

# Aluminium Release and Fluid Warming: Provocational Setting and Devices at Risk

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## Research Article

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# Abstract

**BACKGROUND:** Fluid warming, recommended for fluid rates of  $> 500 \text{ ml h}^{-1}$ , is an integral part of patient temperature management strategies. Fluid warming devices using an uncoated aluminum containing heating element have been reported to liberate aluminum resulting in critical aluminum concentrations in heated fluids. We investigated saline solution (0.9%), artificially spiked with organic acids to determine the influence of fluid composition on aluminum liberation using the uncoated enFlow® device. Additionally the Level1® as a high volume fluid warming device and the ThermoSens® device were investigated.

**RESULTS:** Saline solution spiked with lactate more than acetate, especially at a non acid pH, led to high aluminum liberation. Next to the enFlow® device, aluminum liberation was observed for the Level1® device, but not for the coated ThermoSens®-device.

**CONCLUSION:** Uncoated aluminum containing fluid warming devices lead to potential toxic levels of aluminum in heated fluids, especially in non acid fluids containing organic acids and their salts.

## Summary

Aluminum liberation by anodized und uncoated fluid warming devices may lead to concerning aluminum concentration in intravenous fluids. The chemical background of this problem is addressed in this investigation with six fluids and two different fluid warming devices.

## Introduction

Fluid warming is next to active body surface warming and prewarming an integral part of patient temperature management and is recommended for fluid amounts of more than 500 ml or fluid rates of  $> 500 \text{ ml h}^{-1}$  [1, 2]. For fluid warmers using anodized aluminum as a heating element, a concerning aluminium liberation to fluids passing the heating element was demonstrated [3, 4]. After this observation the Medicines and Healthcare products Regulatory Agency (MHRA) reacted immediately with an information about potentially higher than expected aluminium levels by using the enFlow® fluid warming device (VyAire Medical Inc., Mettawa, IL, USA), and after confirmation of these results with Medical Device Alerts (MDA). Finally these observations [3, 4] led to withdrawal of the device by manufacturer.

However, fluid warming devices as medical products undergo defined test in approval procedures by notified bodies, including tests for inadvertent leaching of substances like aluminum. These test protocols use saline solutions as test fluid. However, excessive aluminum liberation with an uncoated, anodized heating element was observed mainly for a balanced electrolyte solution and much lesser for a saline solution [3]. A further investigation to characterize the aluminum liberation by the enFlow® device described corresponding high amounts of aluminium with lactated solutions [4]. In contrast, the amount of aluminium liberation using human albumin solution, fresh frozen plasma and resuspended, expired

red cells was much lesser [4]. The exact mechanism or chemical condition facilitating the liberation of aluminum from anodized heating elements remains unclear.

The aim of this study was to shed some light to the chemical conditions facilitating aluminium liberation. In a second step we investigated the amount of aluminum liberation by two other previously not tested fluid warming devices with an aluminum containing heating element.

## Methods

### Investigated solutions

To identify the most reactive substances of a balanced electrolyte solution we created several solutions (Table 1). In addition a clinical used balanced electrolyte solution (Sterofundin® ISO 1/1 E ISO, B. Braun Melsungen AG, Melsungen, Germany) was used. Electrolyte concentrations of this balanced fluid are as follows: sodium 145.0 mmol l<sup>-1</sup>; potassium 4.0 mmol l<sup>-1</sup>; magnesium 1.0 mmol l<sup>-1</sup>; calcium 2.5 mmol l<sup>-1</sup>; chloride 127.0 mmol l<sup>-1</sup>; acetate 24.0 mmol l<sup>-1</sup>; malate 5.0 mmol l<sup>-1</sup>.

Table 1

List of used fluids. Saline 0.9% (B.Braun Melsungen AG, Melsungen, Germany) was used pur or spiked with organic acid-salt (column 2) and additionally pH-modified (column 3). All chemicals were purchased from Fisher-Scientific (Schwerte, Germany) [1] or Sigma-Aldrich (Munich, Germany) [2].

