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RESEARCH

Evaluation of severe hypoglycemia management in children and adolescents with type 1 diabetes in a Belgian tertiary pediatric care center: impact of intranasal glucagon and cost analysis

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Abstract

To evaluate the management and costs of severe hypoglycemia (SH) in children and adolescents with type 1 diabetes (T1D) in our Belgian tertiary pediatric care center. In the EPI-GLUREDIA study, clinical parameters from children and adolescents with T1D were retrospectively analyzed from July 2017 to June 2024. The characteristics of SH and its treatment were collected during the medical consultation following the SH episode. Between July 2017 and June 2024, 208 cases of SH were recorded in 113 children and adolescents with T1D, with an average age of 13.6 years and T1D duration of 6.2 years. Oral glucose was the most common treatment (47.4%), while glucagon was used in only 25.4% of cases and more frequently in boys (30.8%) than in girls (18.7%). Notably, only 43% of SH episodes were treated according to international guidelines. A significant increase in glucagon use was observed after reimbursement of its intranasal form in Belgium in January 2022. After 2022, glucagon use significantly increased (28/81 vs. 25/129; $p = 0.013$), particularly among teachers and educators (18/49 vs. 10/78; $p = 0.002$). The average direct cost of treating SH was €187.9, with costs ranging from €0 to €1092.5 depending on the treatment method.

Conclusion: Our study underscores the difficulty in managing SH in young people with T1D, with only 43% being treated as per guidelines. Since 2022, the increased use of the intranasal form of glucagon in Belgium led to reduced healthcare costs and improved care of patients experiencing SH.

Keywords Children · Direct costs · Glucagon · Type 1 diabetes · Severe hypoglycemia

Introduction

Hypoglycemia, manifested by a significant drop in blood glucose concentration below 70 mg/dL—whether measured at plasma, capillary, or subcutaneous level—is a common complication in the management of type 1 diabetes (T1D) treated with exogenous insulin. It is recognized as a one of the major factors impairing the optimal management of T1D, significantly impacting the quality of life for patients [1]. Despite adherence to intensive insulin therapy protocols, hypoglycemia remains frequent, occurring in 5–15% of all blood glucose measurements, as it is often necessary to accept these episodes to maintain target average blood glucose levels, typically below 150 mg/dL [2, 3].

Depending on the severity of the accompanying symptoms, hypoglycemia can be classified as mild to severe. Severe hypoglycemia (SH) is characterized by an event leading to significant impairment of consciousness, including convulsions and coma, and requiring external assistance by another person to administer the appropriate treatment [4].

Current guidelines suggest a choice of two treatments for SH: intravenous glucose or glucagon [5]. Several studies have shown glucagon to be as effective as oral glucose in relieving symptoms of hypoglycemia [6]. Potential side effects are generally described as infrequent and mild and correspond to minor digestive disorders [7].

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However, despite its efficacy, glucagon is often underused by patients, partly because of the difficulties involved in administering the treatment. Indeed, for many years, the only route to administer glucagon was by intramuscular injection. As a result, relatives and entourage of patients experiencing SH preferred to make use of oral glucose instead opting for an invasive procedure [8, 9]. Since 2019, intranasal glucagon has been available on the market and was developed with the aim of facilitating the administration of glucagon during SH [10]. In Belgium, since January 2022, intranasal glucagon has been reimbursed for all patients with T1D followed up in a diabetes convention center.

The main objective of our EPI-GLUREDIA study is to evaluate the management of SH in children and adolescents with T1D in our cohort. Finally, a second objective of the study is to assess the direct costs and the economic impact of managing SH.

Methodology

Study design and participants

The EPI-GLUREDIA study, a part of the GLUREDIA consortium, is a retrospective, single-center study evaluating the management of SH in children and adolescents with T1D. Conducted at the pediatric diabetology department of Cliniques universitaires Saint-Luc (CUSL) in Brussels, Belgium, the study adhered to the Helsinki Declaration and was approved by the CUSL Ethics Committee (2022/02/FEV/043). Patient enrollment spanned from July 1, 2017, to June 30, 2024.

