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Dasiglucagon for the Treatment of Insulin-induced Hypoglycemia in Patients with Type 1 Diabetes Mellitus: A Meta-analysis

Shampa Maji[1], Rashmi Ranjan Mohanty[2], Rituparna Maiti[1]

[1]Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, India
[2]Department of General Medicine, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, India

Background: The use of conventional glucagon for managing insulin-induced hypoglycemia is obscured by its chemical instability and the need for reconstitution of the lyophilized powder, leading to delayed rescue. Dasiglucagon, a glucagon analog, may potentially overcome these shortcomings.

Aims: To evaluate the efficacy and safety of dasiglucagon in insulin-induced hypoglycemia in patients with type 1 diabetes mellitus (T1DM).

Study Design: Meta-analysis.

Methods: PubMed/MEDLINE, Scopus, Embase, and Cochrane databases along with clinical trial registries were searched to include data from five randomized controlled trials conducted using dasiglucagon for the treatment of insulin-induced hypoglycemia in T1DM patients published until May 2023. We performed a risk of bias assessment to determine the quality of the included studies and a random-effects model analysis for determining the effect size. Subgroup analysis and meta-regression were done as applicable.

Results: The time to recovery (in minutes) with dasiglucagon was earlier than placebo [mean difference (MD): -24.73; 95% confidence interval (CI): -30.94 to -18.52; $p < 0.00001$) or oral glucose (MD: -15.00; 95% CI: -20.33 to -9.67; $p < 0.00001$); however, the difference between dasiglucagon and glucagon was not statistically significant (MD: -0.76; 95% CI: -2.19 to 0.66; $p = 0.29$).

Conclusion: Dasiglucagon is safer and more effective than placebo or oral glucose for insulin-induced hypoglycemia in T1DM patients; however, it is not superior to conventional glucagon.

INTRODUCTION

Insulin-therapy-related diabetic hypoglycemia is a serious complication characterized by a decrease in blood glucose levels.[1] About one-third of patients with type 1 diabetes mellitus (T1DM) report at least 1-3 episodes of hypoglycemia annually.[2] The American Diabetes Association (ADA) classifies hypoglycemia into three levels depending on blood glucose concentration; accordingly, severe hypoglycemia often requires prompt medical interventions for treating or preventing potentially life-threatening conditions, such as seizures, loss of consciousness, coma, and even death.[3,4] In pediatric patients, repeated hypoglycemic episodes may have detrimental consequences on cognitive development when occurring in their early years.[5] Thus, determining the most efficient management and treatment options for hypoglycemia in people with diabetes is essential.

The United States Food and Drug Administration (USFDA) has approved conventional parenteral glucagon therapy for the management of severe hypoglycemia in T1DM.[6,7] The ADA treatment guidelines also recommend that patients with a higher risk of developing level 2 hypoglycemia should be prescribed glucagon.[8,9] However, native glucagon is unstable in liquid form and easily degrades, losing its bioactivity.[6] Commercially, conventional glucagon is produced and marketed as a lyophilized powder[10] which must be reconstituted before administering the injection. Presumably, this multistep reconstitution process of lyophilized glucagon powder included in glucagon emergency kits constitutes

Corresponding author: Rituparna Maiti, Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Bhubaneswar, India
e-mail: pharm_rituparna@aiimsbhubaneswar.edu.in

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ORCID iDs of the authors: S.M. 0000-0002-5249-1505; R.R.M. 0000-0003-4935-6713; R.M. 0000-0003-4063-9178.

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a major cause of delayed rescue and causes underutilization of glucagon.[11] Thus, a ready-to-use glucagon formulation that is stable in liquid form is required for early hypoglycemic rescue.

Dasiglucagon, a glucagon analog approved by the USFDA in 2021,[12,13] does not form aggregates in aqueous solutions in contrast to natural glucagon; thus, it retains its efficacy on glucagon receptors and promptly elevates the glycemic index upon subcutaneous injection.[14] In preclinical studies, dasiglucagon significantly increased blood glucose levels, which was comparable to glucagon.[14] Furthermore, a few randomized clinical trials also evaluated dasiglucagon and reported a significant increase in plasma glucose level which was achieved within less time as compared to glucagon or placebo.[15-19] Nevertheless, for a successful clinical translation, there is a need to produce conclusive proof of the extent of the efficacy and safety of dasiglucagon. Therefore, the current meta-analysis was conducted to assess the efficacy and safety of dasiglucagon in insulin-induced hypoglycemia in patients with T1DM in comparison to placebo/oral glucose/glucagon.

MATERIALS AND METHODS

Protocol development

We designed the study protocol as per PRISMA-P guidelines of 2015[20] and registered the protocol with PROSPERO (CRD42022322686). The meta-analysis was carried out and reported in compliance with the PRISMA statement.[21,22] Additionally, the Cochrane Handbook for Systematic Reviews of Interventions was consulted for standard methods of meta-analysis.[23]

Literature search

Two authors independently searched the PubMed/MEDLINE, Embase, Scopus, and Cochrane databases, along with the clinical trials registries for randomized clinical trials conducted using dasiglucagon for the treatment of insulin-induced hypoglycemia in patients with T1DM published until May 2023. The authors followed the PICO format to select key terms.