Number	Saline 0.9% spiked with	pH modification	CAS
1	pur	-	
2	50 mmol Sodium acetate	-	CAS 127-09-3 [1]
3	50 mmol sodium DL-lactate	-	CAS 867-56-1 [2]
4	50 mmol sodium DL-lactate	hydrochloric acid (pH 4)	CAS 867-56-1 [2]
5	50 mmol sodium DL-lactate	Sodium hydroxide (pH 9)	CAS 867-56-1 [2]
6	pur	hydrochloric acid (pH 4)	

## Measurements

Prepared fluids were pumped with an peristaltic pump (Infusomat® fms, B. Braun Melsungen AG, Melsungen, Germany) at a flow rate of 4 ml min<sup>-1</sup> through the fluid warming device. All fluids were tested with an uncoated device known for critical aluminum liberation [3] [4] (enFlow®, Vital Signs, Inc., a GE Healthcare Company, Totowa New Jersey, USA). Baseline measurements were performed from samples before the fluids passed into the heating device. Instantly after baseline measurements, fluids were pumped through the warming units for 60 min. Samples of the heated infusion fluids were collected after 30 min and 60 min at the distal end of the infusion line. All samples were analysed with a graphite

furnace atomic absorption spectrometry (GFAAS) (GFAAS AA6800/6650 Shimadzu Corporation, Japan). Each measuring sequence was performed 6 times with a new infusion warming disposable. All results are presented as median (IQR [range]).

The limit of detection (LOD) and the limit of quantification (LOQ) for the determination of aluminium were calculated according to standard DIN 32645 (German Institute for Standardisation), allowing for dilution [5]. The LOD is the lowest quantity of a substance that can be distinguished from the absence of that substance with 99%, and was  $4 \mu\text{g l}^{-1}$ . The LOQ is the limit at which the difference between two distinct values can be reasonably discerned and was  $14 \mu\text{g l}^{-1}$ .

## Tests Of Two Fluid Warming Devices

In a second step two fluid warmers with a potential risk of aluminum liberation due to aluminum containing heating element were tested:

- The level 1® (Level 1® H-1025 and DI-300 disposable, Smith medical, Minneapolis, USA). This device is a high volume fluid warmer designed to warm fluids with flow rates up to  $1400 \text{ ml min}^{-1}$  and uses an uncoated aluminium tube as a heat exchanger.
- The ThermoSens® (Barkey GmbH & Co. KG, Leopoldshöhe, Germany). This device is designed for fluid warming with flow rates of up to  $150 \text{ ml min}^{-1}$  and uses a coated aluminum heating chamber as a heat exchanger.

According to the results of the first experiment, we choose the saline solution (0.9%) spiked with 50 mmol sodium DL-lactate titrated to a pH of 9 and a commercial, balanced electrolyte solution (Sterofundin®ISO 1/1 E ISO, B. Braun Melsungen AG, Melsungen, Germany). Flow rate ( $4 \text{ ml min}^{-1}$ ) and sample time (baseline, 0 min., 30 min. and 60 min.) were same like in the first experiment.

## Results

Results of the enFlow® device with saline solutions are displayed in Fig. 1. If saline was used as a fluid, the aluminum concentration was  $7.6 (6-8.2 [5.5-8.8]) \mu\text{g l}^{-1}$  after 60 minutes. Highest measured aluminium concentrations were measured with saline when spiked with 50 mmol lactate with  $2462.4 (2109.6-2954.3 [1921.1-3379.8]) \mu\text{g l}^{-1}$  and  $1692 (433.1-3152.4 [282.8-3938.6]) \mu\text{g l}^{-1}$  when spiked with lactate at a pH 9 induced by sodium hydroxide. In lactate spiked saline at a pH of 4 induced by hydrochloric acid the aluminium concentration was  $369.4 (157.1-624.7 [29.6-1134.7]) \mu\text{g l}^{-1}$  after 60 min. Aluminum concentration in saline spiked with 50 mmol acetate was  $210.6 (0-450.2 [0-537]) \mu\text{g l}^{-1}$  measured after 60 min (Fig. 1).