Eligible participants were aged 2–20 years and diagnosed with T1D based on American Diabetes Association criteria, including specific blood glucose levels and the presence of anti-islet autoantibodies (e.g., anti-insulin, anti-IA2, anti-GAD65, anti-ZnT8) [11, 12].

Exclusion criteria included patients outside the age range, absence of anti-islet autoantibodies, use of medications affecting insulin secretion or sensitivity, recent celiac disease diagnosis, other autoimmune or autoinflammatory diseases, active malignancy, morbid obesity (BMI Z-score > 3 SD) [13], hepatic, renal, or adrenal insufficiency, suspected genetic syndrome, history of bone marrow transplant or post-hemolytic-uremic syndrome diabetes, and recent participation in another study.

After applying the inclusion and exclusion criteria, a total of 358 patients were deemed eligible to participate in the study. In our center, we estimated the frequency of SH to be 0.08 SH/patient/year.

Study procedure

The EPI-GLUREDIA study analyzed SH events and their management recorded in medical records (EPIC® software) of patients enrolled in the CUSL pediatric diabetes care agreement. SH-related clinical information is documented at each consultation following such events.

Treatment of SH

The study identified six SH treatment types: no treatment (none), intake of sugary food or drink (oral glucose), intramuscular or intranasal glucagon (glucagon), emergency medical intervention (emergency), emergency intervention after oral glucose failure (emergency after treatment failure), and hospitalization for at least 24 h (hospitalization).

Costs of SH

The cost analysis of SH was based on prices from the National Institute for Health and Disability Insurance (INAMI) for medical care and from the Federal Agency for Medicines and Health Products (AFMPS) and the Belgian Centre for Pharmacotherapeutic Information (CBIP) for drug costs. Only direct medical costs, defined as expenses for medical care and necessities, were evaluated.

Statistical analyses

Statistical analyses were conducted using the R software (R Core Team [2021]. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org) with a significance level of 0.05. Demographic and clinical data are presented as mean ± standard deviation for continuous variables and as numbers and proportions for categorical variables. Group comparisons used Student's *t*-test or the Mann–Whitney *U* test, and proportion comparisons employed the Chi-square test or Fisher's exact test, with Bonferroni correction for multiple testing [14].

Results

From July 2017 to June 2024, we recorded a total of 208 cases of SH in 113 children and adolescents with T1D. These SH involved children aged 13.6 years (± 3.8 years) and with T1D for 6.2 years (± 4.7 years). Of these 208 SH episodes, 117 occurred in boys and 91 in girls. The preferred treatment for these episodes was oral glucose, chosen in almost half the cases (47.4%), in both girls (49.2%) and boys

(46.2%). Glucagon, on the other hand, was used in only 53 SH episodes (25.4%), with 18 of these cases involving intranasal delivery. Noteworthily, the use of glucagon was more frequent in boys than in girls (30.8% vs 18.7%; $p < 0.05$). Of these patients, only 43% of SH were treated according to guidelines (glucagon or intravenous glucose) (Table 1, Fig. 1). However, a positive temporal trend in the frequency of glucagon use has been observed since 2017 (Fig. 2).

We then performed an in-depth analysis of the treatments used to manage SH in our cohort. Regardless of patient age, duration of T1D or identity of relatives providing treatment, oral glucose was the predominant treatment except in young adults where admission to an emergency department was the care of. Moreover, we analyzed the management of SH before and after the reimbursement of intranasal glucagon in Belgium (January 2022). No significant difference was observed while comparing the cohort before 2022 (pre-2022) with the cohort after 2022 (post-2022) in terms of patient age, diabetes duration, or gender. However, we found a higher frequency of glucagon use after 2022 compared with before 2022 (28/81 vs. 25/129; $p = 0.013$) (Fig. 3). While we observed no difference in glucagon administration by parents between the two cohorts (15/50 vs. 10/30; $p = 0.76$), we noticed that teachers or educators have been administrating glucagon more frequently since 2022 than before (18/49 vs 10/78; $p = 0.002$). Finally, no difference was observed in the frequency of glucagon administration between the two cohorts based on patient age or diabetes duration.

