# Safety of glucose-containing solutions during accidental hyperinfusion in piglets

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# **Key points**

- Hypotonic glucosecontaining i.v. solutions in infants has been questioned due to possible hyponatraemia and hyperglycaemia.
- Alternatively, co-infusion of isotonic electrolytes and concentrated glucose solutions could be harmful with accidental hyperinfusion.
- In piglets, high glucosecontaining solutions cause potentially hazardous changes in blood electrolytes, glucose, and osmolality.
- These experimental findings challenge the safety of concentrated glucose solutions in paediatric anaesthesia.

**Background.** Errors in fluid management can lead to significant morbidity in children. We conducted an experimental animal study to determine the margin of safety in accidental hyperinfusion of different glucose and electrolyte containing solutions.

**Methods.** Fifteen piglets [bodyweight 12.1 (sp 2.0) kg] were randomly assigned to receive either 100 ml kg<sup>-1</sup> of balanced electrolyte solution with glucose 1% (BS-G1), hypotonic electrolyte solution with glucose 5% (HE-G5), or glucose 40% solution (G40) over 1 h. Blood electrolytes, glucose, and osmolality and intracranial pressure (ICP) were measured before, during, and after fluid administration.

**Results.** Hyperinfusion of BS-G1 led to moderate hyperglycaemia [baseline 3.4 (sp 1.3) mmol litre<sup>-1</sup>, study end 12.6 (1.8) mmol litre<sup>-1</sup>], but no other relevant pathophysiological alterations. Hyperinfusion of HE-G5 produced marked hyperglycaemia [baseline 3.9 (1.2) mmol litre<sup>-1</sup>, study end 48.6 (4.3) mmol litre<sup>-1</sup>, P<0.05] and hyponatraemia [baseline 136.4 (1.3) mmol litre<sup>-1</sup>, study end 119.6 (2.1) mmol litre<sup>-1</sup>, P<0.05], whereas osmolality remained stable during the course of the study. Hyperinfusion of G40 induced acute hyperglycaemic/hyperosmolar decompensation with an extreme decrease in serum electrolytes [e.g. sodium baseline 138 (1.1) mmol litre<sup>-1</sup>, 30 min 87.8 (6.4) mmol litre<sup>-1</sup>, P<0.01], leading to cardiac arrest after infusion of 50–75 ml kg<sup>-1</sup>. ICP remained within a physiological range in all groups.

**Conclusions.** In an animal model of accidental hyperinfusion, BS-G1 showed the widest margin of safety and can therefore be expected to enhance patient safety in perioperative fluid management in children; HE-G5 proved significantly less safe; and G40 was found to be outright hazardous.

Keywords: blood glucose; critical incident; hyperglycaemia; i.v. infusions

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In 1957, Holliday and Segar<sup>1</sup> first presented a practical method for clinicians to prescribe i.v. fluids in children. The authors first estimated the daily fluid requirements by the metabolic rate and secondly defined the daily electrolyte requirements by considering the electrolyte composition of human and cow's milk. These recommendations have resulted in the widespread use of hypotonic fluids with glucose 5% in paediatric patients for nearly half a century.<sup>2–4</sup> Recently, the safety of this practice has been questioned as hyperglycaemia and hyponatremia leading to hyponatraemic encephalopathy have been reported in association with the use of these hypotonic fluids.<sup>5 6</sup> As a consequence, recent guidelines of several associations of

paediatric anaesthesiologists have recommended the perioperative use of isotonic instead of hypotonic electrolyte solutions with or without glucose 1–2.5%.<sup>7</sup>  $^{\rm 8}$ 

Isotonic solutions with a reduced glucose concentration are currently not available commercially in most European countries and the USA.<sup>2 9</sup> Therefore, the use of concentrated glucose solutions (e.g. glucose 40%), infused via a separate infusion (bypass) to an isotonic electrolyte solution, is clinical practice in some hospitals during anaesthesia in newborns and infants. However, several case reports have shown that in the case of accidental hyperinfusion of these concentrated glucose solutions, this practice may lead to potentially fatal brain damage.<sup>10–12</sup> We conducted an experimental study in

