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ORIGINAL ARTICLE

Impact of insulin adsorption in various containers during hyperkalaemia treatment

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ABSTRACT

Background. Insulin–glucose therapy in hyperkalaemia treatment has a narrow therapeutic index for a safe and efficient use. We assess the variability of the effective delivered insulin under conditions used in the setting of hyperkalaemia treatment.

Methods. A range of simulated insulin infusions was studied using different containers (bag or syringes) according to the different hyperkalaemia treatment procedures of our institution. Insulin concentration was assayed using a chromatographic method on an automatic high-performance liquid chromatography. We calculated the effective delivered insulin and compared the time average of percentage delivered insulin (TAdi) between all the procedures.

Results. The TAdi was significantly decreased to 63.3% of the expected insulin delivery in the polyurethane (PE) bag compared with allover container. The procedure duration and the insulin concentration influenced the variability of the insulin delivery in the PE and glass bag. The polyvinyl chloride bag had the highest TAdi at 93.8%, without significant variation during the time. TAdi reaches ∼90% of the expected insulin with all the syringe procedure without variation according to the solute used to dilute insulin.

Conclusions. Clinically significant variations in intravenous insulin delivery occur in the setting of hyperkalaemia treatment according to the container. The use of propylene syringe limits the insulin delivery variation. In the future, clinical studies on hyperkalaemia treatment by insulin–glucose therapy should detail the procedure precisely.

Keywords: adsorption, hyperkalaemia, insulin–glucose treatment

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INTRODUCTION

Critical hyperkalaemia is a potentially life-threatening emergency, requiring timely treatment with an intravenous infusion of a combination of glucose and soluble insulin. Most intravenous infusion systems use polyvinyl chloride (PVC) or polyurethane (PE) tubings, which are hydrophobic and adsorb insulin.

Insulin adsorption is dependent on the infusion rate [1], insulin concentration [2], tubing material [3] and whether the tubing surface has been primed [2, 4]. Insulin adsorption on various infusion tubings has been studied in the setting of glycaemic control, where losses of >50% of insulin activity have been reported [1], and occur mostly in the first 30 min of infusion [3].

There is an inverse relationship between the concentration of insulin and the per cent of insulin bound to the container or infusion set materials. Insulin concentration used to treat hyperkalaemia is low and exposed to higher adsorption. Glass (G), PVC, PE and polypropylene are the main materials used to contain intravenous fluids. Glass is the container with the smaller insulin adsorption phenomenon, compared with the others. Maximal insulin adsorption can take from a few minutes to several hours. Containers with large surface increase the phenomenon. Container–insulin adsorption phenomenon may decrease the effectiveness of the hyperkalaemia treatment. It is important to consider interactions between drugs and container materials.

We examined the extent of insulin adsorption in syringe and in different bag containers for intravenous insulin infusion in the setting of treatment of hyperkalaemia used in our institution.

MATERIALS AND METHODS

Setting

Ethical approval and permissions were not necessary because the research did not involve human subjects, animals or cell lines. We compared four different containers available in our institution: PE bag (500 mL glucose 5%, Ecoflac®, B. Braun, Boulogne, France), PVC bag [500 mL sodium chloride (NaCl) 0.9%, Viaflo®, Baxter SAS, Guyancourt, France], G (500 mL glucose 10% Lavoisier®, CDM Lavoisier, Paris, France) and polypropylene syringe (Penta 60 LL®, Pentaferte, Italy). Insulin was diluted in the different commercial containers. The bag containers are connected to PVC infusion line (Carefusion®, L = 150 cm, V = 20 mL, BD) without flushing.

The commonly used treatment of hyperkalaemia in our institution uses a PE bag in which insulin is added to reach a final insulin concentration of 0.02 IU/mL (10 IU of insulin in 500 mL of D10% solution) and is infused into the patient for 2 h. We modified the institutional procedure to treat hyperkalaemia with 20-fold higher insulin concentration because of the quantification limit of the dosing method (≥0.1 IU/mL). We monitored insulin concentration every 30 min for 2 h from the infusion line at two final different insulin concentrations: 0.4 IU/mL and 0.8 IU/mL.

