REVIEW

Co-administrating subcutaneous insulin glargine in the management of diabetic ketoacidosis: a systematic review and meta-analysis

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ABSTRACT

Background and Objective: Diabetic ketoacidosis (DKA) is a serious and increasingly common complication of diabetes with high morbidity and mortality. Early use of long-acting basal insulin alongside IV insulin may improve outcomes. This systematic review and meta-analysis aim to evaluate the efficacy and safety of co-administering insulin glargine with IV insulin in DKA management.

Methods: A literature search was conducted to identify relevant studies. Key outcomes included time to DKA resolution, hospital stay length, and hypoglycemia risk. RCT quality was assessed using the Cochrane risk of bias tool, and retrospective studies with the Newcastle–Ottawa Scale. Standardized mean differences with 95% CIs were used for continuous outcomes, and risk ratios for dichotomous outcomes. A random-effects model was applied using RevMan (version 5.4).

Results: A total of six studies were included in this meta-analysis comprising of a cumulative sample size of 302 patients with 127 in the intervention group and 175 in the control group, the pooled results showed that co-administration of insulin glargine resulted in significantly reduced time to DKA resolution, along with decreased length of hospital stay as compared to the group receiving IV infusion alone, while the rate of hypoglycemia and hypokalemia were comparable between the two groups.

Conclusion: When treating DKA, a combination of IV insulin infusion and long-acting basal insulin glargine may shorten hospital stays and speed up the time to resolution without increasing the risk of hypoglycemia or hypokalemia.

Keywords: Diabetes Mellitus, Diabetic ketoacidosis, Insulin glargine, IV insulin infusion, Meta-analysis.

Introduction

Diabetic ketoacidosis (DKA) is a very serious, acute, life-threatening complication in people suffering from diabetes and is a leading cause of morbidity and mortality in patients presenting in the emergency department. Insulin dose omission, infections, stroke, or Myocardial infarction and trauma are some of the risk factors [1,2]. Recently, there has been a global increase in the presentation of DKA worldwide, varying between countries such as Taiwan (65%), Romania (67%), Saudia Arabia (44.9%), and UAE (80%) have the highest rates of DKA episodes in patients diagnosed with type 1 diabetes [3]. Moreover, it is estimated that approximately 220,340 individuals are diagnosed with DKA each year in the United States, with a higher incidence among ages 1-17 [4]. In individuals younger than 24 years suffering from diabetes, DKA as a cause accounts for 50% of mortality. Especially, in individuals younger than 24

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years suffering from diabetes, DKA as a cause accounts for 50% of mortality [5].

Importantly, however, DKA is not only associated with type 1 diabetes but also type 2 diabetes; as a matter of fact, one third of patients presenting with DKA have type 2 diabetes [6]. The criteria to diagnose DKA according to the American diabetes association are a plasma glucose level > 250 mg/dL, increased serum ketone levels, a pH < 7.3, and a bicarbonate level < 18 mEq/L [5]. In addition, alongside the health factor, DKA also has a very costly impact on the financial situation for families as an average cost for a DKA hospitalization is around 30,836.19 as of 2017, with a mean hospital stay of atleast 3.22 days [4].

The treatment of DKA involves initially administering fluids and insulin intravenously (IV). Following this initial phase, patients are gradually switched to subcutaneous (SC) insulin. This transition from IV to SC insulin can increase the likelihood of rebound hyperglycemia, hypoglycemia, or electrolyte imbalances [7]. The IV analogs usually used have a half-life of less than 10 minutes [8]; thus, according to the American Diabetes Association (ADA) [9], an appropriate administration of SC insulin is necessary 15 to 120 minutes before stopping the IV infusion. However, a key point of consideration is that the quantity of SC insulin after transitioning is contingent upon the requirement of the IV insulin employed a day before [7] which, as pointed out by a previously published systematic review and meta-analysis evaluating the efficacy of co-administration versus IV infusion, is erroneous. Insulin Glargine, a commonly used SC insulin, provides a constant plateau in serum levels for over 24 hours. As pointed out by a recent clinical trial, administering SC basal insulin at a designated time, concurrently with intravenous insulin, would facilitate an efficient transition to a SC insulin regimen followed at home after the resolution of diabetic ketoacidosis DKA [8].

Since, the last published meta-analysis [10] only included four studies on this topic, newer original studies have been published, thus, we decided to evaluate the efficacy of co-administration of basal insulin SC compared to IV infusion alone on the management of DKA patients including both children and the adult population with the latest data, analyzing through a robust updated systematic review and meta-analysis focusing on the primary outcomes of DKA resolution, length of hospital stay and incidence of hypoglycemia.

