How to safely use diluted insulin in an automated insulin delivery system in very young children: an educator perspective

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Abbreviations:

AID: automated insulin delivery; CSII: continuous subcutaneous insulin infusion; DKA: diabetic ketoacidosis; GV: glucose variability; IU: international units; MDI: multiple daily injections; OOH: out of hours; T1D: Type 1 diabetes; TDD: total daily dose; TBR: time below range; TIR: time in range

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ABSTRACT

Managing type 1 diabetes in infants and very young children poses unique challenges due to their low insulin requirements, high insulin sensitivity, and rapidly changing metabolic needs. Standard insulin formulations (U100) may prove inadequate for this age group, especially when utilizing continuous subcutaneous insulin infusion or automated insulin delivery (AID) systems.

This article presents our clinical experience with diluted insulin (U10) in very young children using the AID system CamAPS, along with a literature review, highlighting its potential benefits, such as reduced incidence of hypoglycemia and rates of technical malfunctions. We also discuss key practical considerations for implementing insulin dilution in clinical practice, including the establishment of safety protocols, caregivers and healthcare professionals training, and the importance of accurate preparation and labeling of diluted formulations to mitigate potential serious dosing errors.

INTRODUCTION

The standard insulin concentration in current practice is 100 international units (IU)/mL (U100) (1). The move to standardized insulin concentration worldwide was a major accomplishment, allowing the use of uniform, volumetric insulin syringes and reducing dosing errors. However, this one-size-fits-all approach to insulin concentration may not be easily applicable in the management of diabetes in infants and toddlers who have low insulin requirements (2,3). The use of diluted insulin via continuous subcutaneous insulin infusion (CSII) is recognized as an option to overcome the challenges associated with the delivery of minimum insulin dosages, allowing for more precise dosing (4). At present, there are no definitive guidelines on the use of diluted insulin, although dilution is a strategy discussed for the management of young children in the ISPAD guidelines (1,2).

Insulin can be diluted with a diluting medium obtained from the manufacturer, or if this is not available, normal saline may be an alternative (1). When using the specific diluting medium, diluted insulin maintains stability in terms of purity, potency, antimicrobial safety, and pharmacokinetics (5,6) (table 1).

Several case reports, including our own, have highlighted that using diluted insulin in CSII is associated with lower hypoglycemia incidence, reduced absorption variability and better HbA1c compared to U100 insulin (7-15). (Table 1). In addition, a clinical study comparing diluted insulin (U20) with standard insulin in children younger than 7 years, using an automated insulin delivery (AID) system, showed reduced inter-individual variability in time to peak insulin action with diluted insulin (16), thus supporting diluted insulin use in children with a very low total daily dose (TDD). The main randomized trial comparing AID with diluted (U20) versus standard-strength insulin over three weeks in 24 children aged 1-7 years showed no significant differences in glycemic outcomes between the two groups (17).

However, in that trial average TDD was around 18 IU, and few children were younger than 3 years, which limits the generalizability of the findings to younger children or situations where TDD is less than 10 IU.

Despite these potential benefits, dosing errors with diluted insulin can occur and may have serious consequences. The greatest risk is insulin overdose, which can be life-threatening. Therefore, utmost care must be taken when diluting insulin, and proper training should be provided, to ensure its safe implementation.

In this article, we share our practical experience of using U10 diluted insulin (10 IU/mL) in the AID system CamAPS FX in very young children. We also discuss key points related to its efficacy, safety, and the education required for both healthcare professional (HCP) and parents/caregivers.

WHY TO CONSIDER INSULIN DILUTION IN VERY YOUNG CHILDREN?

Low insulin requirements: The management of type 1 diabetes (T1D) in infants and young children presents unique challenges due to their high insulin sensitivity, rapidly changing insulin needs, low TDD, variable eating and exercise patterns, and limited ability to communicate symptoms of hypoglycemia (2,3). Insulin requirements often decline during the honeymoon period, which adds further complexity to diabetes management (2,18). CSII and AID systems are the recommended approaches to achieving satisfactory glycemic targets in this age group (2,19).

Limitation with current CSII and AID systems: As highlighted in the ISPAD guidelines (1,2), the low TDD required in children with a body weight below 10 kg demands special consideration when using commercially available insulin pumps and insulin preparations. The

guidelines suggest considering the dilution of U100 insulin or using an intermittent basal rate of 0 IU/hour for limited periods (e.g., every other hour) (1,2).