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order to determine the margin of safety of different glucose and electrolyte containing solutions mimicking accidental hyperinfusion in an approved infant animal model.<sup>13 14</sup> We hypothesized that hyperinfusion of a hypotonic electrolyte solution with glucose 5% and of a glucose 40% solution will cause significant hyperglycaemia, hyponatraemia, and cerebral oedema compared with an isotonic balanced electrolyte solution with glucose 1%.

### **Methods**

After approval by the local animal experimentation committee (Protocol no. 42502-04-08/1555), 15 4-week-old female German landrace piglets were studied. After a water-only overnight fast, they received i.m. premedication with azaperone and atropine. The piglets were then anaesthetized with i.v. propofol and fentanyl, orotracheally intubated, and mechanically ventilated with isoflurane 1.5% in oxygen/air (FI<sub>02</sub> 0.5). The tidal volume was adjusted to maintain an endtidal carbon dioxide tension of 5.3 kPa. All animals received fentanyl 20  $\mu g~kg^{-1}~h^{-1}$  and rocuronium 0.5 mg  $kg^{-1}~h^{-1}$ during the surgical interventions. Body temperature was maintained using an infrared lamp (LP1, Lister, Germany) and a circulating water mattress (HICO Aquatherm 650, Hirtz, Cologne, Germany). Heart rate, body temperature, and end-tidal carbon dioxide were measured using a patient monitoring system (Cardiocap 5, Datex-Ohmeda, Freiburg, Germany). Using standard cut-down techniques, 5 F percutaneous sheath introducer sets (Arrow, Reading, PA, USA) were inserted into the right jugular vein and the right common carotid artery. Through the venous introducer set, a 4 F two-lumen central venous catheter (Arrow) was placed in the superior vena cava for central venous pressure (CVP) recording. Through the arterial introducer set, a 4 F thermodilution catheter (Pulsiocath, 4 F PV 2024L; Pulsion, Munich, Germany) was inserted to determine mean arterial pressure (MAP) and cardiac output (CO) with a standard haemodynamic monitor system (PiCCO plus, Pulsion). Cardiac index (CI) adapted to the piglets body surface was calculated using the formula of Mack (K equals the piglets' body surface area constant):  $CI = CO/K \times \sqrt[3]{bodyweight^2}$ .<sup>15</sup>

A 20 G cannula was placed in the right saphenous vein to facilitate fluid administration. In addition, animals underwent burr hole craniotomy (9 mm) 1 cm paramedian to the sagittal suture over the right cortex in order to fix a 1.65 mm precision pressure catheter (Neurovent P, Raumedic, Helmbrechts, Germany) for intracranial pressure (ICP) measurements. Continuous ICP was monitored by transduction of the cortex tissue with pressure lines set to zero at the external auditory meatus.

After catheter placement and burr hole craniotomy, the first blood samples for blood gas analysis using a standard blood gas oximetry system (ABL 735, Radiometer, Copenhagen, Denmark) were collected into heparinized syringes. In each sample, pH,  $Pa_{o_2}$ ,  $Pa_{co_2}$ , actual base excess, actual bicarbonate, sodium, chloride, potassium, lactate, haemoglobin, and haematocrit were measured. Additionally, a further

 Table 1
 Composition of piglet blood at baseline [expressed as mean (sp)], BS-G1, HE-G5, and G40