Some departments of our institution use the 50 mL syringe with 10 IU of insulin diluted in a 50 mL D5% solution (final concentration 0.2 IU/mL), which is usually infused to the patient for 15 min. We tested three different solutions: D5%, D10% and NaCl 0.9% with or without flushing [PE tubing (V-green extension®, L = 150 cm, V = 1.5 mL, Vygon) primed with 10 mL of insulin solution]. Solution was infused using electric syringe pump with a fixed infusion rate of 150 mL/h for 15 min at room temperature according to the usual institutional procedure. The distal end of the syringes were connected to infusion set (V-green tubular in PE). We monitored insulin concentration every 5 min on three successive samples for 15 min from the infusion set.

All the experiments for bag and syringe were repeated six times.

Short-acting soluble insulin aspart (Novorapid, Novo Nordisk) was withdrawn from a 10 mL bottle and concentrated to 100 IU/mL using a 0.5 mL NiproMyshot U-100 graduated insulin syringe.

Insulin assay measurement

The assay method was adapted from a method described in the literature [5]. This chromatographic method was carried out on an automatic high-performance liquid chromatography Dionex Ultimate 3000® with a UV diode array detector. The apparatus was connected to an HP 1702 computer equipped with chromatographic data processing software (Chromeleon® Chromatography Management System, Version 6.80 SRH Biold 3161, 1994-2011 Dionex Corporation). A C18 column (XTerra®, 4.6 mm × 100 mm, 3.5 μm) was used to achieve insulin separation. Volumes were aliquoted with a precision pipette (Thermo Scientific Finnpipette® F2 500 μL) and pHs were measured with a Thermo Scientific Orion 4 Star® pH-meter, calibrated with Radiometer Analytical® standard(pH 4.005, pH 7.000 and pH 10.012).

The mobile phase consisted in a mixture of acetonitrile (26%, v/v), methanol (12%, v/v) and a 0.10 M of monopotassium phosphate aqueous solution (62%, v/v). pH was adjusted at 3.1 with phosphoric acid. The mobile phase was filtered through a Millipore 0.45 μm cellulose filter and used in isocratic mode with a flow of 2 mL/min for 15 min. Wavelength for insulin detection was 214 nm, injection volumes were 20 μL and column temperature was 25°C.

Standard curves were realized with a commercial 100 IU/mL insulin of pharmaceutical quality (Novorapid, Novo Nordisk®), at seven concentrations (from 0.1 to 0.9 IU/mL). Linearity of the method was determined with standard curves prepared in sextuplicate. Limit of detection and limit of quantification were established at the lowest level of linearity (0.1 IU/mL). Repeatability, intermediate precision, accuracy and uncertainty were determined at three levels of concentration (0.2, 0.3 and 0.4 IU/mL).

Briefly, samples were analysed as follows: 980 μL of the insulin solutions were aliquoted in a 5 mL haemolysis tube. The 20 μL of hydrochloric acid 0.1 M were added and the mixture was vortexed for 1 min, and 600 μL were aliquoted in an opaque glass vial to be analysed.

Statistical analysis

Continuous variables were presented as mean and standard deviation (SD). We calculated the effective delivered insulin as follow: $\frac{[Measured\ insulin\ concentration]}{[Theoric\ insulin\ concentration]} \times 100$.

Time average of percentage delivered insulin (TAdi) represents an average of every percentage of delivered insulin measurements during each procedure. All tests were two-tailed. We used Friedman test to compare percentage of delivered insulin at each time during the infusion for each bag container. We used two-way analysis of variance (ANOVA) to determine how delivered insulin was affected by the following two factors: infusion time and container. The two-way ANOVA assessed the

main effect of each independent variable and if there was any interaction between them. All statistical analyses were performed using GraphPad PRISM® software (Version 8). Statistical test were significant for $P < 0.05$.