Study selection criteria

Types of studies

We included randomized controlled trials that were carried out to evaluate the efficacy of dasiglucagon in managing insulin-induced hypoglycemia in patients with T1DM using time to increase plasma glucose ≥ 20 mg/dl (1.1 mmol/l) an outcome parameter. Preclinical studies, review articles, clinical trials for other indications, observational studies, commentaries, letters to the editor, opinions, case reports/series, and studies with inadequate data were excluded from this meta-analysis.

Study participants

Children (aged ≥ 6 years and ≤ 18 years) and adults (aged 18-75 years) of either sex with pre-diagnosed T1DM for at least one year (ADA criteria), continuing on stable insulin treatment since at least one year (the variation in total daily insulin dose should not be more than a 10-unit) one month prior to screening, and having an HbA1c value of < 10% were included in the study. The included studies had excluded patients with a history of allergy to dasiglucagon, hypoglycemic episodes with seizures, any clinically significant medical and surgical disorders, known alcoholics, or who had received any investigational drug within three months before screening.

Types of interventions

Experimental group: Received a single parenteral dose of dasiglucagon following insulin-induced hypoglycemia.

Control group: Received either placebo, glucagon, or oral glucose.

Outcome parameters

Primary: Time to recovery (in minutes): time taken to raise plasma glucose to ≥ 20 mg/dl.

Secondary: Number of patients recovered at the end of 10-, 20-, and 30-minutes post-intervention, and the number of patients with treatment-emergent adverse events (TEAE).

Study selection and data collection

Selection of studies

First, the reviewing authors went through all the titles, abstracts, and keywords of potentially relevant publications obtained after a thorough literature search. Accordingly, the relevant clinical studies were selected, and the full texts of those articles were evaluated by the authors. The studies that fulfilled the selection criteria and used our outcome of interest as an outcome measure were included in the meta-analysis. The reasons for the exclusion of each article were noted, and any disagreement regarding the study selection was solved via discussion among the authors.

Data extraction

The quality of the included studies was evaluated by two authors independently as per the Cochrane Collaboration guidelines.[23] Data regarding study location, methodology, subjects, intervention, comparators, and outcome metrics were included in the data extraction. Any differences of opinion among the authors were settled through consensus or discussion with a third reviewer.

Data analysis

We used the Cochrane Programme Review Manager (version 5.4) to carry out this meta-analysis.[24] Additionally, we used the Meta-Essentials software to conduct meta-regression and publication bias with trim and fill analyses.[25]

Risk of bias in included studies

Using the risk of bias 2 (RoB 2) assessment tool (developed by the Cochrane Collaboration), three review authors independently evaluated the internal validity of included trials and the risk of bias in each study.[23,26]

Unit-of-analysis issue

The term "study" has been used in the current meta-analysis as a "unit of design." The studies with different doses of dasiglucagon

or more than one comparator were considered separate units of analysis.

Measures of treatment effect

The primary outcome measure, time to recovery of glucose level, is a continuous variable for which the effect size is presented as the mean difference (MD) with a 95% confidence interval (CI). For categorical variables, such as the number of patients recovered within 10, 20, and 30 minutes of intervention and TEAEs, the odds ratio (OR) was calculated. Haldane's correction was applied for calculating the OR when one or more cells representing the event in the 2 x 2 matrix had a value of zero. The random-effects model was used for overall between-group analyses. The prediction interval (PI) for the primary outcome measure was also been reported.

Assessment of heterogeneity

The chi-square test and I^2 statistics were used to quantify the heterogeneity. In case of high heterogeneity, subgroup analysis and sensitivity analysis were done to investigate into high heterogeneity.

Sensitivity analysis

In the case of significant heterogeneity, forest plots were constructed again after removing each study separately to evaluate the impact of each exclusion on individual parameters.

Meta-regression

Meta-regression was performed to estimate how the primary outcome parameter (time to recovery) changed with the independent variable (dose of dasiglucagon). The statistical significance of the regression coefficient was determined to check for any linear relationship between the dependent and the independent variables.

Assessment of publication bias

Publication bias was qualitatively assessed across randomized controlled trials using the funnel plot and quantitatively using the Begg and Mazumdar rank correlation test. The trim and fill method was used to adjust for funnel plot asymmetry.