	Serum at baseline (n=15)	BS-G1	HE-G5	G40
Sodium (mmol litre <sup>-1</sup> )	137 (2.5)	140	70	_
Potassium (mmol litre <sup>-1</sup> )	3.7 (0.3)	4	2	-
Calcium (mmol litre <sup>-1</sup> )	1.4 (0.1)	2	1.3	_
Chloride (mmol litre <sup>-1</sup> )	102 (2.2)	118	66	_
Actual bicarbonate (mmol litre <sup>-1</sup> )	26.3 (1.5)	_	_	—
Acetate (mmol litre <sup>-1</sup> )	_	30	_	_
Lactate (mmol litre <sup>-1</sup> )	1,1	_	_	_
Malate (mmol litre <sup>-1</sup> )	_	_	10	—
Glucose (mmol litre <sup>-1</sup> )	3.6 (1.4)	55.5	278	2220

blood sample was drawn to measure serum osmolality using standard laboratory techniques. Piglets were then randomly assigned to receive either 100 ml kg<sup>-1</sup> balanced electrolyte solution with glucose 1% (BS-G1, Table 1, E148 G1 PÄD, Serumwerk Bernburg, Bernburg, Germany), hypotonic electrolyte solution with glucose 5% (HE-G5, Table 1, Sterofundin HEG-5, B. Braun Melsungen, Melsungen, Germany) or glucose 40% (G40, Table 1, Glucose-Lösung 40%, Delta Select, Dreieich, Germany) over 1 h. During fluid administration, blood samples were collected every 15 min. When the infusion was stopped, the last blood sample was collected and the piglets were euthanized by i.v. injection of pentobarbital. Brain tissue samples for gross and microscopic examination were collected from each piglet after postmortem examination. Tissues for histopathology were fixed in 4% neutral buffered formalin, processed routinely, and embedded in paraffin. Sections (4 mm) were stained with haematoxylin and eosin (HE).

#### Statistical analyses

The power calculation was carried out using the nQuery Advisor software 6.0 (Statistical solutions, Cork, Ireland) with a power of 90% and a significance level ( $\alpha$ ) of 0.05. This showed that a sample size of five piglets per group would allow detection of a difference of 10% in the sodium, chloride, and osmolality values in each infusion group. For data measured before, during, and after hyperinfusion, non-parametric statistical tests were performed. The Kruskal-Wallis test (H test) was used to determine differences between the groups at baseline and 15 and 30 min after the start of the infusion. Wilcoxon's test and the Mann-Whitney U-test were used as appropriate to compare within-group and between-group differences. The level of statistical significance was set at P < 0.05. Values are expressed as means (sp). Recorded data were analysed using SPSS 15.0 software for Windows (SPSS Software, Munich, Germany).

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# Results

All 15 piglets used in the study received their intended treatment and were analysed as reported. The three groups were comparable for weight [BS-G1 group 11.7 (sp 2.0) kg, HE-G5 group 12.0 (2.6) kg, G40 group 12.7 (1.8) kg] and length [BS-G1 group 73.4 (3.5) cm, HE-G5 group 72.3 (3.1) cm, G40 group 75.6 (4.0) cm]. The animals in the BS-G1 group and HE-G5 group completed the study protocol as intended at 60 min, while the piglets in the G40 group died between 35 and 45 min after the start of the infusion. Therefore, study end in this group was defined as 30 min after infusion start for statistical between-group comparisons. At baseline, there were no between-group differences in acid-base variables, concentrations of electrolytes and glucose, serum osmolality, haemoglobin, haematocrit, MAP, CI, CVP, or ICP (Tables 2 and 3). During the experiment, haemoglobin and haematocrit decreased in all groups, whereas MAP, CI, and CVP increased (Table 2). ICP remained stable within the physiological range in all groups (Table 2, Fig. 1). Actual base excess, pH, and actual bicarbonate decreased significantly in the HE-G5 and G40 groups with a simultaneous increase in lactate concentrations in the G40 group (Table 3). The acid-base-electrolyte parameters in the BS-G1 group remained stable within the physiological range (Table 3). Sodium and chloride concentrations decreased significantly after HE-G5, and G40 hyperinfusion (Fig. 1). Osmolality and glucose concentrations increased in all groups, and the greatest increases were seen after administration of G40 (Table 3, Fig. 1). Gross and microscopic examination of the brain tissue in all groups indicated no major cerebral oedema or cell hydrops.