RESULTS

Incompatibility of the insulin syringe with PE bag

First assays on PE bags showed high insulin concentrations at 0 min (T0) followed by the absence of quantifiable insulin (T30, T60, T90 and T120). The origin of this phenomenon was investigated. After eliminating analytical causes, we decided to inject methylene blue instead of insulin. A blue colouration localized under the cap of the PE bag was observed as shown in Figure 1 (left photograph). The PE bag was cut, and we noticed that the methylene blue was trapped between the cap and the internal surface of the bag (Figure 1, centre photograph). The needles of insulin syringes are too short to cross the cap and the internal membrane. Unfortunately, the addition of insulin in PE bags can only be done with a specific insulin syringe to ensure dose accuracy. When the administration tubing was connected to the Ecoflac® bag, its needle was long enough to cross the cap and the internal surface, passing by the undiluted methylene blue solution (Figure 1, right photograph). This phenomenon, applied to insulin solution, will result in a high initial insulin concentration (T0), followed by the administration of pure D10%. We concluded that Ecoflac® bags were not appropriate for insulin dilutions. We therefore continued our assays, injecting insulin by piercing the bottle in a place other than the cap.

Time average delivered insulin in containers

The PE bag had the lowest TAdi (63.3 ± 11.2%) compared with the allover container for 0.4 IU/mL of insulin concentration ($P < 0.0001$). The NaCl 0.9% syringe with flushing has the significant highest TAdi (93.8 ± 5.7%) compared with the bag container, except for the PVC bag with 0.8 IU/mL of insulin concentration (92.6 ± 3.2%; Figure 2; Table 2).

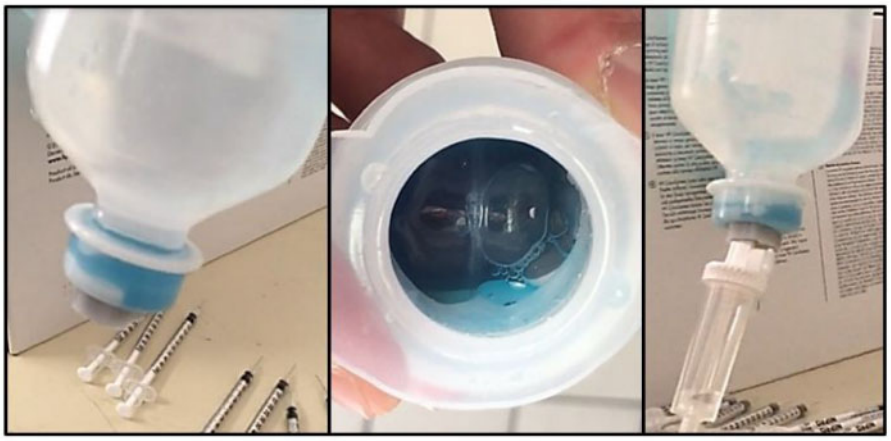

FIGURE 1: PE bag and insulin administration with insulin syringe incompatibility.