Assessment of certainty of the evidence

The GRADE Working Group's guidelines were followed to ascertain the certainty of the evidence for each outcome, and eventually, a "summary of findings" table was created.[27]

RESULTS

Description of included studies

Twenty-five potentially relevant publications were identified through a systematic literature search on the databases, and 17 of them were excluded (11 review articles, 1 pharmacoeconomic study, 1 duplicate study, 1 letter to the editor, and 3 clinical trials conducted on different indications). Subsequently, full texts of the remaining eight studies were retrieved for a thorough evaluation, three of which were excluded because one was a comparative study of the dasiglucagon delivery device, another did not have a comparator group for dasiglucagon, and the third had outcome measures different from our interests. After the final screening, five studies[15,17-19,28] satisfying the selection criteria were included in the present meta-analysis (Table S1).

Studies that used different doses and more than one comparator group were considered separate units; accordingly, a total of 11 units of analysis were studied in this meta-analysis (Figure 1). Table S2 summarizes the reviewers' assessments of the risk of bias in the included clinical trials.

Assessment of efficacy parameters

Time to recovery

All five included studies had reported time to recovery (in minutes) of plasma glucose. There was significant heterogeneity in the included studies (χ^2 =88.51; $p < 0.0001$; I^2 = 89%). The analysis of the random-effects model showed a pooled MD of -8.08 (95% CI: -12.69 to -3.47; $p = 0.0006$; PI = -25.22 to 9.05), favoring the dasiglucagon group.

To investigate for high heterogeneity, a subgroup analysis was done based on different control groups used in the included studies, and the result showed a reduction in the heterogeneity in each subgroup to < 10%. In the placebo-controlled subgroup, the effect size was -24.73 (95% CI: -30.94 to -18.52; $p < 0.0001$) with insignificant heterogeneity (I^2 = 9%). For the oral glucose-controlled subgroup, the effect size was -15.00 (95% CI: -20.33 to -9.67; $p < 0.000$) with insignificant heterogeneity (I^2 = 0%). The pooled MD for the glucagon-controlled subgroup was -0.76 (95% CI: -2.19 to 0.66; $p = 0.29$) with an insignificant heterogeneity (I^2 = 3%) (Figure 2).

Another subgroup analysis of time to recovery was performed based on the age of the participants, which revealed that dasiglucagon had no significant effect in the < 18 years age group (Figure S1). Furthermore, a sensitivity analysis was done for the age group > 18 years by removing one study unit at a time. We found that by removing the study by Bailey et al. and Pieber et al. (both compared dasiglucagon versus placebo), heterogeneity was reduced to 79% without significant change in pooled effect size.

Number of patients recovering at various time points post-intervention

Only three[15,18,28] of the five studies measured the number of participants who recovered at the end of 10-, 20-, and 30-minutes post-intervention. The random-effects model analysis was performed, along with subgroup analysis at each time point based on the comparator used. At 10 minutes, the pooled effect size (in terms of OR) was 7.98 (95% CI: 1.56 to 40.82; $p = 0.01$) with high heterogeneity (χ^2 = 20.32; $p = 0.0004$; I^2 = 80%). After subgroup analysis, the glucagon comparator subgroup had an OR of 1.76 (95% CI: 0.90 to 3.47; $p = 0.10$), which was not statistically significant with low heterogeneity (I^2 = 0%). Lastly, the placebo comparator group had an OR of 33.20 (95% CI: 9.57 to 115.20; $p < 0.000$) and insignificant heterogeneity (I^2 = 0%), suggesting that the dasiglucagon group had a very high recovery rate at 10 minutes as compared to the placebo group.