A few case reports highlight the issues associated with insulin delivery suspensions and high glucose variability when using AID systems in children with a very low TDD (10,20). These issues include frequent cannula occlusions, air bubbles in the tubing, and infusion sets lasting barely 2 days. Such complications can lead to pump malfunctions, causing stress for parents/caregivers and affecting the achievement of desirable glycemic outcomes. Notably, switching to diluted insulin has been associated with a reduced incidence of pump malfunctions, and longer duration of infusion circuits (10,20).

CamAPS FX delivers a patency bolus of 0.04 IU (displayed as 0.2 IU on Glooko) approximately every 90 minutes, when basal insulin delivery is automatically suspended by the system to prevent the tubing from becoming blocked (21). In our experience, a patency bolus can cause hypoglycaemia in a child with a low TDD using standard-strength insulin.

Licensing: Despite the commercial availability of AID systems, some young children may not meet their licensing criteria, due to age, weight or TDD (11). This means some children could be using an AID system off license regardless of standard or diluted insulin. (Table 2)

In our center, we have been using diluted insulin primarily with the CamAPS FX system. However, other groups have reported diluting with other AID systems (7,14).

HOW TO SAFELY IMPLEMENT DILUTING INSULIN?

Setting: In our tertiary pediatric diabetes center, we typically start diluted insulin with an AID system when children are admitted as inpatients following T1D diagnosis. However, this approach is also feasible in the outpatient setting. Pros and cons of these approaches are reviewed in Table 3.

Safety considerations:

Labels on pumps: it is essential to highlight that diluted insulin is not a standard-strength formulation. Diluted insulin is filled into regular reservoirs; therefore, it appears to be "standard" insulin. To prevent any confusion and potential dosing errors, we label the pump and specify "U10 diluted insulin (10 IU/mL)" prominently. This ensures that if the child is hospitalised or interacts with healthcare professionals (HCP), the pump will be immediately recognised as containing diluted insulin.

Flag on Hospital records: we also add alerts to the children's hospital records. This is to inform any HCP who encounters the child that they are using diluted insulin.

Care plan: As part of our education package, we provide families with a care plan which clearly displays "U10 DILUTED INSULIN IN INSULIN PUMP" on the first page. We recommend that families bring this care plan with them whenever seeking medical advice, ensuring that the HCP are aware of the non-standard concentration of insulin in the pump.

Out of hours (OOH) support: Our diabetes team participate in an OOH pediatric diabetes consortium, a regional service where diabetes teams rotate coverage. Since children using diluted insulin may not follow standard diabetes management protocols, we instruct these families to contact our pediatric diabetes consultant on call for specialized advice in urgent situations.

Insulin pens at home: Depending on the child's TDD and insulin sensitivity factor (ISF), they may not be able to receive a suitable insulin dose via insulin pen to correct hyperglycemia. For example, 0.5 IU of U100 rapid-acting insulin may equate to a large percentage of their TDD. Despite this, we would always provide a stock of rapid-acting and long-acting insulin pens for families to have at home for administration if required, such as in the event of a pump failure. In this situation, families are instructed to contact the diabetes team for

advice on insulin doses. If an insulin pen correction is not safe to be given, families are advised to attend the nearby hospital for further management of insulin therapy.

PRACTICAL CONSIDERATIONS

Guideline: A "Non-standard insulin concentrations: Usage in clinical practice" guideline was written by our pediatric diabetes educators and consultants with input and approval from pharmacy and the hospital Trust document's body. The guideline includes: 1) the rationale for diluting insulin, 2) expectations for those involved in the care of the child (for example inpatient ward nurses), 3) instructions for preparing the correct diluted insulin solution, 4) guidance on interpreting insulin pump settings using U10 preparations, 5) safety considerations, 6) practical considerations. (Appendix 1, Table S1)

Pump setup: In order to program the pump so it can deliver U10 insulin, the settings need to be ten-fold greater than the desired amount so this can achieve U10 delivery (Appendix 1, Table S2).

Practical equipment: A child may need to start on an insulin pump before a new pump can be delivered. Therefore, having a spare pump readily available is essential. Maintain a supply of infusion sets (preferable option in this age group is steel cannulas) and reservoirs for the pump, and glucose sensors is also required. The supplies for diluting insulin are also required: U100 insulin syringes, IV syringes (various sizes), U100 rapid-acting insulin and diluting medium.

Care plan: To provide the required training and education of parents/caregivers, we have developed a care plan, which covers: 1) management of hypoglycemia and hyperglycemia; 2) troubleshooting potential issues with the pump or CamAPS FX app; 3) instructions for

using the pump without the CamAPS FX app (manual mode); 4) guidance on inserting glucose sensors; 5) information about pump settings; 6) Personalised Sick Day Rules (SDR); 7) how to revert to subcutaneous injections, in the event of pump failure.