Saline spiked with lactate in a not acidified solution was identified to be most corrosive and therefore used for the tests with the two additional tested fluid warming devices.

Aluminum concentration in saline spiked with 50 mmol lactate after 60 min perfusion with a high flow fluid warmer (Level 1® H-1025 and DI-300 disposable, Smith medical, Minneapolis, USA) was measured 2609.3 (2135.6–3043 [1891.8-3172.2])  $\mu\text{g l}^{-1}$  and titrated to a pH of 9 with sodium hydroxide 2798.8 (691.7-3050.7 [6.9-3645.7])  $\mu\text{g l}^{-1}$  (Fig. 2). The same setting of fluids warmed with a coated low flow device (ThermoSens®, Barkey GmbH & Co. KG, Leopoldshöhe, Germany) led to not quantifiable aluminum concentrations.

Measurements of the three tested devices with a standard balanced fluid (Sterofundin 1/1 ISO) showed after 60 min aluminum concentrations of 243 (65.2–400 [10.9-2608.6])  $\mu\text{g l}^{-1}$  for the Level1® and 102.6 (80.6-209.6 [35.8-371.8])  $\mu\text{g l}^{-1}$  for the enFlow® device (Fig. 3). There was no aluminum detectable for the ThermoSens® (Barkey GmbH & Co. KG, Leopoldshöhe, Germany) device.

## Discussion

The main result of our study is that lactate under non acid conditions is most effective in aluminum liberation with uncoated heating devices. It was confirmed, that sodium chloride solution itself has only very limited capacity of aluminum liberation. However, aluminum concentrations measured with the use of acetate buffered sodium solutions or commercial balanced electrolyte solutions are reasonable.

Aluminium is one of the most studied toxic metals and associated with many diseases [6] like encephalopathies such as Alzheimers [7], impaired neurologic development of (preterm) infants [8] and osteomalacia [9]. Although soluble aluminum in plasma underlies renal clearance, a deposition of up to 20% is possible [10].

One possible safety threshold is the recommended threshold for parenteral nutrition as this threshold reflects an intravenous administration. For preterm infants with need of parenteral nutrition a repeated intravenous aluminum supply of  $>4-5 \mu\text{g kg}^{-1} \text{d}^{-1}$  is a risk for encephalopathy, impaired neurologic development and osteomalacia [8, 9]. The American Society for Clinical Nutrition (ASCN) and the American Society for Parenteral and Enteral Nutrition (ASPEN) therefore recommended a threshold of  $25 \mu\text{g l}^{-1}$  [11] which is also noted by the United States FDA [12].

A different approach is to apply the oral minimum risk level for aluminum, derived by the Agency for Toxic Substances and Disease Registry to be at  $1 \text{ mg.kg}^{-1} \text{d}^{-1}$  [13] [14]. Aluminum shows a poor bioavailability with only 0.1% resorption after oral administration [15]. If the calculated threshold with a correction factor of 1000 based on the bioavailability is applied, the proposed calculations lead to a tolerable parenteral minimal risk level of not more than  $1 \mu\text{g kg}^{-1} \text{day}^{-1}$  or  $70 \mu\text{g kg}^{-1} \text{day}^{-1}$  for a 70 kg adult. However, the nonrecurring use of a fluid warmer is different to long term use of parenteral nutrition or a daily oral dose and therefore the limits cannot be transferred directly to the occasional use of fluid warming. A third way of estimating the maximum safe aluminum exposure is to apply the threshold for aluminum salt in vaccines of  $850 \mu\text{g dose}^{-1}$  [16]. To date there are no regulations for maximal tolerable aluminium concentrations of iv fluids available.