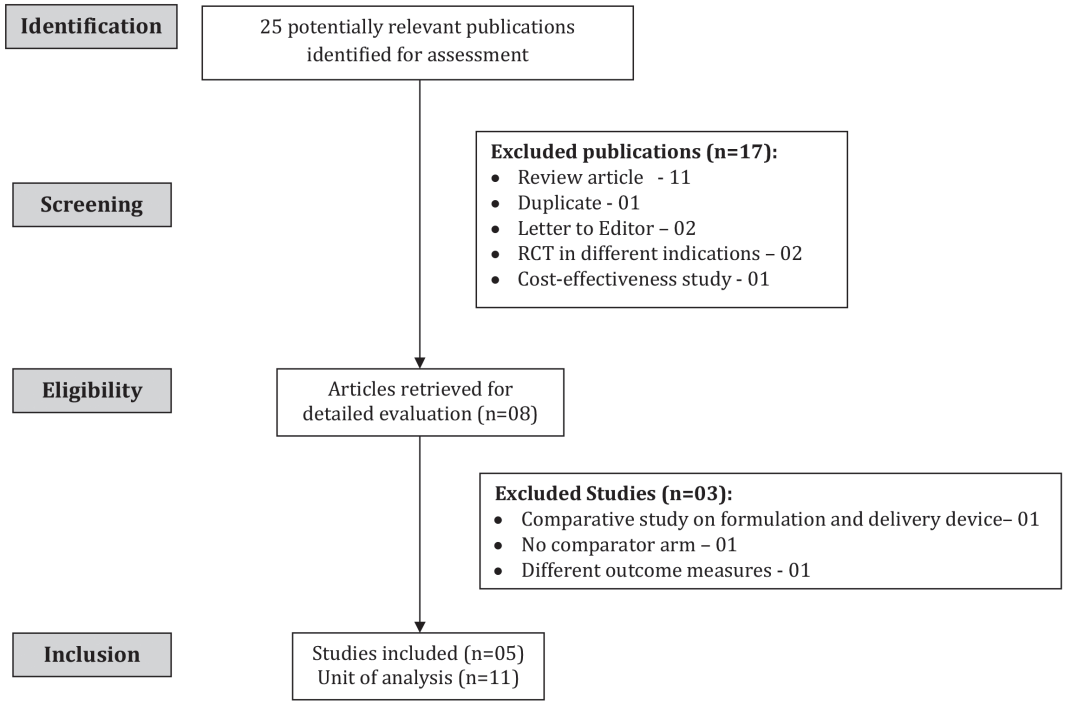

FIG. 1. PRISMA flow diagram for the study selection process.

At the end of 20 minutes, the pooled effect size was OR = 36.63 (95% CI: 3.54 to 379.54; $p = 0.003$) with a statistically significant heterogeneity ($\chi^2 = 15.41$; $p = 0.004$; $I^2 = 74\%$). As per subgroup analysis, the glucagon comparator subgroup had an OR of 2.02 (95% CI: 0.27 to 15.0; $p = 0.49$), whereas the placebo comparator group had an effect size OR of 257.33 (95% CI: 60.42 to 1095.94; $p < 0.000$); both subgroups had low heterogeneity ($I^2 = 0\%$).

At 30 minutes post-intervention, 100% of patients recovered in both dasiglucagon and glucagon groups. Hence, the OR (95% CI) was not estimable by RevMan 5.4.1. To get an estimate, we deducted one from each cell representing the event in the 2 x 2 matrix. At 30 minutes, the pooled effect size was OR = 15.46 (95% CI: 2.72 to 87.80; $p = 0.002$) with nonsignificant heterogeneity ($I^2 = 49\%$). After subgroup analysis, the glucagon comparator subgroup had no statistical significance for both effect size (OR = 2.02; 95% CI: 0.27 to 15.00; $p = 0.49$) and heterogeneity ($I^2 = 0\%$). In contrast, the placebo comparator group had a significant effect size (OR = 54.78; 95% CI: 11.60 to 258.71; $p < 0.000$) and nonsignificant heterogeneity ($I^2 = 0\%$) (Figure 3).

Safety assessment

The number of patients with TEAEs was presented in four studies[15,18,19,28] reported. The commonly reported TEAEs were nausea, vomiting, headache, and injection site erythema. The overall effect size was OR = 2.42 (95% CI: 0.90 to 6.55; $p = 0.08$) with statistically significant heterogeneity ($\chi^2 = 22.01$; $p = 0.001$; $I^2 = 73\%$).

A subgroup analysis based on the comparator group revealed a significantly higher number of TEAEs with dasiglucagon compared to placebo/oral glucose group (OR = 3.99; 95% CI: 1.36 to 11.71; $p = 0.01$) with moderate heterogeneity ($\chi^2 = 11.03$; p = 0.03; $I^2 = 64\%$). For the glucagon subgroup, there was no statistically significant difference from the dasiglucagon group (OR = 0.92; 95% CI: 0.44 to 1.90; $p = 0.82$) with nonsignificant heterogeneity ($I^2 = 0\%$) (Figure 4a).

We also performed a subgroup analysis to determine the dose dependence of TEAEs. The 0.6 mg dose dasiglucagon group had an OR of 2.60 (95% CI: 0.62 to 10.87; $p = 0.19$), which was not statistically significant; however, this group showed high heterogeneity ($\chi^2 = 21.91$; $p = 0.0002$; $I^2 = 82\%$). For a dasiglucagon dose of ≤ 0.12 mg, the OR was 1.93 (95% CI: 0.69 to 5.34; $p = 0.21$), but the heterogeneity was not significant ($I^2 = 0\%$). The data analysis did not suggest any dose dependence of TEAEs (Figure 4b).

Incidence of nausea and vomiting

All included studies reported nausea as a common adverse event, with significant heterogeneity ($\chi^2 = 33.55$; $p = 0.0002$; $I^2 = 70\%$). The result from the random-effects model analysis showed a pooled OR of 2.62 (95% CI: 1.06 to 6.44; $p = 0.04$), suggesting that the incidence of nausea was significantly higher in the dasiglucagon group compared to the control groups (Figure S2). For vomiting, the heterogeneity was low ($I^2 = 30\%$) and the pooled OR was 3.20 (95% CI: 1.56 to 6.57; $p = 0.001$) suggesting a significantly higher incidence of vomiting in the dasiglucagon group compared to the control groups (Figure S3).

