The impact of modified fluid gelatin 4% in a balanced electrolyte solution on plasma osmolality in children—A noninterventional observational study

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Abstract

Background: Intravenous fluids for perioperative infusion therapy should be isotonic to maintain the body fluid homeostasis in children. Modified fluid gelatin 4% in a balanced electrolyte solution has a theoretical osmolarity of 284 mosmol L⁻¹, and a real osmolality of 264 mosmol kg H₂O⁻¹. Because both values are lower than those of 0.9% saline or plasma, gelatin would be expected to be hypotonic in vitro and in vivo.

Aim: We thus hypothesized that the infusion of gelatin would be expected to decrease plasma osmolality. We performed an in vitro experiment and an in vivo study to evaluate the impact of gelatin on the osmolality in children.

Methods: In the in vitro experiment, full blood samples were diluted with gelatin 4% or albumin (50 g L⁻¹) from 0% (pure blood) to 100% (pure colloid), and the osmolality was measured by freezing-point depression. In the in vivo study, blood gas analyses from children undergoing major pediatric surgery were collected before and after gelatin infusion, and the osmolality was calculated by a modified version of Zander’s formula.

Results: In the in vitro experiment, 65 gradually diluted blood samples from five volunteers (age 25–55 years) were analyzed. The dilution with gelatin caused no significant changes in osmolality between 0% and 100%. Compared with gelatin, the osmolality in the albumin group was significantly lower between 50% and 100% dilution (p < .05). In the in vivo study, 221 children (age 21.4 ± 30 months) were included. After gelatin infusion, the osmolality increased significantly (mean change 4.3 ± 4.8 [95% CI 3.7–4.9] mosmol kg H₂O⁻¹; p < .01) within a normal range.

Conclusions: Gelatin in a balanced electrolyte solution has isotonic characteristics in vitro and in vivo, despite the low theoretical osmolarity, probably caused by the (unmeasured) negative charges in the gelatin molecules contributing to the plasma osmolality. For a better evaluation of the (real) tonicity of gelatin-containing solutions, we suggest to calculate the osmolality (mosmol kg H₂O⁻¹) using Zander’s formula.
1 | INTRODUCTION

In our German guidelines, we recommend that modified fluid gelatin (GEL) or hydroxyethyl starch (HES) can be used as an alternative during major pediatric surgery if crystalloids alone are not effective, and blood products are not indicated.1 In 2018, the European Medicines Agency considered removing HES from the market because it possibly results in a renal function impairment in adult intensive care patients.2 As a consequence, HES has been used more restrictively, including in pediatric anesthesia, which has resulted in increased interest in gelatin as a possible alternative. Even though gelatin has been used clinically for a long time, there is still a surprising lack of studies evaluating the safety and the physicochemical properties of gelatin in children.

Generally, infusion solutions for plasma and extracellular fluid replacement should be isotonic with a theoretical osmolarity (without glucose) comparable to 0.9% saline (308 mosmol·L⁻¹) or a real osmolality comparable to plasma (288 mosmol·kg⁻¹·H₂O⁻¹) to maintain the body fluid homeostasis in children.3 The disparity is due to some of the infused electrolytes not being osmotically effective.4 Modified fluid gelatin in a balanced electrolyte solution has a theoretical osmolarity of 284 mosmol·L⁻¹ and a (calculated) real osmolality of 264 mosmol·kg⁻¹·H₂O⁻¹ (Table 1). Since both values are lower than those of 0.9% saline (theoretical osmolality 308 mosmol·L⁻¹) or plasma (real osmolality 288 mosmol·kg⁻¹·H₂O⁻¹), gelatin would be expected to be hypotonic in vitro and in vivo.

As a consequence, we hypothesized that the infusion of gelatin would be expected to decrease plasma osmolality, and we performed an in vitro experiment and an in vivo study to evaluate the impact of gelatin on osmolality in children.