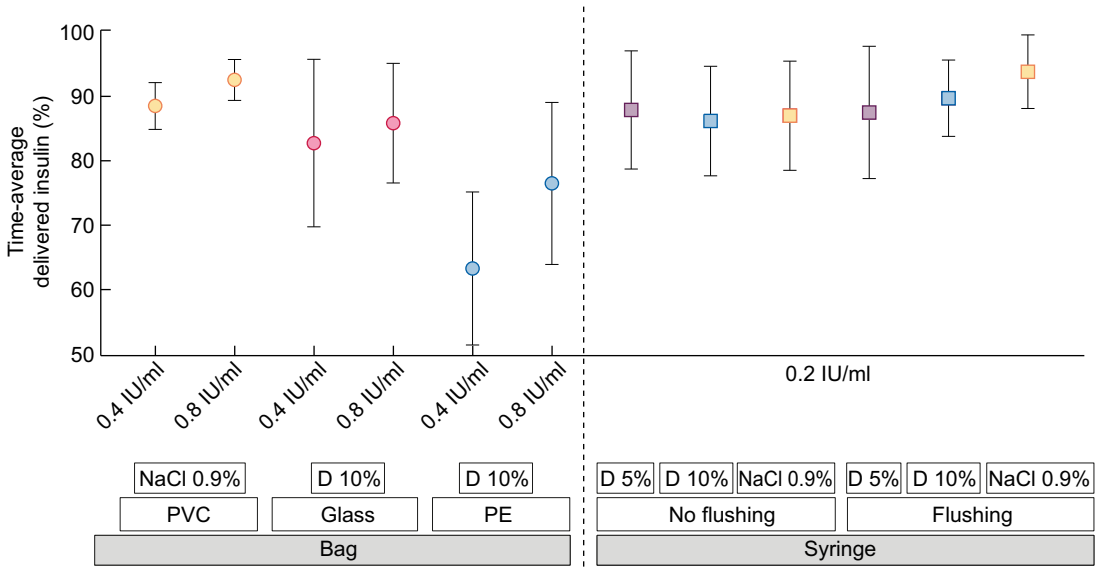

FIGURE 2: TAdi (expressed as a percentage of expected delivery). Data are represented with mean and SD. Significativity of the paired-wise comparison is reported in Table 1.

Table 1. Significativity matrix of paired-wise comparison of TAdi between all the procedure

Bag	PVC	NaCl 0.9%	0.4 IU/ml															
			0.8 IU/ml	0.4														
	Glass	D10%	0.4 IU/ml	>0.9	**0.005**													
			0.8 IU/ml	>0.9	0.06	>0.9												
	PE	D10%	0.4 IU/ml	**<0.0001**	**<0.0001**	**0.0004**	**<0.0001**											
			0.8 IU/ml	0.08	**<0.0001**	>0.9	0.5	0.8										
Syringe	No flushing	D5%	0.2 IU/ml	>0.9	>0.9	>0.9	>0.9	**<0.0001**	**0.014**									
		D10%		>0.9	0.3	>0.9	>0.9	**<0.0001**	0.4	>0.9								
		NaCl 0.9%		>0.9	0.7	>0.9	>0.9	**<0.0001**	0.1	>0.9	>0.9							
	Flushing	D5%		>0.9	>0.9	>0.9	>0.9	**<0.0001**	**0.01**	>0.9	>0.9	>0.9						
		D10%		>0.9	>0.9	>0.9	>0.9	**<0.0001**	**0.004**	>0.9	>0.9	>0.9	>0.9					
		NaCl 0.9%		**0.05**	>0.9	**0.0004**	**0.006**	**<0.0001**	**<0.0001**	0.6	**0.04**	0.1	0.7	>0.9				
				0.4 IU/ml	0.8 IU/ml	0.4 IU/ml	0.8 IU/ml	0.4 IU/ml	0.8 IU/ml	0.2 IU/ml								
				NaCl 0.9%		D 10%		D 10%		D5%	D 10%	NaCl 0.9%	D5%	D 10%	NaCl 0.9%			
				PVC		Glass		PE		No flushing			Flushing					
				Bag						Syringe								

Statistical significant correlation are indicated with p-value in bold.

Table 2. Comparison of percentage delivered insulin (expressed as a percentage of expected delivery) between 0.4 IU and 0.8 IU insulin concentration in the different bag

A		
Delivered insulin (%) in the PE bag		
Time (min)	Insulin 0.4 IU/mL	Insulin 0.8 IU/mL
0	61 ± 8.8	71.4 ± 13.9
30	65.8 ± 12.4	80.2 ± 12.3
60	56.4 ± 15.5	76.4 ± 15.9
90	63.6 ± 12.7	74.2 ± 10.4
120	69.6 ± 8	80.2 ± 11.9
B		
Delivered insulin (%) in the G bag		
Time (min)	Insulin 0.4 IU/mL	Insulin 0.8 IU/mL
0	84.9 ± 5.8	90.0 ± 2.9
30	89.8 ± 4.9	89.2 ± 6.9
60	84.1 ± 6.9	90.5 ± 1.8
90	87.5 ± 8.9	84.6 ± 7.6
120	67.4 ± 20.5	75.0 ± 13.4
C		
Delivered insulin (%) in the PVC bag		
Time (min)	Insulin 0.4 IU/mL	Insulin 0.8 IU/mL
0	85 ± 5.2	91.2 ± 3.2
30	88 ± 3.8	91.6 ± 5.3
60	89.9 ± 2.5	93.6 ± 2
90	90.6 ± 0.9	92.9 ± 2.5
120	89.1 ± 2.3	93.5 ± 2.1

For quantitative variables, values are expressed as mean ± SD.