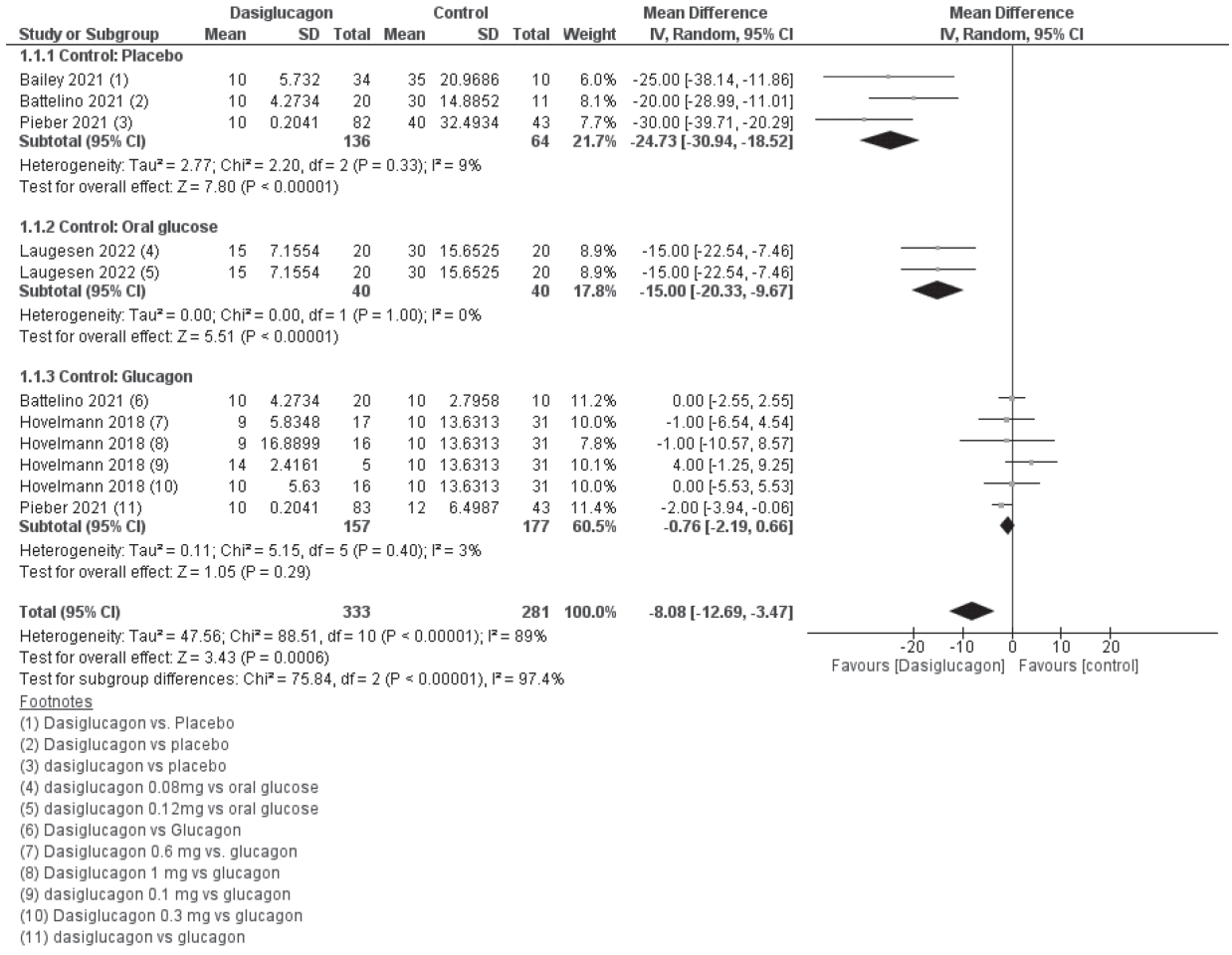

FIG. 2. Forest plot for the included studies pooled together using a random-effects model for assessing the time taken for recovery of plasma glucose levels to ≥ 20 mg/dl Included studies are identified by first author and year. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% confidence intervals (CIs). The diamond represents the pooled effect size, and its width represents its 95% CI. A subgroup analysis has been done to show the changes in different comparator groups.

Incidence of headache

Headache was another common adverse event reported by all studies; however, the heterogeneity among the included trials was moderate (I^2 = 0%). The random-effects model analysis revealed a pooled OR of 1.87 (95% CI: 1.13 to 3.08; p = 0.01), suggesting a significantly higher incidence of headache in the dasiglucagon group compared to the control groups (Figure S4).

Meta-regression

There was no statistically significant association between the MD of time to recovery with different doses of dasiglucagon [B = 3.62; slope coefficient (β) = 0.11; p = 0.320] (Figure S5).