Even if these values are inconsistent, it can be assumed that any kind of aluminum infusion is inadvertent and a dosage of more than 1000 µg for adults is unsafe. Regarding the results of this investigation not only the concentration of aluminum in the warmed fluid alone is relevant. For the estimation of safety, the concentration has to be multiplied with the administered volume. Fluid warming is indicated and recommended fluid rates of more than 500 ml h<sup>-1</sup>. For bleeding patients e.g. after major trauma high volume fluid demands of more than 5 l.h<sup>-1</sup> are reasonable. In consequence the observed concentrations of aluminum liberated by uncoated fluid warming devices as enFlow® and Level1® are both not safe and bear a potential risk of aluminum intoxication and maybe long term effects like encephalopathy [17] [18]. Our study confirms the observation of aluminum liberation by the enFlow® device [3] [4] and the Level1 [19]. Higher observed aluminum concentrations in this study compared to the investigation of Cabrera et al. [19] may be explained by the use of a high flow disposable (Level1® DI-300) in this investigation rather than the moderate flow disposable (Level1® DI-100) [19]. The difference between these disposables is a higher efficacy for the DI-300, presumably by enlarged surface of the heat exchanging element.

In the previous study [3] the increase of temperature was associated with an increase in aluminum liberation by an uncoated device. Temperature is influential and heat may theoretically enhance both chemical reactions and dissolution rates. It was also demonstrated previously that the flow rate has an effect on aluminum concentration. Higher flow rates are accompanied with lower aluminum concentrations, but of course the amount of aluminum infused will be less affected. The results from the actual investigation describe a strong effect of pH on aluminum liberation mediated by organic acids (lactate, acetate or malate) and their salts. At a pH of 9, aluminum hydroxide is formed and this is coordinated to the lactic acid or the corresponding salt [20]. At a high lactate concentration, the aluminum complex is also formed to a greater extent. But unlike acetic acid, lactic acid forms a stable complex with aluminum. This finding is in accordance with Fig. 1 and Fig. 2. This effect may also explain the results of an investigation of the enFlow® device using blood products [4] reporting rather low levels of aluminum in expired packed red blood cells because these blood products do not only contain high levels of lactate but also have a low pH.

The strength of a bench investigation is the standardized examination of aluminum liberation. However, a problem of any bench investigation is that no resulting plasma concentrations of aluminum can be reported. We can't also assess any patient outcomes such as cognitive dysfunction induced by the infused aluminium. However, the exposition of patients resulting from uncoated fluid warming devices using aluminum as heating element can be estimated and bear a potential risk of toxic levels.

In conclusion, uncoated fluid warming devices using aluminum as heating element bear the risk of aluminum liberation in a potential toxic amount. Organic acids and their salts like lactate and acetate are compounds provoking the reaction, especially under non acid conditions. Test protocols for leaching of aluminum from fluid warming devices should apply lactate spiked saline better than saline solution.

## Declarations

**Ethics approval, guidelines and consent to participate:** Not applicable

**Consent for publication:** Not applicable

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files. [raw data.xlsx]

**Competing interests:** T.P. received consulting honorary from The 37Company The Netherlands and Barkey, Germany. A.B. received in the last years consulting honorary from 3M Germany and honorary from The 37Company The Netherlands. M.Q., N.K.S., T.R., K.K. and U.T. declare no competing interests.

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**Authors' contributions:** T.P. designed the study. T.R., K.K. and U.T. performed the main experiments. T.P., A.B., M.Q. and N.K.S. wrote the main manuscript. T.P. and N.K.S. drafted all figures. All authors reviewed the manuscript and approved the final version of the manuscript.