# Discussion

The objective of this experimental animal study was to determine the margin of safety in the case of accidental hyperinfusion of various glucose and electrolyte containing solutions commonly used in routine paediatric anaesthesia. Key findings were stable acid-base-electrolyte parameters and moderate hyperglycaemia after administration of an isotonic balanced electrolyte solution with glucose 1% (BS-G1), severe hyperglycaemia with simultaneous hyponatraemia after infusion of HE-G5, and lethal hyperglycaemic/hyperosmolar decompensation after administration of glucose 40% (G40). A limitation of our study is the lack of a control group that only got a balanced electrolyte solution without glucose. Theoretically, such a solution should have the greatest margin of safety in the case of accidental hyperinfusion, although many avoid using balanced electrolyte solutions without glucose during routine anaesthesia in infants due to concerns about lipid mobilization and metabolic acidosis.<sup>16</sup>

The experimental study design was chosen to explore the risks associated with accidental hyperinfusion because case reports and recent daily press articles have shown the potential risk of harmful complications from accidental hyperinfusion of hypotonic electrolyte and concentrated glucose solutions (i.e. glucose 40%), in particular those caused by incorrectly set infusion pumps.<sup>10-12</sup> On the basis of the finding that those patients developed severe neurological complications leading to brain death, we hypothesized that the underlying pathophysiological mechanism may consist of cerebral oedema caused by hyponatraemia<sup>5</sup> <sup>6</sup> or a change in blood-brain barrier permeability as described in diabetic ketoacidotic children.<sup>17</sup> Surprisingly, our study showed that none of the piglets developed major cerebral oedema, cell hydrops, or a significant increase in ICP.

Balanced electrolyte solutions with a physiological electrolyte pattern are recommendable for replacement of extracellular fluid in both adults and infants because the composition of extracellular fluid is similar regardless of age.<sup>8 11 18-20</sup> Several studies have shown that the addition of glucose 1-2.5% instead of 5% in the perioperative maintenance fluid for infants is sufficient to avoid perioperative catabolism and hypoglycaemia.<sup>3 4 21</sup> In our study, no considerable pathophysiological alterations despite moderate hyperglycaemia could be observed during hyperinfusion of BS-G1 and this is the consequence of the near-physiological composition of the solution.

**Table 2** Comparison of haemoglobin, haematocrit, MAP, CI, CVP, and ICP at baseline and at 30 and 60 min after infusion of 100 ml kg<sup>-1</sup> h<sup>-1</sup> of BS-G1, HE-G5, or G40. Piglets in the G40 group died between 35 and 45 min after starting the infusion; therefore, study end in this group was defined as 30 min after infusion start for statistical between-group comparisons. Data are expressed as mean (sd). Differences between values for BS-G1 vs HE-G5 vs G40 at baseline, 30, or 60 min were not significant

Variable	Baseline			30 min			60 min	
	BS-G1	HE-G5	G40	BS-G1	HE-G5	G40	BS-G1	HE-G5
Haemoglobin (g dl <sup>-1</sup> )	8.7 (0.3)	8.5 (0.4)	8.4 (1.3)	7.0 (0.2)*	6.8 (0.2)*	6.4 (1.9)*	6.6 (0.1)*	6.7 (0.3)*
Haematocrit (%)	27.2 (0.8)	26.5 (1.0)	26.3 (2.0)	22.5 (0.5)*	21.2 (0.7)*	20.1 (5.9)*	20.7 (0.4)*	20.9 (1.0)*
Mean arterial pressure (mm Hg)	71.8 (8.7)	70.2 (10.5)	60.0 (9.1)	73.2 (9.3)	82.0 (10.2)	67.6 (18.9)	75.6 (6.5)	82.6 (10.6)
Cardiac index (ml min <sup>-1</sup> m <sup>-2</sup> )	3.5 (0.7)	3.8 (0.5)	2.8 (0.5)	5.0 (0.9)	5.6 (0.9)	4.4 (1.7)	5.5 (1.0)*	5.8 (1.1)*
Central venous pressure (mm Hg)	4.2 (2.1)	4.4 (1.3)	6.2 (3.0)	9.8 (3.6)*	10.6 (2.1)*	18.0 (9.3)*	12.4 (2.0)*	11.2 (3.3)*
Intracranial pressure (mm Hg)	4.2 (1.8)	6.4 (6.3)	5.6 (3.5)	6.6 (1.5)	8.4 (5.0)	4.5 (4.4)	8.0 (2.0)	8.7 (4.7)