Other considerations: Some centers can organize hospital pharmacies to make up the diluted insulin preparation in advance. This is not something we could offer for our families. Therefore, we need to teach parents to dilute the insulin when required, usually every two-three days.

FAMILY SUPPORT

Conversation with parents/caregivers: Current AID systems are only licensed with U100 insulin; therefore, using diluted insulin means operating the system off-license, which carries potential risks. If parents prepare the diluted insulin solution incorrectly, it could lead to hypo- or hyperglycemia. Therefore, it is important to have a conversation with parents about the clinical benefits of using diluted insulin over the standard concentration and the associated risks. This conversation is typically conducted using a multidisciplinary team approach, with the consultant leading the conversation and one of the diabetes educators present to explain the practical implications of diluting insulin. We discuss why, in our view, it is clinically beneficial for the child to use diluted insulin rather than standard concentration, presenting the management options in a balanced manner so that parents can make an informed choice.

Intensity of training for parents/caregivers: Given the potential risks of incorrectly diluting insulin, we strongly encourage that at least two adults in the child's life receive our training. Most frequently, this is the child's parents. We always discuss the importance of completing the diluting process in pairs, both for the professionals delivering the training, and the

family members receiving the training. We also discuss the need for both parents to alternate roles - one leading the diluting process while the other shadows. This approach ensure that both individuals become equally skilled and confident in the process.

ROLE OF EDUCATOR

Skills: It is important that the educators involved in diluting insulin already have good experience of managing very young children with T1D. Although we need to deliver a standard package of education, it is important for educators to be agile in their delivery of the information to meet the diverse learning styles and speeds of parents/caregivers. Educators must possess a solid general knowledge of CSII and AID systems.

Time: Since we typically start children on diluted insulin as an inpatient, this process can be time-intensive for the educator team. We aim to have two educators working together to deliver education and practical sessions. This collaborative approach helps reduce risk of mistakes and oversights. Recognising that education and practical sessions can be overwhelming for parents, we usually schedule several daily sessions of 1-2 hours each over a week, to allow parents to digest the information received.

In-hospital OOH support: While the child is an inpatient and just started on an AID system with diluted insulin, a back-up plan is required for overnight support in case issues arise that could disrupt insulin delivery. This could involve, but not limited to: infusion set failure, technical issue with the insulin pump/AID, pump reservoir unexpectedly empty.

CONCLUSIONS

Insulin dilution can be a beneficial strategy for managing very young children with diabetes Guidelines support its use, particularly in cases where very small doses are required.

It offers improved accuracy, and control of blood glucose levels. However, it requires careful preparation and monitoring to prevent dose errors and ensure safety. The decision to use insulin dilution should be made on an individual basis, as part of a shared decision making with caregivers. The approach used may vary across pediatric diabetes centers. The experience at our center supports its efficacy but also highlights the need for extensive education/training of staff and caregivers.

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Table 1. Summary of studies reporting use of diluted insulin in children

Publication (author, year, ref)	Summary
Stability, pharmacokinetics and pharmacodynamics studies	
Stickelmeyer et al., Diabetes Technol Ther 2000 (6)	• U-10 and U-50 dilutions of insulin lispro (using diluting medium) stored at 5 degrees C and 30 degrees C maintained potency and purity throughout a 32-day testing period. Additionally, both control and diluted vials maintained antimicrobial effectiveness.
Petersen et al., J Phar Pharmacol 2013 (5)	• Diluted insulin maintains its half-life, steady-state plasma concentration, time to steady state during CSII in pigs.
Case reports	
Mianowska et al., J Diabetes Sci aTechnol 2012 (10)	• This case report details the successful use of diluted insulin (U10) to resolve technical issues, such as cannula occlusion, in a 2.5-year-old boy.
McCutcheon et al, Can J Diabetes 2021 (8)	• This case report details the transition from MDI therapy to an AID system utilizing diluted insulin (U10) in a 14-month-old girl. • The switch improved glucometabolic profile, increased TIR, and reduced hypoglycemia. Home insulin dilution was safe.
Sandy et al., Diabetes Technol Ther 2022 (9)	• This case report summarizes the transition from insulin dilution (U20) in MDI to an AID system in a 7-month-old girl. • The transition improved TIR and glucose variability and reduced the family's disease burden.
Wanaguru et al., Acta Diabetol 2023 (7)	• Case series of 4 children: 3 toddlers (age range 7-20 months) with T1D diagnosed before the age of 20 months, and a premature infant with transient neonatal diabetes, all treated with AID systems utilizing diluted insulin (U10/U20). • Diluted insulin was safe and effective leading to improved TIR without any serious side effects.
Tseretopoulou et al., Pediatr Diabetes. 2022(12)	• This case report details the successful use of diluted insulin (U10) in an AID system in a 7-month-old girl with T1D • After 6 months follow-up, TIR was 81%, TBR was 1% and estimated HbA1c was 50 mmol/mol. • The use of diluted insulin in an AID system from the diagnosis was safe and effective in an infant.