2 | METHODS

This is a subgroup analysis of the European prospective noninterventional multicenter observational study evaluating the peroperative use of modified fluid gelatin in pediatrics (GPS),5 which was approved by the local ethics committee of Hannover Medical School, Germany (Chairperson Prof. Dr. H. D. Troeger, No. 6866) on March 13, 2015, and registered in the database ClinicalTrials.gov (ID: NCT02495285).

2.1 | Preliminary in-vitro experiment

Full blood samples from five healthy adult volunteers were diluted with gelatin (Gelaspan 4%; B.Braun) or albumin (Alburex 50 g·L⁻¹; CSL Behring; the compositions of both are presented in Table 1) in steps of 0% (pure blood), 10%, 20%, 30%, 40%, 50% and 100% (pure colloid). In each sample, potassium, sodium, urea, and glucose concentrations were measured by standard laboratory techniques, and osmolality by freezing-point depression (Osmomat 30; Gonotec).

2.2 | Perioperative in-vivo measurements

Children up to 12 years of age with blood gas analyses recruited for the European GPS study at Hannover Medical School were included in this subgroup analysis. All children received a background infusion of 10 ml·kg⁻¹·h⁻¹ of a balanced isotonic electrolyte solution with 1% glucose (E148 G1 PÄD; Serumwerk Bernburg; Table 1). The additional use of GEL (Gelaspan 4%; B.Braun) was at the discretion of the attending anesthetists. The samples for blood gas analysis were collected within 2 h before and up to 2 h after GEL infusion. In each sample, sodium, potassium, chloride, glucose and lactate concentrations were measured (ABL 800 Flex; Radiometer). The osmolality (mosmol·kg⁻¹·H₂O⁻¹) was calculated using a modified Zander’s formula as sum of sodium, potassium, chloride, lactate and glucose (all in mmol·L⁻¹) plus 35.8 (constant for calcium, magnesium, phosphate, sulfate, organic acids, proteinate, bicarbonate and urea) multiplied by 0.985 (correction coefficient to obtain osmolality). The Zander’s formula is based on

What is already known
- Modified fluid gelatin 4% in a balanced electrolyte solution has a theoretical osmolarity of 284 mosmol·L⁻¹ and a real osmolality of 264 mosmol·kg⁻¹·H₂O⁻¹.
- As both values are lower than those of 0.9% saline (theoretical osmolality 308 mosmol·L⁻¹) or plasma (real osmolality 288 mosmol·kg⁻¹·H₂O⁻¹), gelatin would be expected to be hypotonic in vitro and in vivo.

What this article adds
- Gelatin in a balanced electrolyte solution has isotonic characteristics in vitro and in vivo, despite the low theoretical osmolarity.
- The difference is probably caused by the (unmeasured) negative charges of the gelatin molecules contributing to plasma osmolality.
the results of blood gas analysis and showed excellent concordance with measured osmolality.\(^6\)

### 2.3 Statistical analysis

All recorded data were analyzed using MS Excel (Excel 2010; Microsoft), the SAS statistics software (SAS System for Windows; SAS Institute Inc., Version 9.4), MedCalc (MedCalc Statistical Software version 20.015; MedCalc Software Ltd) and GraphPad Prism (Prism 9; Graph Pad Software Inc.), and presented as mean ± standard deviation (range or 95% CI) or frequency (percentage). Normal distribution was tested using Kolmogorov–Smirnov test and Shapiro–Wilk test. Student's \(t\)-test for normally distributed variables and Mann–Whitney \(U\) test for nonparametric variables were used as appropriate to compare between-group differences. In the preliminary in-vitro experiment, a one-way analysis of variance (ANOVA) was used to evaluate the results of the GEL and albumin groups. The level of statistical significance was set at \(p < .05\). According to a post-hoc power analysis, a sample size of 84 per group detects an effect of gelatin infusion on plasma osmolality with 99.9% power and an error probability of 5% if the mean difference was 4.28 mosmol kg\(\text{H}_2\text{O}^{-1}\) and the standard deviation was 5.46 mosmol kg\(\text{H}_2\text{O}^{-1}\) in both groups.