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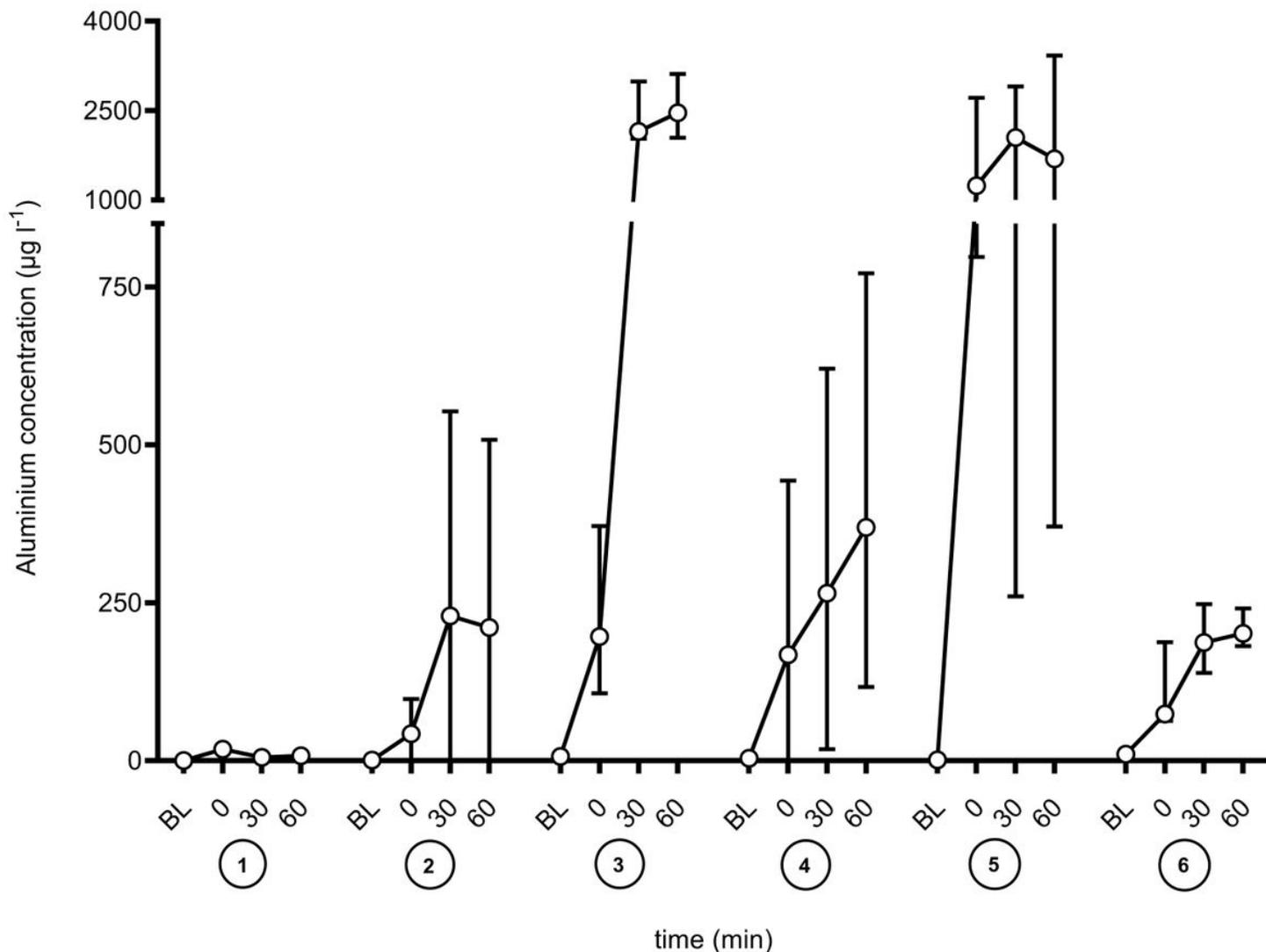
Authors' information (optional)