Publication (author, year, ref)	Summary
Ashford J et al., Horm Res Paediatr 2024 (13)	• Case series of 10 children with T1D, aged 0.6 to 5.1 years, who began an AID system with diluted insulin (U10) at a median of 4.5 days after diagnosis. • After 10-month follow-up, TIR was 62.9±8.4% and TBR <4%. There were no hospitalizations, nor severe hypoglycemia or DKA episodes. TDD remained low.
Phan et al., Acta Diabetol 2024 (14)	• Case series of 12 children with T1D, younger than 3 years, who used AID therapy with diluted insulin (U20-50) for 6 up to 24 months • No episodes of DKA or hypoglycemia requiring medical intervention; TBR was 1%.
Clinical studies	
Elleri et al., BMJ Open Diabetes Res Care 2014 (22)	• Open label randomized two-period (2–6 weeks apart) crossover study comparing overnight AID systems using diluted (U20) versus standard insulin (U100). • Participants: 11 children, age range 3.75–6.96 years; HbA1c 60 mmol/mol, diabetes duration 2.2±1.0 years, TDD 12.9 IU/day. • No significant differences between regular and diluted insulin in TIR, mean blood glucose, or plasma insulin concentration. However, diluted insulin reduced the risk of nocturnal hypoglycemia, GV and TBR.
Mianowska et al., Diabetes Technol Ther 2015 (20)	• Clinical trial assessing changes in glycemic patterns and incidence of technical issues in very young children with T1D on CSII, transitioning from U100 to U10 insulin. • Participants: 3 children, age range 1.3-3.8 years, CSII duration 5.5 months-2.5 years, HbA1c ≥67 mmol/mol (before transitioning to diluted insulin) • The use of diluted insulin resulted in a reduction in GV, HbA1c and frequency of infusion-related technical issues.
Ruan et al., Diabetologia 2015 (16)	• Open-label, single center randomized, crossover study comparing diluted insulin (U20) vs standard concentration insulin (U100) via CSII as a meal bolus and then overnight by AID system in random order over 2-6 weeks. • Participants: 11 children with T1D, age range 3.75–6.96 years, T1D duration 2.2±1.0 years, TDD 12.9 units • Insulin dilution does not alter its plasma concentration, time to peak, metabolic clearance, but reduced inter-subject absorption variability.

Publication (author, year, ref)	Summary
Tauschmann et al. Diabetes Care 2019 (17)	• Open-label, multicenter randomized crossover study (21 days) comparing AID with diluted insulin (U20) vs standard strength insulin (U100) in random order. • Participants: 24 children with T1D on CSII; median age 5 [range 1-7] years. • No differences between U100 vs U20 in TIR and other glycemic metrics. TDD was on average 18 units.

Search strategy for the articles: PubMed and Google Scholar online databases were comprehensively searched for peer-reviewed articles. The search was limited to English-language publications, with no restrictions on publication date or geographic location. Relevant articles were identified using combinations of keywords, including "diluted insulin," "insulin dilution," "10 U/ml insulin," "insulin concentration," "type 1 diabetes," "diabetes in infancy".

T1D: type 1 diabetes, AID: automated insulin delivery; TIR: time in range: TBR: time below range; TDD: total daily dose; CSII: continuous subcutaneous insulin infusion; DKA: diabetic ketoacidosis; GV: glucose variability

Table 2. Minimum age, weight and total daily dose of commercially available automated insulin delivery systems

Minimum requirements	CamAPS FX	Medtronic 780G SmartGuard	Omnipod 5 SmartAdjust	Tandem T:Slim Control IQ
Age (years)	1	7	2	6
Body weight (kg)	10	Not specified	Not specified	25
Total Daily Dose (IU)	5	8	5	10

Table 3. Pros and cons of starting insulin dilution in different settings

	Inpatient	Outpatient
Pros	• Parents readily available for education. • It feels safe, as the child is within a hospital setting with readily accessible nursing staff and medical professionals if anything untoward happens. • Regular review of glucose profile and insulin settings during ward rounds	• CSII is started after days/weeks from the diagnosis meaning the family has had some time to adapt with T1D and make easier receiving further training/education • More flexibility for parents with appointment planning based on their daily schedule.
Cons	• Parents can struggle due to the recent diagnosis and related adjustments and the additional training related to insulin dilution • Longer hospital stays (up to a week) with related implications	• It can be challenging to troubleshoot practical problems over the phone. • Frequent in person appointments, leading to interference with working hours and additional costs for the family.