### 3 RESULTS

#### 3.1 Preliminary in-vitro experiment

Sixty-five gradually diluted blood samples from five adult volunteers (age 25–55 years) were analyzed. The dilution with GEL caused no significant changes in osmolality between 0% and 100%. The dilution with albumin caused a continuous decrease in osmolality, which was significant between 30% and 100% (\(p < .01\)). When compared with GEL, the osmolality in the albumin group was significantly lower between 50% and 100% dilution (\(p < .05\); Figure 1). The concentrations of the measured osmotically active molecules and the osmolality in this dilution series are displayed in Table 2.

#### 3.2 Perioperative in-vivo study

A total of 221 patients (28 neonates, 122 infants, 71 children) were included between May 2015 and March 2020. The relevant demographic data are displayed in Table 3. The mean infused

| TABLE 1 Composition of plasma and intravenous fluids (ns = not specified) |
|-------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Cations                | Unit            | Plasma          | Gelatin         | Albumin         | E148 G1         | 0.9% saline     |
| Na\(^+\)               | mmolL\(^{-1}\)  | 142             | 151             | 140             | 140             | 154             |
| K\(^+\)                | mmolL\(^{-1}\)  | 4.5             | 4               | ns              | 4               | –               |
| Ca\(^{2+}\)            | mmolL\(^{-1}\)  | 2.5             | 1               | ns              | 1               | –               |
| Mg\(^{2+}\)            | mmolL\(^{-1}\)  | 1.25            | 1               | ns              | 1               | –               |
| Anions                 | Unit            | Plasma          | Gelatin         | Albumin         | E148 G1         | 0.9% saline     |
| Cl\(^-\)               | mmolL\(^{-1}\)  | 103             | 103             | ns              | 118             | 154             |
| HCO\(_3\)-              | mmolL\(^{-1}\)  | 24              | –               | –               | –               | –               |
| Acetate\(^-\)          | mmolL\(^{-1}\)  | –               | 24              | –               | 30              | –               |
| Theoretical osmolarity\(^a\) | mosmolL\(^{-1}\) | 291             | 284             | ns              | 296             | 308             |
| Real osmolality\(^b\)  | mosmolkg\text{H}_2\text{O}^{-1} | 288             | 264             | ns              | 275             | 286             |

\(^a\)\(\sum\) (cations + anions).

\(^b\)Theoretical osmolarity • osmotic coefficient 0.926 • water content 0.997.\(^{-1}\)
TABLE 2  Concentrations of osmotically active molecules and measured osmolality after in-vitro dilution of human blood with gelatin (GEL) or albumin (ALB) respectively, presented as mean±SD

|          | 0%       | 10%       | 20%       | 30%       | 40%       | 50%       | 100%      |
|----------|----------|-----------|-----------|-----------|-----------|-----------|-----------|
| Unit     |          | GEL:      | ALB:      | GEL:      | ALB:      | GEL:      | ALB:      |
| Na⁺      | mmol L⁻¹ | 139.8 ±13 | 141.0 ±1.2 | 142.0 ±0.6 | 143.6 ±0.9 | 145.0 ±1.2 | 146.2 ±1.3 | 149.2 ±1.3 |
|          |          | ±         | ±         | ±         | ±         | ±         | ±         |
| K⁺       | mmol L⁻¹ | 3.9 ±0.2  | 3.9 ±0.2  | 4.0 ±0.2  | 4.0 ±0.1  | 4.0 ±0.1  | 4.0 ±0.1  | 4.0 ±0.0  |
|          |          | ±         | ±         | ±         | ±         | ±         | ±         |
| Urea     | mmol L⁻¹ | 4.7 ±0.6  | 4.2 ±0.7  | 3.8 ±0.5  | 3.3 ±0.4  | 2.9 ±0.3  | 2.5 ±0.4  | 0.5 ±0.0  |
|          |          | ±         | ±         | ±         | ±         | ±         | ±         |
| Glucose  | mmol L⁻¹ | 4.5 ±0.5  | 4.1 ±0.4  | 3.6 ±0.3  | 3.1 ±0.3  | 2.6 ±0.3  | 2.2 ±0.2  | 0.3 ±0.0  |
| Osmolality|mosmol kgH₂O⁻¹ | 289.0 ±2.6 | 289.6 ±3.4 | 290.2 ±5.5 | 288.4 ±2.3 | 287.6 ±5  | 288.2 ±3.6 | 283.4 ±4.6 |