Table 1 Different proportions of each treatment

	Total	None	Oral glucose	IM/IN Glucagon	Emergency	Emergency after treatment failure	Hospitalization
Total, *n* (%)	208 (100)	4 (1.9)	99 (47.4)	53 (25.4)	37 (17.8)	8 (3.8)	7 (3.4)
Gender							
Male, *n* (%)	117 (100)	2 (1.7)	54 (46.2)	36 (30.8)	19 (16.2)	1 (0.9)	5 (4.3)
Girl, *n* (%)	91 (100)	2 (2.2)	45 (49.5)	17 (18.7)	18 (19.8)	7 (7.7)	2 (2.2)
Age							
Early childhood, *n* (%)	6 (100)	0 (0)	2 (33.3)	0 (0)	2 (33.3)	2 (33.3)	0 (0)
Later childhood, *n* (%)	52 (100)	1 (1.9)	25 (48.1)	9 (17.3)	12 (23.1)	2 (3.8)	3 (5.8)
Adolescence, *n* (%)	126 (100)	2 (1.6)	64 (50.8)	32 (25.4)	21 (16.7)	4 (3.2)	3 (2.4)
Adult, *n* (%)	23 (100)	1 (4.3)	8 (34.8)	12 (52.2)	2 (8.7)	0 (0)	1 (4.3)
Diabetes duration							
< 1 year old, *n* (%)	15 (100)	0 (0)	4 (26.7)	2 (13.3)	9 (60)	0 (0)	0 (0)
1–2 years old, *n* (%)	26 (100)	0 (0)	13 (50)	2 (7.7)	6 (23.1)	3 (11.5)	2 (7.7)
2–3 years old, *n* (%)	28 (100)	0 (0)	16 (57.1)	5 (17.9)	5 (17.9)	1 (3.6)	1 (3.6)
3–4 years old, *n* (%)	19 (100)	1 (5.3)	12 (63.2)	4 (21.1)	1 (5.3)	1 (5.3)	0 (0)
4–5 years old, *n* (%)	12 (100)	1 (8.3)	5 (42.7)	3 (25)	2 (16.7)	1 (8.3)	0 (0)
> 5 years old, *n* (%)	108 (100)	2 (1.9)	49 (45.4)	37 (34.3)	14 (12.3)	2 (1.9)	4 (3.7)
Chronic treatment							
2 injections, *n* (%)	28 (100)	0 (0)	12 (42.9)	4 (14.3)	8 (28.6)	2 (7.1)	2 (7.1)
Basal-prandial, *n* (%)	153 (100)	3 (2.0)	73 (47.7)	42 (27.4)	24 (15.7)	6 (3.9)	3 (2.0)
Pump, *n* (%)	29 (100)	1 (3.4)	14 (48.3)	7 (24.1)	5 (17.2)	0 (0)	2 (6.9)
Timing of SH							
Wake-up, *n* (%)	49 (100)	1 (2.0)	22 (44.9)	14 (28.6)	10 (20.4)	2 (4.1)	0 (0)
School, *n* (%)	54 (100)	0 (0)	31 (57.4)	11 (20.4)	9 (16.7)	2 (3.7)	1 (1.9)
Hobby, *n* (%)	73 (100)	2 (2.7)	32 (43.8)	17 (23.3)	15 (20.5)	2 (2.7)	5 (6.8)
Rest, *n* (%)	32 (100)	1 (3.1)	14 (43.8)	11 (34.4)	3 (9.4)	2 (6.3)	1 (3.1)
Year of SH							
2017–2021, *n* (%)	129 (100)	2 (1.6)	70 (54.3)	25 (19.4)	20 (15.5)	7 (5.4)	5 (3.9)
2022–2024, *n* (%)	81 (100)	2 (2.5)	29 (35.8)	28 (34.6)	17 (21.0)	1 (1.2)	2 (2.4)