Supplementary material

Table S1. How to dilute insulin from U100 to U10 (extract from our guideline)

	How to make up U10 (10 IU/mL) diluted insulin Insulin must be drawn up using a calibrated insulin syringe.	
	DANA pump	**Ypsopump**
Summary of process	To make up 3mL insulin pump reservoir for DANA-i or DANA-RS pumps: Add 30 IU (0.3mL) of rapid-acting insulin (100 IU/mL) to 2.7mL of diluting medium to make up a 3mL reservoir with rapid-acting insulin at a concentration of U10 (10 IU/mL)	To make up 4mL solution to fill 2 x 1.6mL insulin pump reservoir for YpsoPump: Add 40 IU (0.4mL) of rapid-acting insulin (100 IU/mL) to 3.6mL of diluting medium to make up a 4mL solution with rapid-acting insulin at a concentration of U10 (10 IU/mL)
Supply list	• Bottle of U100 rapid-acting insulin (100 IU/mL) • Bottle of insulin diluting medium • Calibrated insulin syringe • 1mL, 2mL and 5mL IV syringes • 3x IV needles • 3mL Dana pump reservoir	• Bottle of U100 rapid-acting insulin (100 IU/mL) • Bottle of insulin diluting medium • Calibrated insulin syringe • 1mL, 3mL and 5mL IV syringes • 3x IV needles • 2x 1.6mL Ypsopump reservoirs
Step-by-step instructions	1. Draw up 30 IU of U100 rapid-acting insulin (100 IU/mL) into the insulin syringe 2. Draw up 0.7mL of insulin diluting medium using the 1mL IV syringe 3. Draw up 2mL of insulin diluting medium using the 2mL IV syringe 4. Add the 2.7mL of insulin diluting medium to the 5mL IV syringe 5. Also add the 30 IU rapid-acting insulin to the 5mL IV syringe containing the insulin diluting medium and mix well (do not shake) 6. Transfer the entire contents of the 5mL syringe containing U10 rapid-acting insulin to the Dana insulin reservoir and prime all air bubbles out Continue as per usual set change procedure	1. Draw up 40 IU of U100 rapid-acting insulin (100 IU/mL) into the insulin syringe 2. Draw up 0.6mL of insulin diluting medium using the 1mL IV syringe 3. Draw up 3mL of insulin diluting medium using the 3mL IV syringe 4. Add the 3.6mL of insulin diluting medium to the 5mL IV syringe 5. Also add the 40 IU of rapid-acting insulin to the 5mL IV syringe containing the insulin diluting medium and mix well (do not shake) 6. Open a 1.6mL Ypsopump reservoir packet and set aside the priming needle adapter, then remove the green plunger from reservoir 7. Turn reservoir upside down then slowly fill with U10 rapid-acting insulin insulin until just past 1.6mL 8. Re-insert the green plunger into the reservoir. This will feel difficult to do as the reservoir is pressurised. Hold it in place as best as you can 9. Turn right way up and clip on priming needle adaptor, then prime all air bubbles out 10. Remove priming needle adaptor and unscrew green plunger from red bung 11. Repeat steps 6 to 10 to fill the second reservoir Continue as per usual set change procedure

In our center, due to local supplies, we currently use Novorapid with the NovoNordisk diluting medium. However, other rapid-acting insulin formulations and available diluting medium can be considered.

Table S2. Example of insulin settings when using diluted insulin U10

Basal pattern setting		
Time	Insulin pump setting	True insulin delivery
00:00	0.80 IU/hr	0.08 IU/hr
04:00	1.00 IU/hr	0.10 IU/hr
17:00	1.10 IU/hr	0.11 IU/hr
22:00	0.80 IU/hr	0.08 IU/hr
Insulin to carbohydrate ratio setting (ICR)		
Time	Insulin pump/app setting	True ICR
00:00	1IU : 2.2g	1IU : 22g
09:30	1IU : 2.4g	1IU : 24g
17:00	1IU : 2.8g	1IU : 28g
Insulin sensitivity factor setting (ISF)		
Time	Insulin pump/app setting	True ISF
00:00	1IU : 3.0mmol/L	1IU : 30mmol/L
16:00	1IU : 2.7mmol/L	1IU : 27mmol/L