*p<0.05 albumin vs. gelatin.

4 | DISCUSSION

We hypothesized that the infusion of gelatin would decrease plasma osmolality, but, surprisingly, our study showed that plasma osmolality increased after gelatin infusion. The reason for this increase is probably not appropriate for gelatin-containing solutions for the use in pediatric anesthesia. Therefore, the theoretical osmolality (mosmol L⁻¹), which can be derived from the theoretical osmolality of NaCl and the water content of plasma (94%) relative to 1 kg of NaCl, is probably not appropriate for gelatin-containing solutions for the use in pediatric anesthesia.
following reasons. Modified fluid gelatin is a polydisperse mixture of polypeptides that carry negative charges, as do plasma proteins. In body fluids and infusion solutions, the sums of negative and positive charges have to be identical to maintain electroneutrality. In the studied GEL solution, the sum of anions (chloride 103 + acetate 24 = 127 mmol L−1) is lower compared to the sum of cations (sodium 151 + potassium 4 + calcium 1 + magnesium 1 = 157 mmol L−1). The numerical difference (30 mmol L−1) reflects the (unmeasured) negative charges of the gelatin molecules. In plasma, proteins also contribute to the osmolality, which is included in Zander’s formula as a constant. Therefore, we assume that the gelatin molecules have an osmotic effect similar to plasma proteins. The effect is not included in the calculation of the theoretical osmolality, which explains the low results. Interestingly, the osmolality of the gelatin solution (mean 283.4 mosmol kg H2O−1) measured in the in-vitro part of this study corresponds closely to the calculated osmolality (284.2 mosmol kg H2O−1 = sodium 151 + potassium 4 + chloride 103 + acetate 24 + 6.5(0.985)) when using Zander’s formula with acetate instead of bicarbonate.

Measuring the osmolality by freezing point depression is the gold standard, but, because of the observational study design of the GPS study, this was not possible in the in-vivo part. Therefore, we calculated the osmolality using a modified version of Zander’s formula, which showed excellent concordance with measured osmolality. The results of our in-vitro experiment can be explained by simple dilution. Albumin was intended as control, but the theoretical osmolality was not reported by the manufacturer, and we learnt from this study that 5% albumin is hypotonic. In the in-vivo part, the increase in osmolality was also influenced by the concomitant background infusion of an isotonic balanced glucose-containing electrolyte solution as well as by the surgical stress. In line with this, Bradley et al. also found a slight increase in osmolality within a normal range after infusion of gelatin in adult volunteers.

In conclusion, gelatin in a balanced electrolyte solution has isotonic characteristics in-vitro and in-vivo despite the low theoretical osmolality. For a better evaluation of the (real) toxicity of gelatin-containing solutions, it is suggested to calculate the osmolality (mosmol kg H2O−1) using Zander’s formula.

**CONFLICT OF INTEREST**

The in-vitro study was funded by departmental sources. The in-vivo study was a subgroup analysis from the GPS study, which was funded by B.Braun, Melsungen, Germany. RS received fees for lectures. The other authors declared no conflicts of interest.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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