Kinetic of the delivered insulin in containers

In the PE bag, the effective delivered insulin tends to increase at 120 min for 0.4 IU/mL insulin concentration and increases significantly at 0.8 IU/mL insulin concentration (respective Friedman test P = 0.08 and 0.02). In the G bag, the effective delivered insulin tends to decrease at 120 min for 0.4 IU/mL insulin concentration and decreases significantly at 0.8 IU/mL insulin concentration (respective Friedman test P = 0.05 and 0.03). In the PVC bag, no variation of the effective delivered insulin was observed either at 0.4 or 0.8 IU/mL insulin concentration (respective Friedman test P = 0.24 and 0.25; Figure 3; Table 2).

In the syringe, we observed variation of the delivered insulin only for D5% solute. The effective delivered insulin increases significantly at 15 min with or without flushing (respective Friedman test P = 0.006 and 0.03; Figure 4; Table 3).

Delivered insulin variance determinant in the bag and syringe containers

In the PE bag, insulin concentration accounts for 23.16% of the delivered insulin total variance after adjusting for matching ($F = 4.27$; DFn = 1; DFd = 10; P = 0.065). Infusion time accounts for 6.6% of the delivered insulin total variance after adjusting for matching ($F = 4.65$; DFn = 4; DFd = 40; P = 0.01).

In the G bag, insulin concentration accounts for 1.9% of the delivered insulin total variance after adjusting for matching ($F = 1.12$; DFn = 1; DFd = 10; P = 0.3). Infusion time accounts for 35.2% of the delivered insulin total variance after adjusting for matching ($F = 8.25$; DFn = 4; DFd = 40; P = 0.004).

In the PVC bag, insulin concentration accounts for 26.7% of the delivered insulin total variance after adjusting for matching ($F = 11.74$; DFn = 1; DFd = 10; P = 0.0065). Infusion time accounts for 13.2% of the delivered insulin total variance after adjusting for matching ($F = 3.81$; DFn = 4; DFd = 40; P = 0.03).

Comparing all the different conditions for syringe, the time accounts for 18.8% of the delivered insulin total variance after adjusting for matching ($F = 15.99$; DFn = 3; DFd = 90; P < 0.0001). The solute and the flushing account for 9.2% of the delivered insulin total variance but are not significant after adjusting for matching ($F = 1.61$; DFn = 5; DFd = 30; P = 0.18).

DISCUSSION

In this study, we observed reduction of the delivered insulin compared with the expected delivered concentration in all the containers, which may significantly impact the correction of