\*P < 0.05, baseline vs. 30 minutes or 60 minutes

Table 3 Comparison of acid – base, electrolyte parameters, osmolality, and glucose at baseline, 30, and 60 min after infusion of 100 ml kg<sup>-1</sup> h<sup>-1</sup> of BS-G1, HE-G5, or G40. Piglets in the G40 group

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alea between 35 ana 45 min arter expressed as mean (sp), <sup>1</sup> P-value at	starting the ir baseline, BS-	irusion; therei G1 vs HE-G5 v	rore, stuay en /s G40; <sup>2</sup> P-val	la in this grot lue at 30 min	up was aerinea 1, BS-G1 vs HE-(	l as 30 min arte 35 vs G40; <sup>3</sup> P-vi	er intusion start ti alue at 60 min, B.	or statistical f S-G1 vs HE-G	between-grou¦ 5. *P<0.05, bc	p comparisons. I iseline vs 30 or (	Jata are 60 min
Variable	Baseline				30 min				60 min		
	BS-G1	HE-G5	G-40	P-value <sup>1</sup>	BS-G1	HE-G5	G-40	P-value <sup>2</sup>	BS-G1	HE-G5	P-value <sup>3</sup>
Hd	7.42 (0.0)	7.44 (0.0)	7.42 (0.0)	NS	7.41 (0.0)	7.36 (0.0)*	7.17 (0.1)*	< 0.05	7.38 (0.0)	7.31 (0.0)*	< 0.05
$Pa_{co_2}$ (kPa)	5.5 (0.7)	5.3 (0.2)	5.6 (0.5)	NS	5.4 (0.4)	5.5 (0.2)	6.1 (0.4)	NS	5.7 (0.3)	5.5 (0.2)	NS
Actual base excess (mmol litre <sup>-1</sup> )	1.9 (1.7)	2.5 (1.7)	2.2 (1.2)	NS	0.9 (1.5)*	-2.7 (1.2)*	-11.8 (3.5)*	< 0.05	0.2 (1.7)*	-5.0 (1.5)*	<0.05
Osmolality (mosmol kg <sup>-1</sup> )	289 (5.4)	292 (4.1)	291 (2.5)	NS	313 (17.3)	322 (26.5)	477 (22.8)	<0.05	299 (4.9)*	307 (12.0)*	NS
Sodium (mmol litre <sup>-1</sup> )	137 (4.2)	136 (1.3)	138 (1.1)	NS	135 (2.8)	124 (1.1)*	87.8 (6.4)*	<0.05	135 (2.8)	120 (2.1)*	< 0.05
Potassium (mmol litre <sup>-1</sup> )	3.7 (0.3)	3.7 (0.2)	3.6 (0.3)	NS	3.5 (0.2)	3.5 (0.2)	6.3 (0.9)*	<0.05	3.4 (0.2)	3.4 (0.3)	NS
Chloride (mmol litre $^{-1}$ )	102 (3.4)	102 (2.1)	103 (1.3)	NS	102 (3.0)	93.0 (1.6)*	63.3 (3.7)*	<0.05	103 (1.8)	89.8 (1.1)*	< 0.05
Actual bicarbonate (mmol litre <sup>-1</sup> )	26.1 (1.7)	26.5 (1.6)	26.4 (1.6)	NS	24.9 (1.6)*	22.0 (1.0)	15.6 (1.7)	<0.05	24.7 (1.7)*	20.2 (1.1)*	< 0.05
Lactate (mmol litre <sup>-1</sup> )	1.1 ( 0.5)	1.3 (0.6)	1.2 (0.5)	NS	1.1 (0.4)	1.2 (0.5)	2.5 (1.4)*	<0.05	1.3 (0.2)	1.5 (0.4)	NS
Glucose (mmol litre $^{-1}$ )	3.4 (1.3)	3.9 (1.2)	3.6 (0.7)	NS	10.8 (1.2)*	38.6 (2.1)*	264 (31.2)*	< 0.05	12.6 (1.8)*	48.6 (4.3)*	< 0.05



