the fluid challenge in either group.

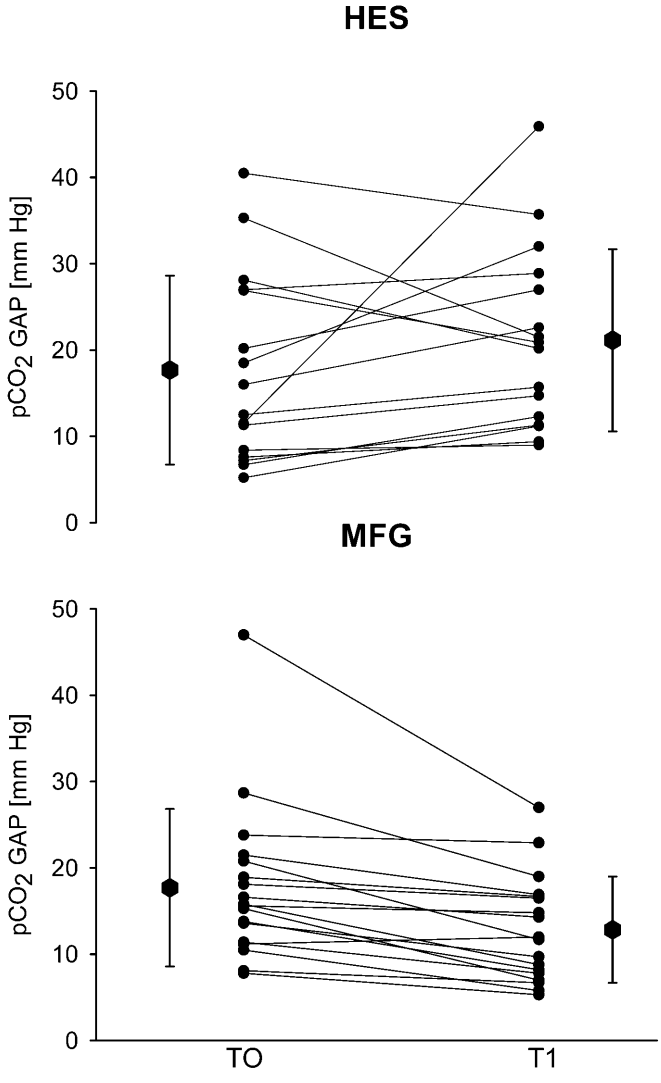

Fig. 1 Individual patient plots for the PCO_2 gastric arterial gradient in HES group *(top)* and in MFG group *(bottom)*, before (T0) and after 60 min post fluid challenge (T1). Mean values ± SD values. $^{*}p = 0.0006$ between T0 and T1 in MFG group; $^{\#}p < 0.02$ between the two groups at T1

Tonometric data are shown in Table 3 and individual changes in Fig. 1. There were no differences between the two groups at baseline. Patients who received MFG exhibited a significant improvement in the measured and calculated tonometric values, while HES patients showed a non-significant increase of their gastric intramucosal PCO_2 and PCO_2 gap.

Discussion

We tested, under routine clinical conditions, two colloids widely used for hypovolemia in septic hemodynamically controlled patients. In both groups, hypovolemia was ascertained with a pulmonary artery occlusion pressure below 12 mmHg and a gastric mucosal pH below 7.35 or PCO_2 gap above 8 mmHg, because gastric mucosal pH correlates well with low gastric mucosal blood flow [8, 11, 13] and is a sensitive parameter with which to detect hypovolemia [11]. Urinary output was not considered as the unique hypovolemia criterion because of the various thresholds of oxygen delivery supply and dependency among organs. Only patients with stable hemodynamic status were included due to the time required for PCO_2 equilibration in the saline tonometer.

There was no significant difference between HES and MFG on systemic hemodynamic and oxygenation parameters. Similar results have been reported by other authors with HES, MFG and albumin [14, 15]. Both colloids decreased hemoglobin concentration by the same amount and increased cardiac index. This explains why oxygen delivery remained stable after the fluid challenge. Urinary output has to be analyzed cautiously because one patient exhibited a urinary output of 460 ml/h just after the fluid challenge, explaining the significant difference between HES and MFG (Table 2).