Percentages may not total 100 due to rounding. Early childhood, patients under 6 years of age; late childhood, patients between 6 and 11 years of age; adolescence, patients between 12 and 18 years of age; adult, patients over 18 years of age; wake-up, severe hypoglycemia between waking up and leaving for school; school, severe hypoglycemia at school; hobby, severe hypoglycemia during hobbies; rest, severe hypoglycemia at home in the evening

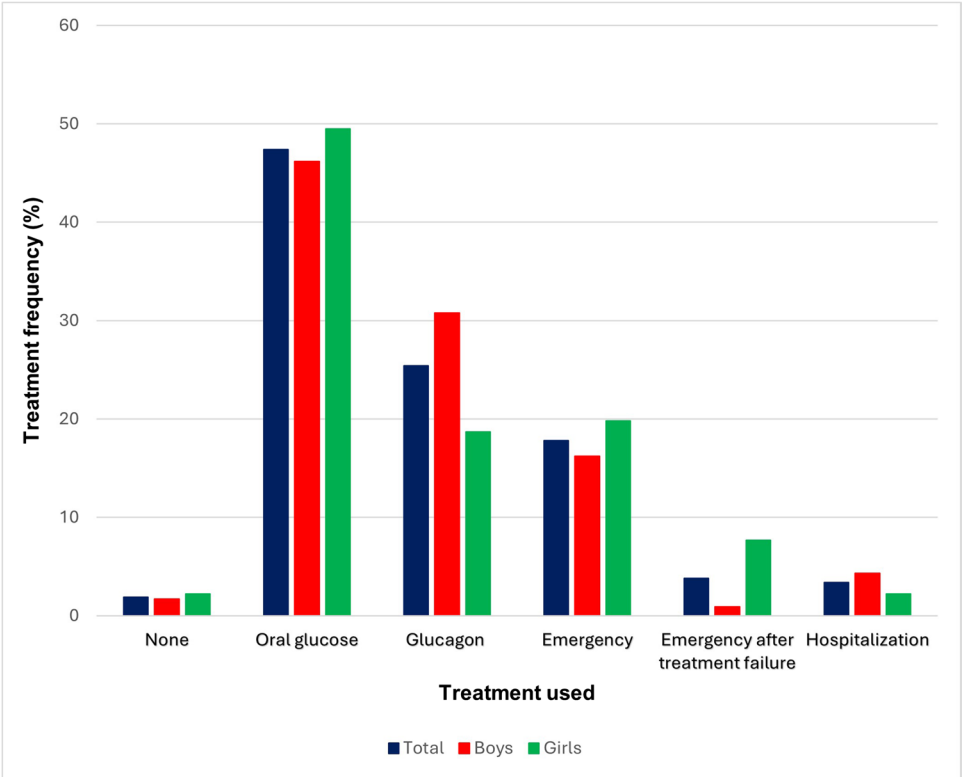

Fig. 1 Analysis of management of severe hypoglycemia between 2017 and 2024 in children and adolescents with type 1 diabetes. The x axis represents the different treatments used for severe hypoglycemia. The y axis represents the frequency of use of each treatment. Each color used for the bars of the histogram corresponds either to the total cohort, or to a specific gender. The numbers above the bars correspond to the proportion of the treatment used for the corresponding bar

Finally, we studied the direct cost of SH in Belgium. During this period, the average cost of treating SH was €187.9. Treatment costs ranged from €0 for treatment abstention to €1092.5 for hospitalization. Depending on the form of administration, the price of glucagon ranged from €25.25 (intramuscular glucagon) to 66.97€ (intranasal glucagon). It is important to specify that only direct costs are considered, with exclusion of indirect expenses such as absenteeism from work or travel costs, for example. All data are presented in Table 2.