Publication bias in included studies

The funnel plot created was visually asymmetric. Furthermore, the results of Begg and Mazumdar's rank correlation test revealed a significant bias in the included studies (Kendall's tau: -0.69; 2-tailed p value = 0.002). Therefore, to adjust funnel plot asymmetry, a trim and fill analysis was performed, which simulated the included clinical trials and added four more imputed data points; the adjusted plot is presented with observed combined effect size (CES), adjusted CES, and imputed data points (Figure 5). The adjusted effect size after correcting for asymmetry was -1.26 [95% CI: -2.63 to 0.11; PI: -20.86 to 18.34], which was not significant.

Certainty of the evidence

For the primary outcome measure (time to recovery), the grade of certainty of the evidence was determined as moderate, which means that authors are moderately confident in the effect estimate; although the true effect is likely to be close to the pooled effect, there is a possibility that it may differ. However, the certainty of the evidence for the number of patients who recovered at different time points post-intervention (10, 20, and 30 minutes) and the number of patients with TEAEs was found to be high, suggesting that authors are very confident that the true effect lies close to that of the estimated pooled effect (Table S3).

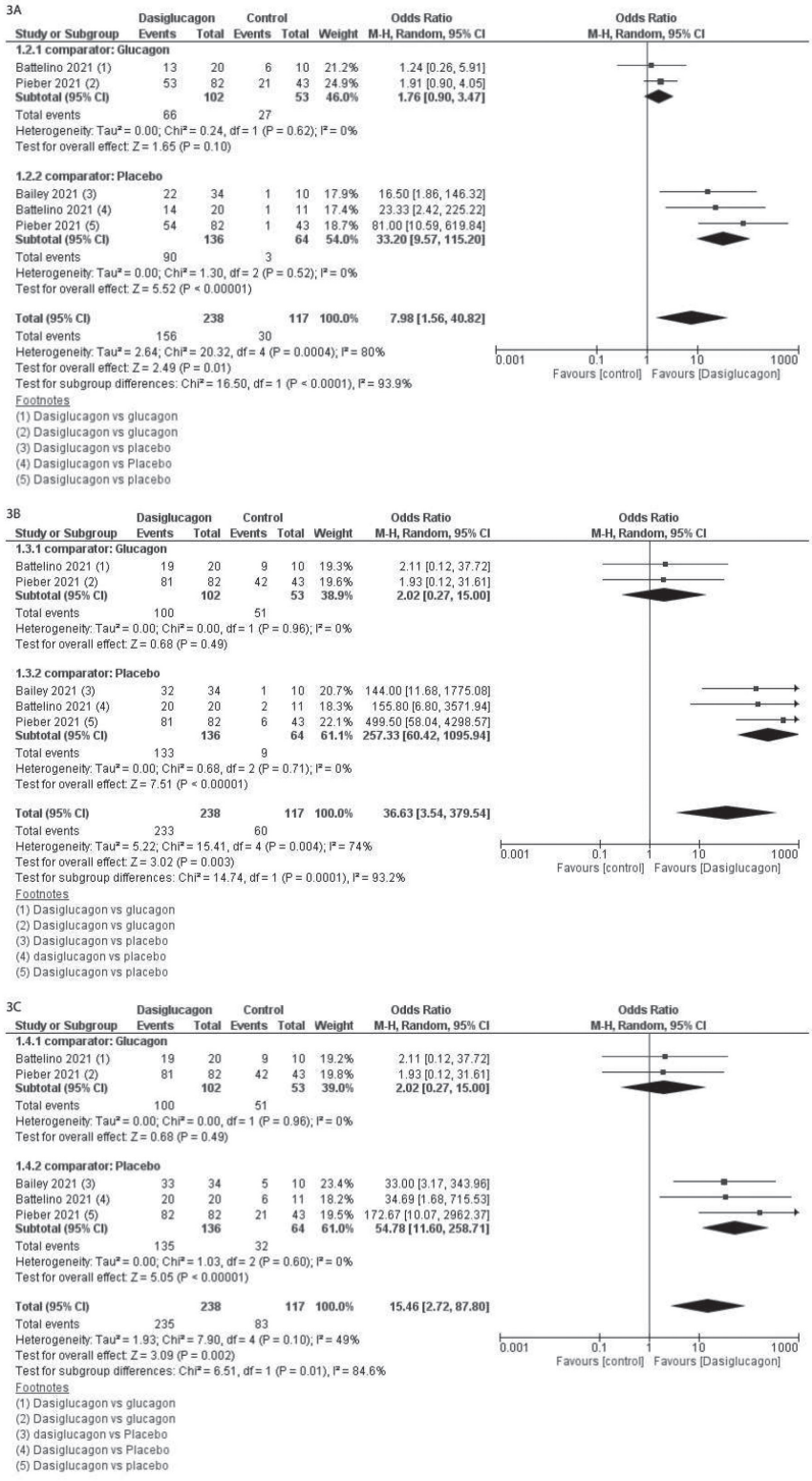

FIG. 3. Forest plots for included studies pooled together using a random-effects model for assessing the difference in the number of patients recovered at 10 minutes post-intervention (3a), 20 minutes post-intervention (3b), and 30 minutes post-intervention (3c).
Included studies are identified by first author and year. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% confidence intervals (CIs). The diamond represents the pooled effect size, and its width represents its 95% CI. A subgroup analysis has been done to show the changes in different comparator groups.