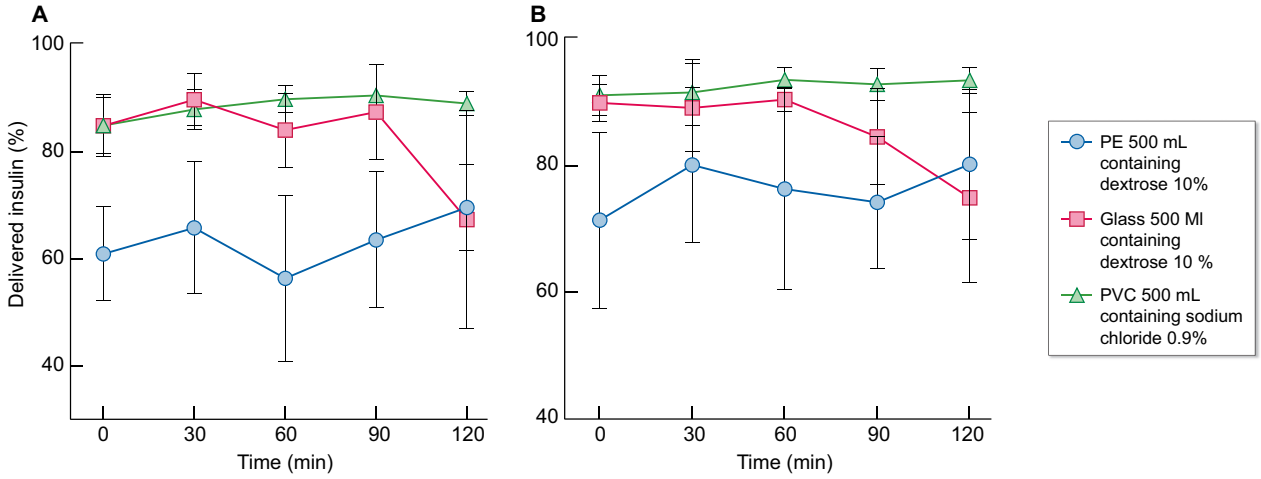

FIGURE 3: Percentage of delivered insulin (expressed as a percentage of expected delivery) in bag container with two different insulin concentrations. (**A**) Procedure with 0.4 IU/mL insulin concentration. (B) Procedure with 0.8 IU/mL insulin concentration. Mean and SD of six independent experiments

Table 3. Comparison of percentage delivered insulin (expressed as a percentage of expected delivery) according to flushing preconditioning in syringe A

A		
Delivered insulin (%) with D5%		
Time (min)	No flushing	Flushing
0	80.2 ± 13.1	78.9 ± 15.8
5	87.5 ± 7.7	89.3 ± 8.2
10	91.1 ± 5.2	90.6 ± 6.4
15	92.8 ± 4.4	91.1 ± 6.2
B		
Delivered insulin (%) with D10%		
Time (min)	No flushing	Flushing
0	81.9 ± 9.6	84.6 ± 8
5	84.8 ± 9.2	91.5 ± 3.7
10	86.2 ± 9.1	91.4 ± 4.8
15	91.7 ± 3.3	91.4 ± 4.4
C		
Delivered insulin (%) in NaCl		
Time (min)	No flushing	Flushing
0	81.7 ± 12.9	88.2 ± 7.7
5	89.05 ± 7.6	96.4 ± 2.9
10	87.2 ± 6.8	94.6 ± 3.4
15	90.3 ± 3.1	96.3 ± 4.3

For quantitative variables, values are expressed as mean ± SD.

hyperkalaemia. The infusion container materials (bag or syringe) have to be considered for insulin administration. The PE bag is not reliable for adding insulin in the setting of hyperkalaemia treatment.

Lower delivered insulin was observed for the PE bag containing dextrose, which is usually used in our institution for the treatment of hyperkalaemia, regardless of insulin concentration. Considering the inverse relationship between adsorption rate and insulin concentration, we assume that the impact is even greater at the 20 times lower concentrations used in our institutional procedure for the treatment of hyperkalaemia (0.02 IU/mL) with bag container [2]. The G bag containing dextrose has a similar rate of delivered insulin during the first hour compared with the PVC bag, which decreases significantly during the second hour, with significant impact on the delivered insulin. The PVC bag containing 0.9% NaCl had the higher TAdi without significant variation during the 2 h infusion, which confirmed the literature data [6]. The duration of insulin infusion also influences the rate of insulin adsorption regardless of the mode of administration. At insulin concentrations ≤0.05 units/mL in the bag container, we assume that insulin is not reliably delivered in the PE bag used in our institution [7].

The 15-min infusion procedure with a propylene syringe appears to be the most appropriate. The delivered insulin rate was between 80% and 90% all along the perfusion duration without variation, except for D5% solute with significant increase of the delivered insulin at the end of the infusion. Interestingly, the solute and the flushing (in order to prime the tubing) do not influence the TAdi for the syringe. No in-line filter was used for the syringe procedure based on their known insulin adsorption properties [8]. We used a low dextrose concentration (5% and 10%) in the syringe to allow intravenous peripheral infusion and avoid vein irritation, vein damage and/or thrombosis. However, the amount of glucose is not sufficient to prevent hypoglycaemia and therefore needs to be associated with 250 mL bag dextrose 10% infusion with careful blood glucose monitoring to detect hypoglycaemia for 4 h thereafter.