Discussion

SH is an acute complication of T1D that worries patients and their families due to its clinical manifestations and impact on quality of life [15, 16]. The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends intravenous glucose or glucagon injections to treat SH and advises that every patient with T1D should have glucagon readily available [5]. Several studies have demonstrated the effectiveness of glucagon in rapidly relieving SH symptoms with minor side effects [6, 7]. However, oral glucose is not recommended for SH due to its reduced effectiveness and potential swallowing difficulties and side effects [5, 15–17].

In our EPI-GLUREDIA study, only 43.2% of SH episodes were treated according to guidelines and 25% of patients received glucagon. Two main reasons can explain these results: a lack of adequate therapeutic education and the fear of intramuscular glucagon injections. Training medical staff could improve the education of patients and their families [6, 18]. Moreover, the recent availability of intranasal glucagon form in the market could improve SH management as an effective and easier to use treatment compared to intramuscular injections [19–21]. Since its reimbursement in Belgium in 2022, glucagon use has significantly increased. Results show a positive evolution in the management of SH. Systematic prescription of intranasal glucagon, along with appropriate therapeutic education, could improve SH management in young T1D patients [10, 19, 21].

A financial advantage of intranasal glucagon is the reduction in SH management costs. In our study, the use of intranasal glucagon would have reduced direct costs by 87% for the intramuscular form and 64% for the intranasal form. Several recent studies highlight the positive financial impact of glucagon, especially the intranasal formulation, and suggest reinvesting the savings to improve overall diabetes management [22–24].

Compared to previous studies, SH management in Belgium appears less costly. However, methodological differences, such as the exclusive inclusion of patients requiring medical assistance and a focus on type 2 diabetes patients with comorbidities, explain the higher costs observed elsewhere [25–28].