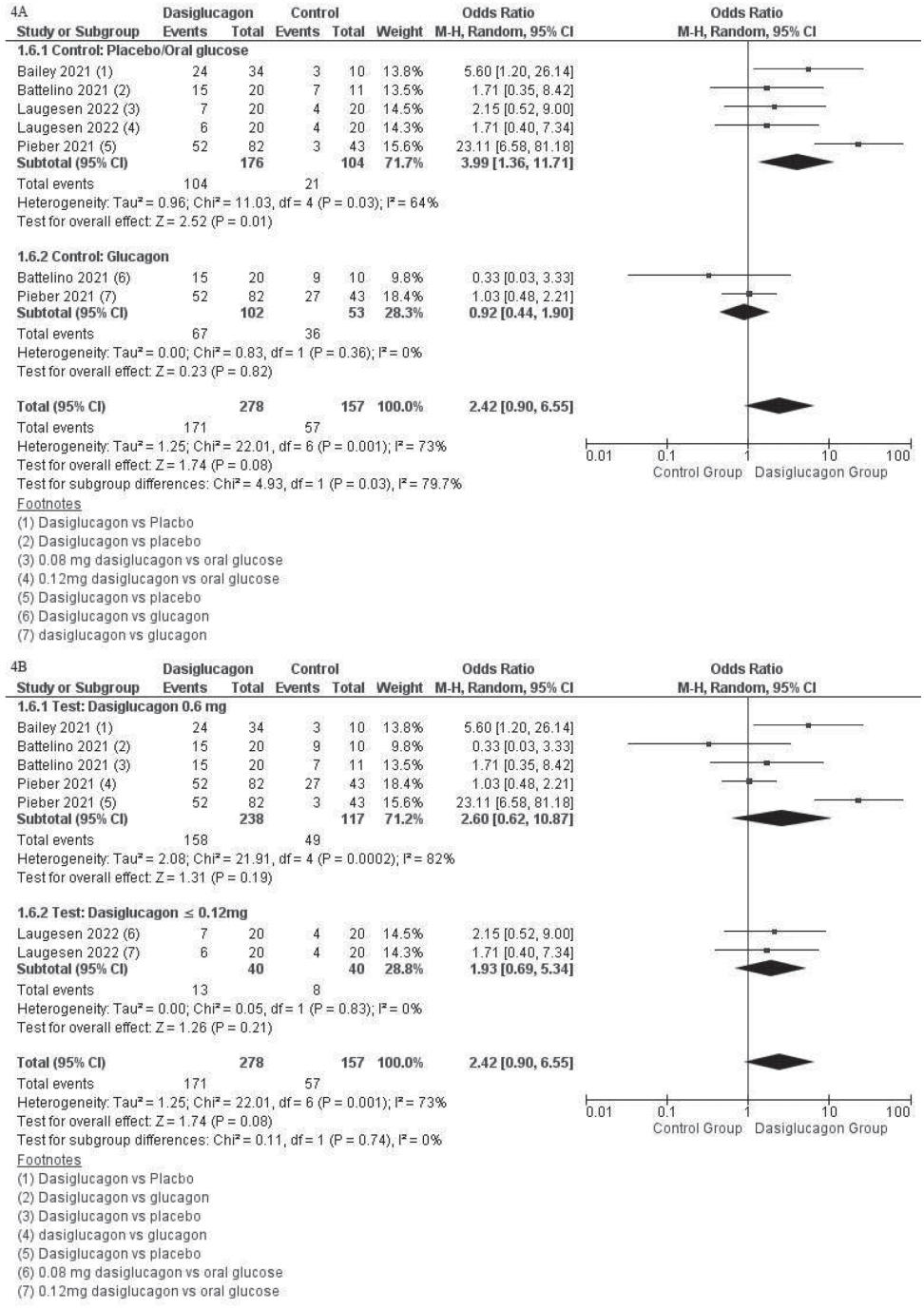

FIG. 4. Forest plot for the included studies pooled together using a random-effects model for assessing the difference in the number of patients with treatment-emergent adverse events (TEAEs). (4a) Results of subgroup analysis based on different comparator groups; (4b) Results of the subgroup analysis based on the dose of dasiglucagon.
Included studies are identified by first author and year. The boxes are proportional to the weight of each study in the analysis, and the lines represent their 95% confidence intervals (CIs). The diamond represents the pooled effect size, and its width represents its 95% CI.