Gastric tonometry allows an indirect assessment of intramucosal pH and has been validated in different animal models of intestinal hypoperfusion [16]. The measurement of intramucosal pH has been validated as a prognosis index [16, 17, 18, 19] and as a therapeutic index of gut tissue oxygenation in critically ill patients [20]. This parameter has prompted numerous studies attempting to increase mucosal blood flow with red blood cell transfusions [21, 22] or with different vasoactive drugs, with varied success [23, 24, 25, 26].

Our study protocol was designed to allow accurate measurements with saline tonometry which need a minimum of 30 min of intragastric equilibrium time. The measurement delay of 60 min after the end of fluid challenge was selected with regard to the pharmacodynamic properties of vascular expansion of 6 % HES and the intravascular efficiency of the MFG. Our tonometric results were unexpected: HES worsened, but not significantly, the intramucosal pH and PCO_2 gastric-arterial gradient compared to MFG. Individual analyses of patients showed large interindividual changes of tonometric variables in the HES group. By contrast, MFG induced a significant increase of gastric mucosal pH and a significant decrease in PCO_2 gap. The mechanism of this difference is not clear, but the design of the study does not allow for elucidation of these discrepancies.

However HES has a number of theoretical advantages with regard to microcirculation in sepsis. The highly-branched molecules aggregate in the gaps between endothelial cells along the basement membrane, effectively sealing leaky capillaries [27]. Nevertheless a narrow-range, medium molecular weight HES was more ef-

ficient in maintaining capillary patency and alveolar capillary barrier thickness than hetastarch (400,000/0.7) in a porcine model of fecal peritonitis [28]. This theoretical advantage of starches was confirmed in studies involving septic and trauma patients, which demonstrated an improvement of endothelial associated-coagulation [29, 30] and an improvement of gastric mucosal acidosis and liver function with 10 % HES solution (mean weight 200,000 daltons, degree of substitution 0.5) [31]. Other authors reported, in patients undergoing elective cardiac surgery, a beneficial effect of repeated HES short bolus on gastric mucosal ischemia [32]. In the same way an improvement of microvascular blood and tissue oxygenation, assessed by measuring intramucosal pH with HES, has been reported in patients undergoing major abdominal aortic aneurysm repair [33].

The discrepancies between the published data and our study are probably related to the degree of substitution of our starch, which was 0.62 versus 0.5 in the above reported studies. All medium starches are not the same [34]. Haring et al. [35] compared, in a clinical double-blind study, the influence of the degree of substitution on hemorheologic parameters and showed an enhanced viscosity and red blood cell aggregation with HES 200,000/0.62 compared to HES 200,00/0.5. Treib et al. [36] demonstrated the same results 2 years later. The influence of the degree of HES substitution on cutaneous microcirculation was studied with laser Doppler technique and, after normovolemic hemodilution, confirmed a rapid improvement of microcirculatory flow with HES 200,000/0.5 and a worsening with HES 200,000/0.62 [37].

The influence of catecholamine on microcirculatory splanchnic blood flow can be questioned. A subgroup analysis in patients without catecholamines showed the same results. The PCO_2 gap increased non-significantly in the HES group (16 ± 12 to 22 ± 13 mmHg, $p = 0.069$, 8 patients) and decreased significantly in the MFG group (19 ± 9 to 14 ± 6 mmHg, $p = 0.003$, 12 patients).

In conclusion, although both colloids have the same effect on macrocirculatory parameters, this study highlights the different time courses of gastric mucosal acidosis with 4 % succinylated MFG and 6 % mean weight HES (200,000/0.62). Both colloids are likely to influence the gastric mucosal microcirculatory blood flow in septic patients. Our study demonstrates that MFG improves gastric mucosal acidosis in septic, arterial pressure-controlled and ventilated patients and should be preferred to HES 200,000/0.62 when tonometric variables are considered.

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