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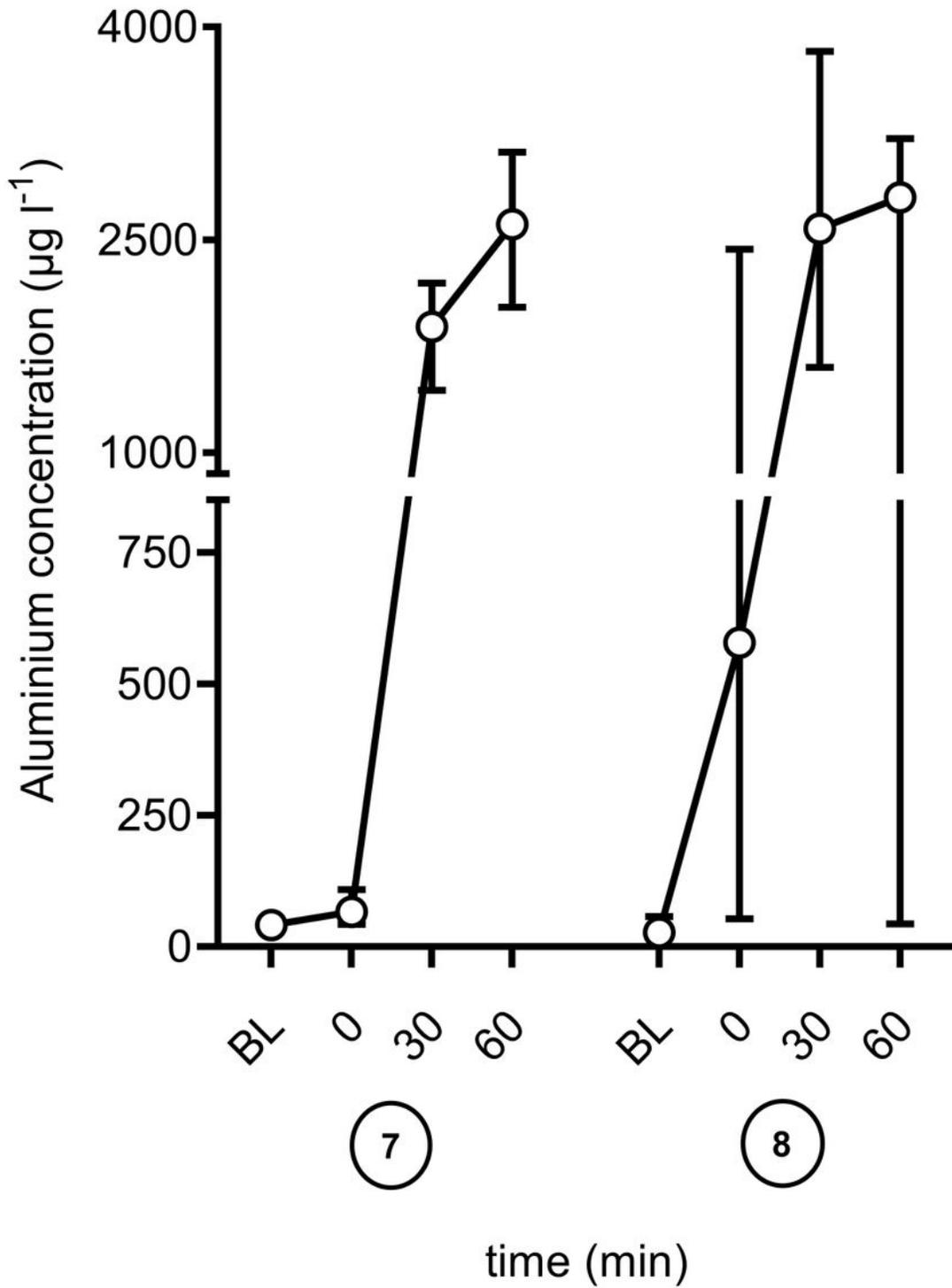
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## Figures