The adsorptive properties of different plastics are recognized by paediatricians, thus explaining the use exclusively of procedures using polypropylene syringes with insulin concentrations of at least 0.2 IU/mL. The adult insulin–glucose procedure used at our institution to treat hyperkalaemia does not use syringe, contrary to that in the the paediatrician and neonatal units.

Our study has some limitations. First, we did not reproduce the insulin concentration commonly used in the bag procedure to treat hyperkalaemia due to the limit of quantification of the dosing method (≥ 0.1 IU/mL). We did not compare for the same container if there was a difference between saline and glucose, because we were limited by commercial availability but being as close as possible to reality.

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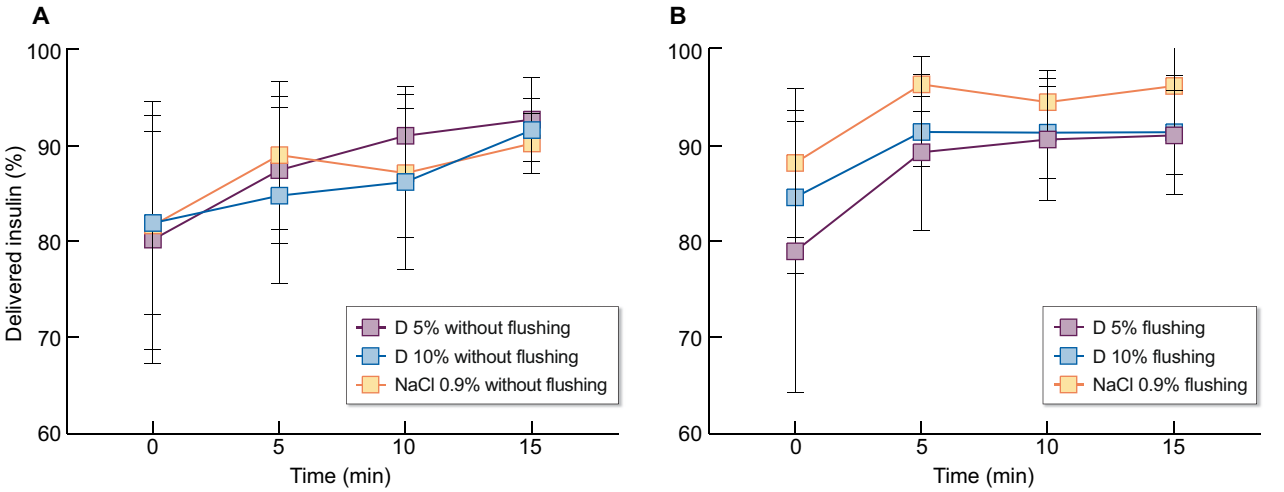

FIGURE 4: Percentage of delivered insulin (expressed as a percentage of expected delivery) in syringe. (**A**) Procedure without flushing. (**B**) Procedure flushing. Data are represented with mean and SD.

CONCLUSION

This study demonstrates the potential significant variations in insulin delivery with the insulin–glucose procedure during treatment of hyperkalaemia, especially using a bag container. The polypropylene syringe procedure appears to be the most effective and reliable to reach the goal of insulin–glucose therapy in hyperkalaemia. In the future, clinical studies on hyperkalaemia treatment by insulin–glucose therapy should detail the procedure used precisely. This study design could also be performed for other types of molecules with a narrow therapeutic index, such as antibiotics.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during this study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST STATEMENT

None declared.

AUTHORS' CONTRIBUTIONS

T.R., N.M. and C.C. designed the study, analysed the data and made the tables; T.R. wrote and revised the article; C.C., S.B., P.B. and P.V. revised the article. All authors approved the final version of the manuscript.

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