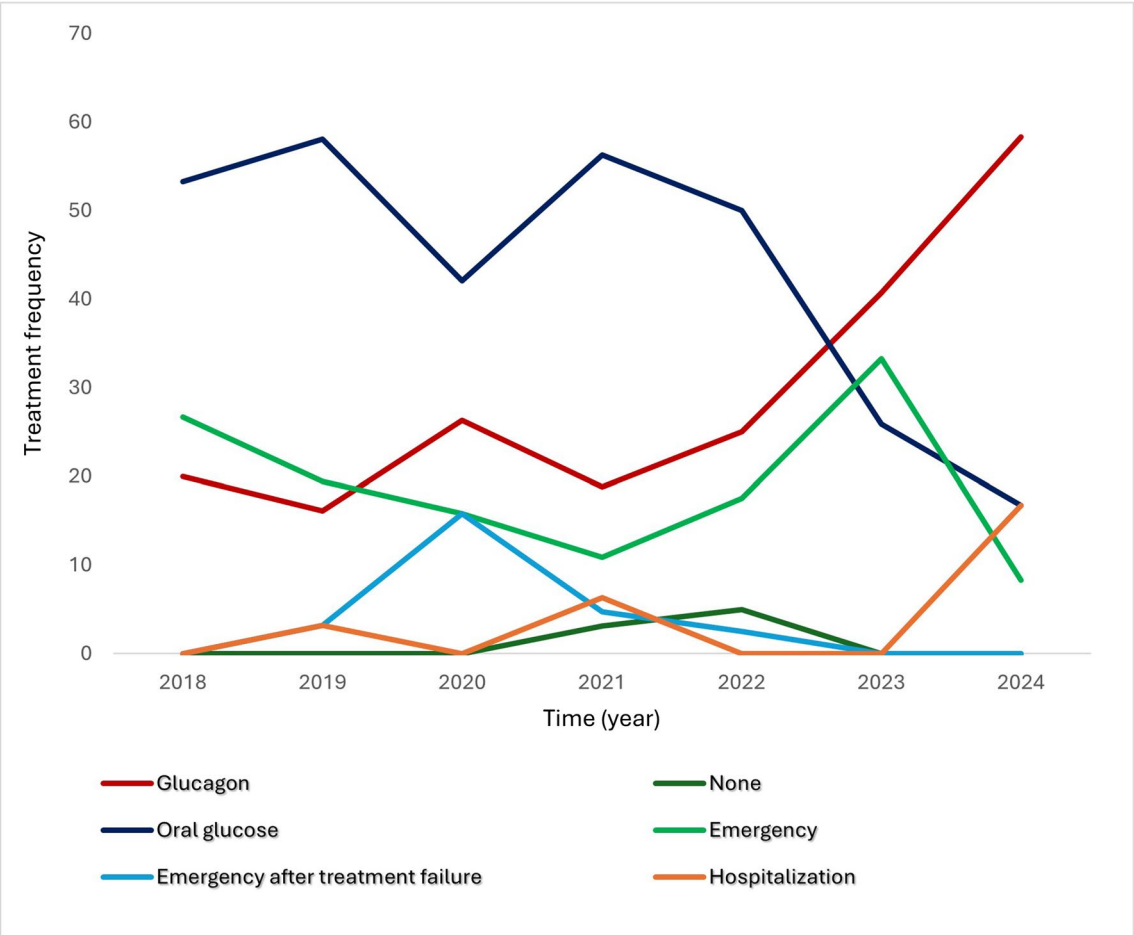

Fig. 2 Temporal evolution of the management of severe hypoglycemia in Belgium between 2018 and 2024. The horizontal axis corresponds to time measured in years. The vertical axis corresponds to the frequency of treatment used, measured as a percentage. Each color corresponds to a specific treatment. The red–orange colors correspond to the management of hypoglycemia in accordance with ISPAD guidelines. Colors tending toward blue correspond to the management in disagreement with the guidelines

Conclusion

Our study highlights the challenge of managing SH in children and adolescents with T1D. Despite the ISPAD guidelines, only 43% of SH episodes were treated according to guidelines. However, the approval and reimbursement of intranasal glucagon in Belgium in 2022 have led to a significant increase in its use, particularly among teachers and educators. Enhanced therapeutic education and the systematic prescription of intranasal glucagon could further optimize care and reduce the financial burden associated with SH.

Limits and perspectives

It should be noted that our study was performed in a single hospital center, which limited the generalizability of the obtained results. In addition, the recent introduction of an intranasal glucagon form raises questions about its use in the long-term. Therefore, further multicenter, longer-term studies are needed to better evaluate the efficacy of this treatment and to confirm our preliminary results.

However, a notable strength of our study relies in the fact that it considered the management of SH both by a medical team and by the patient relatives.