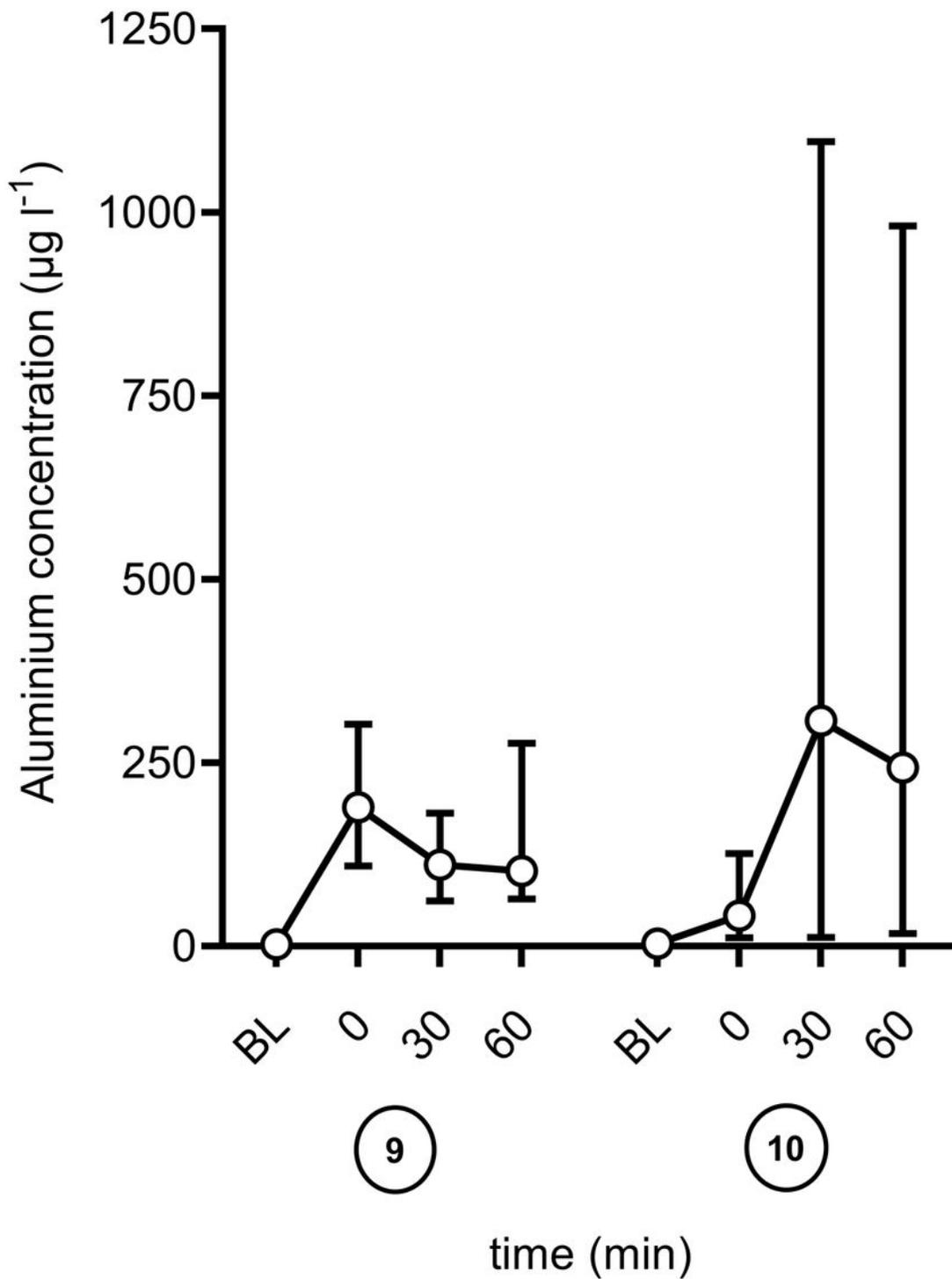
**Figure 1**

Mean (SD) aluminum concentration over the time (BL – Baseline; 0 to 60 minutes) for the enFlow® (Vital Signs, Inc., aGE Healthcare Company, Totowa New Jersey, USA) with different fluids as follows: □ saline 0.9% □ saline 0.9% with 50 mmol acetate □ saline 0.9% with 50 mmol lactate □ saline 0.9% with 50 mmol lactate at pH 4.0 □ saline 0.9% with 50 mmol lactate at pH 9 □ saline 0.9% at pH 9.



**Figure 2**

Mean (SD) aluminum concentration over the time (BL – Baseline; 0 to 60 minutes) for the Level 1® (H-1025 and DI-300 disposable, Smith medical, Minneapolis, USA) with different fluids as follows: □ saline 0.9% with 50 mmol lactate □ saline 0.9% with 50 mmol lactate at pH 9.



**Figure 3**

Mean (SD) aluminum concentration over the time (BL – Baseline; 0 to 60 minutes) with balanced electrolyte solution Sterofundin 1/1 E ISO: ◻ EnFlow® (Vital Signs, Inc., aGE Healthcare Company, Totowa New Jersey, USA) ◻ Level 1® (H-1025 and DI-300 disposable, Smith medical, Minneapolis, USA).

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