DISCUSSION

The results of this meta-analysis revealed that a single subcutaneous injection of dasiglucagon (0.08-0.6 mg) can increase plasma glucose significantly earlier compared to oral glucose or placebo; however, there was no statistically significant difference in the time taken for plasma glucose recovery compared to conventional glucagon therapy. Similarly, no significant difference was found in the number of patients who recovered at 10, 20, and 30 minutes post-intervention between the conventional glucagon and the dasiglucagon group. However, the frequency of TEAEs was higher

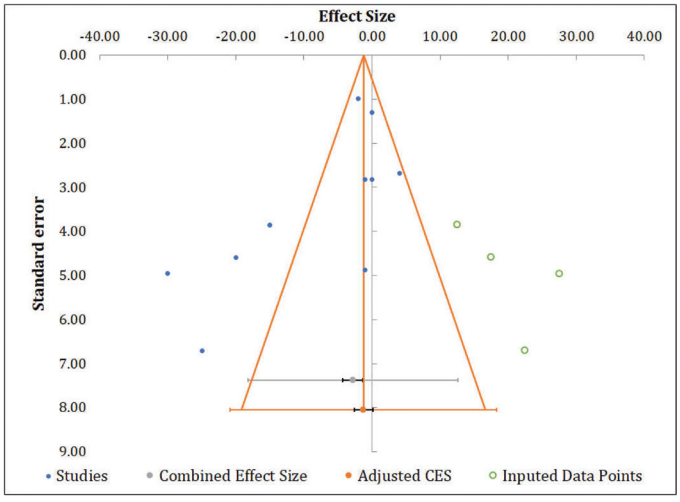

FIG. 5. Funnel plot (after trim and fill analysis) for publication bias in the included studies. The effect size denotes the difference in the time taken for recovery of plasma glucose levels to ≥ 20 mg/dl.
CES, Combined Effect Size.

in the dasiglucagon group when compared to oral glucose and placebo, but no significant difference was found between glucagon and dasiglucagon group. In both the glucagon and dasiglucagon groups, nausea, vomiting, and headache were the most common TEAEs. Lastly, there was no dose dependence for TEAEs. This meta-analysis pooled the effects of all studies and also conducted a subgroup analysis for different comparators, which shows that dasiglucagon and glucagon have almost similar efficacy in the case of plasma glucose recovery time.

Bailey et al.[28] used a placebo as a comparator and found dasiglucagon to be more effective in recovery from hypoglycemic episodes. Similarly, Laugesen et al.[19] reported a very high efficacy of dasiglucagon as compared to oral glucose. Pieber et al.[15] and Battelino et al.[18] used both placebo and glucagon as comparators, while Hövelmann et al.[16] used glucagon as a comparator arm against four different doses of dasiglucagon. These three studies concluded that dasiglucagon had a similar efficacy and safety profile as that of glucagon. Since standard therapy is available, it is always better to conduct active-controlled studies than placebo-controlled studies to assess the safety and efficacy of a drug. Hence, we conducted a subgroup analysis based on the comparator used, in which dasiglucagon was not found to be superior to conventional glucagon. Four studies dealt with adult T1DM patients; only one study conducted by Battelino et al. involved children and adolescents (aged 6-17 years). However, no clinically relevant differences were found in the time to recovery of plasma glucose with respect to the age of the patients.

The main limitation of this meta-analysis was the inclusion of only five randomized controlled trials. Most of the studies presented data in median values with 95% CI (not the interquartile range or range); therefore, means could not be calculated, and the median value was used instead of the mean. Regarding the analysis of the number of patients with TEAE, we could not include the study done by Hövelmann et al., as they had reported the total number of TEAEs and not the number or proportion of patients who experienced TEAE. Finally, although the trim and fill method was used to correct the asymmetry in publication bias, heterogeneity between the studies may affect the results of the trim and fill analysis.

In conclusion, dasiglucagon is safe and effective for the treatment of insulin-induced hypoglycemia in T1DM patients compared to placebo or oral glucose; however, it is not superior to conventional glucagon. Like glucagon, dasiglucagon use is often accompanied by nausea and vomiting. Nevertheless, it offers better stability and other pharmaceutical advantages; therefore, it is a promising option for managing insulin-induced hypoglycemia in emergencies. Further active-controlled noninferiority clinical trials are warranted to compare glucagon and dasiglucagon in the treatment of insulin-induced hypoglycemia in T1DM patients and translate its use in clinical practice.

Ethics Committee Approval: All India Institute of Medical Sciences, Bhubaneswar Institutional Ethics Committee (T/IM-NF/Pharm/22/01 dated: 13.04.2022).

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- S.M., R.R.M.; Design- S.M., R.R.M.; Data Collection or Processing- S.M., R.R.M., R.M.; Analysis or Interpretation- S.M.; Literature Search- S.M., R.M.; Writing- S.M., R.R.M.

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Supplementary: http://balkanmedicaljournal.org/uploads/pdf/2023-7-84-supplemantry.pdf

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