**Fig 1** A comparison of sodium, ICP, glucose concentrations, and osmolality at baseline and at 15, 30, and 60 min after infusion of 100 ml kg<sup>-1</sup> h<sup>-1</sup> of BS-G1, HE-G5, or G40. Piglets in the G40 group died between 35 and 45 min after starting the infusion; therefore, study end in this group was defined as 30 min after infusion start for statistical between-group comparisons. Data are expressed as means (sD), #P<0.05, BS-G1 vs HE-G5 vs G40. \*P<0.05, BS-G1 vs HE-G5.

Hypotonic solutions have been routinely used in paediatric anaesthesia for decades,<sup>2-4</sup> and despite the obvious risks of hyponatraemia and hyperglycaemia, they are still the standard solutions for perioperative fluid therapy in many hospitals.<sup>22 23</sup> In our study, hyperinfusion of HE-G5 led to a significant decrease in bicarbonate, sodium, and chloride concentrations since HE-G5 diluted plasma towards its own hypotonic electrolyte composition. Hyponatraemia carries the risk of hyponatraemic encephalopathy with significant morbidity,<sup>5 6</sup> but in our study, ICP remained within the physiological range. Moreover, gross and microscopic examination of the brain tissue revealed no major cerebral oedema or cell hydrops, suggesting no major changes in blood-brain barrier permeability. These stable cerebral conditions are probably due to the constant serum osmolality that resulted from concurrent hyponatraemia and hyperglycaemia. Nevertheless, there is a risk of severe hyponatraemia leading to encephalopathy after glucose has been distributed and metabolized.

Hyperinfusion of G40 induced extreme changes in acidbase-electrolyte parameters and extreme hyperglycaemic/

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hyperosmolar decompensation which probably caused the observed lethal cardiovascular decompensation in all piglets after infusion of 50–75 ml kg<sup>-1</sup> G40. Up to then the piglets showed stable haemodynamic function and even a moderate decrease in ICP as a result of the hypertonic plasma produced by severe hyperglycaemia up to 295 mmol litre<sup>-1</sup> glucose (Table 3). Similarly, hyperinfusion of HE-G5 was not associated with evidence of cerebral oedema as described in case reports and children with diabetic ketoacidosis.<sup>10</sup> <sup>12</sup> <sup>17</sup> The increase in CVP with a simultaneous increase in CI is probably the consequence of an additional volume shift from intra- to extracellular fluid as a result of the increase in serum osmolality.

In conclusion, firstly hyperinfusion of BS-G1 produced no considerable pathophysiological alterations other than moderate hyperglycaemia. Secondly, hyperinfusion of HE-G5 produced severe hyperglycaemia and hyponatraemia, but caused no immediate life-threatening events. Thirdly, hyperinfusion of G40 induced lethal hyperglycaemic/hyperosmolar decompensation with a pronounced decrease in serum electrolytes leading to cardiac arrest. Contrary to our hypothesis, no piglet developed significant increase in ICP or major cerebral oedema. In summary, BS-G1 showed the widest margin of safety in the case of accidental hyperinfusion, HE-G5 was obviously unsafe, and glucose 40% was outright hazardous and should be avoided during standard paediatric anaesthesia.

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## **Conflict of interest**

None declared.

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