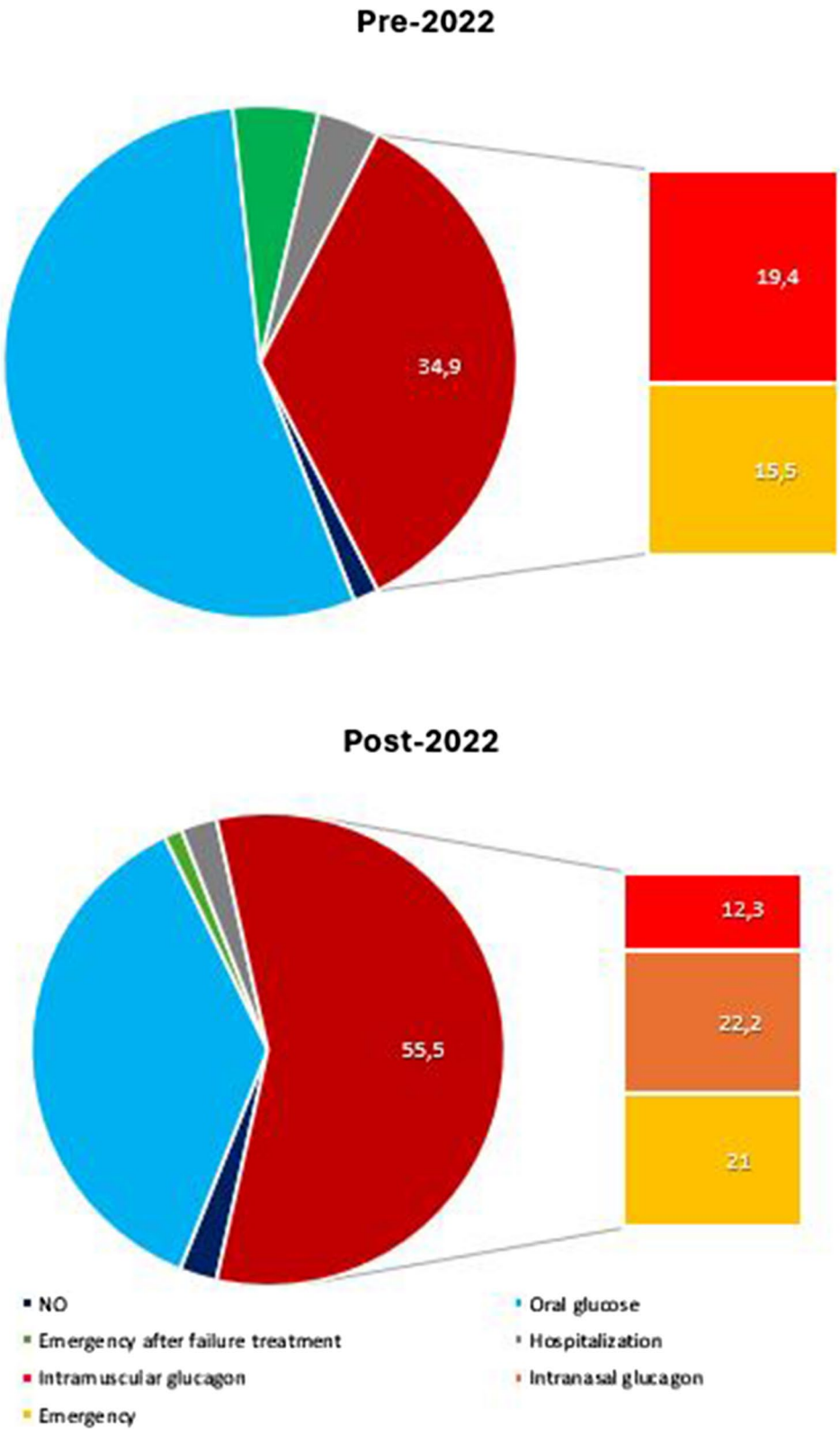

Fig. 3 Pie chart describing the management of severe hypoglycemia before 2022 and after 2022 and the reimbursement of intranasal glucagon in Belgium. The two orange areas correspond to the management of hypoglycemia in accordance with ISPAD guidelines. The dark red zone represents SH treatment in accordance with guidelines. The different proportions for each treatment are shown in Table 1. This graph shows the clear improvement in the management of severe hypoglycemia after 2022 and the reimbursement of intranasal glucagon

Table 2 Data of direct cost of SH in Belgium

	Number of uses	Treatment cost (€) for a single use	Total cost (€)
Treatment of SH			
None	4	0	0
Oral glucose	99	0	0
IM glucagon	35	25.25	883.75
IN glucagon	18	66.98	1205.64
Emergency visits	45	605.88	27,264.60
Medical transport	17	133.56	2270.52
Hospitalization + nursing care	7	1092.60	7648,20
Total			**39,092.71**
Mean cost/patient			**187.94**

Number of uses, number of times the treatment was used; treatment cost, price of a single use of treatment; total cost, total cost per medication of 162 severe hypoglycemia; total, the total cost of 162 severe hypoglycemia; mean cost/patient, mean cost of one severe hypoglycemia

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Data availability No datasets were generated or analysed during the current study.

Declarations

Institutional review board The study was conducted in accordance with the ethical declaration of Helsinki and approved by the Hospital-Faculty Ethics Committee of the CUSL (2022/02/FEV/043).

Informed consent Informed consent was obtained from all subjects involved in the study.

Competing interest The authors declare no competing interests.

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