Methods

Data sources and search

This study followed the 2020 PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [11].

A comprehensive literature search was conducted in the PubMed, Clinicaltrials.gov, and Cochrane Library databases till April 2024 to identify relevant studies. The following medical subject heading (MeSH) terms and keywords were used for the database searches: “diabetic ketoacidosis”, “insulin glargine”, “co-administration”, and “basal insulin”. Every study was thoroughly examined, including the titles, abstracts, and full contents. In addition, the reference lists of relevant literature were examined to find possible suitable research. No restrictions were placed on the studies based on publishing language, nation, or race. To find any other pertinent studies, the reference lists of relevant main studies and review articles were also carefully examined.

Inclusion and exclusion criteria

The inclusion criteria for eligibility were as follows: (a) double-arm studies, (b) studies involving co-administration of insulin glargine with IV insulin compared to IV insulin infusion alone in the management of DKA, (c) children or adult population, and (d) outcomes of interest included time to DKA resolution, length of hospital stay, hypoglycemia, and hypokalemia. The exclusion criteria included: (a) studies with unavailable results, (b) studies involving co-administration of insulin glargine but focusing on early versus delayed administration, (c) single-arm studies, and (d) review articles, nonhuman studies, case reports, case series, editorials, abstracts, reviews, comments, and letters, expert opinions, studies without original data, and duplicate publications.

Data extraction

Two investigators independently extracted the following information from each included study: study characteristics (first author, year of publication, country, sample size, and study type), participant baseline characteristics, time to DKA resolution, length of hospital stay, hypoglycemia, and hypokalemia. Any discrepancy between data extractions was resolved by discussion or by consulting with the third author.

Quality assessment

The included randomized controlled trials (RCTs) were evaluated for quality using the Cochrane Risk of Bias assessment tool (ROB2) [12]. Six components were assessed: [1] random sequence generation, [2] allocation concealment, [3] blinding of participants and personnel, [4] incomplete outcome data, [5] selective reporting, and [6] other bias. According to whether the included studies fully meet the above criteria, we assessed the quality of trials. The Newcastle–Ottawa Scale (NOS) [13] (range: 0–9 stars) was used to rate the methodological excellence of the only included retrospective study. Three categories, namely, selection, comparability, and outcome, were used to grade the studies. A total of ≥5 stars showed that the quality was relatively high. All items were independently assessed by two investigators, with consensus reached after deliberation or consultation with another author.

Statistical analysis

Statistical analyses were conducted using RevMan [version 5.4; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014]. The standard mean difference (SMD) along with 95% confidence intervals (CIs) was computed for continuous variables based on pooled effects. Risk ratios (RR) were calculated for dichotomous outcomes.

To evaluate potential statistical heterogeneity across trials, Higgins I2 statistics and Cochrane's Q test were utilized [14]. Initially, the meta-analysis was performed using fixed-effect modeling, followed by a repetition of the analysis using random-effects methods after assessing heterogeneity with fixed modeling. Consequently, all values reported in the analysis stem from random-effect modeling. Heterogeneity among trials was assessed using I2 statistics, where values below 40% were considered insignificant, 30 to 60% indicated moderate heterogeneity, 50 to 90% represented high heterogeneity, and values exceeding 75% denoted substantial heterogeneity. Subgroup analysis or sensitivity analysis was employed to identify sources of high heterogeneity. The meta-analysis results were visually inspected using a forest plot. Publication bias was not tested as the number of studies did not exceed the criteria of 10. A p-value< 0.05 was regarded as statistically significant.

Results

Literature search and study characteristics:

Three electronic databases were searched thoroughly up until May 1st 2024, which yielded a total of 155 articles, out of which 15 duplicates were removed, which left us with 140 articles, which after abstract and full text screening, resulted into 6 articles [15-20] that were included in this meta-analysis. The detailed Prisma flowchart is shown in Figure 1.

A summary of excluded studies and their reasoning for exclusion is shown in Supplementary Table 1.

The baseline characteristics of the included trials are shown in Table 1. The pooled population in the glargine co-administration group was 127, while 175 patients were in the control group. Participants received treatment and follow-up exclusively during their hospitalization period. Five out of six studies were clinical trials, while one was a retrospective study [19]; furthermore, all studies had an open-label study design.

Quality assessment and publication bias

We evaluated the quality of the five RCTs using the Cochrane risk of bias tool. Overall, all the studies were deemed to be of moderate to low quality with unclear to high risk of bias across all 6 assessment criteria. A detailed evaluation is presented in Supplementary Table 2. The

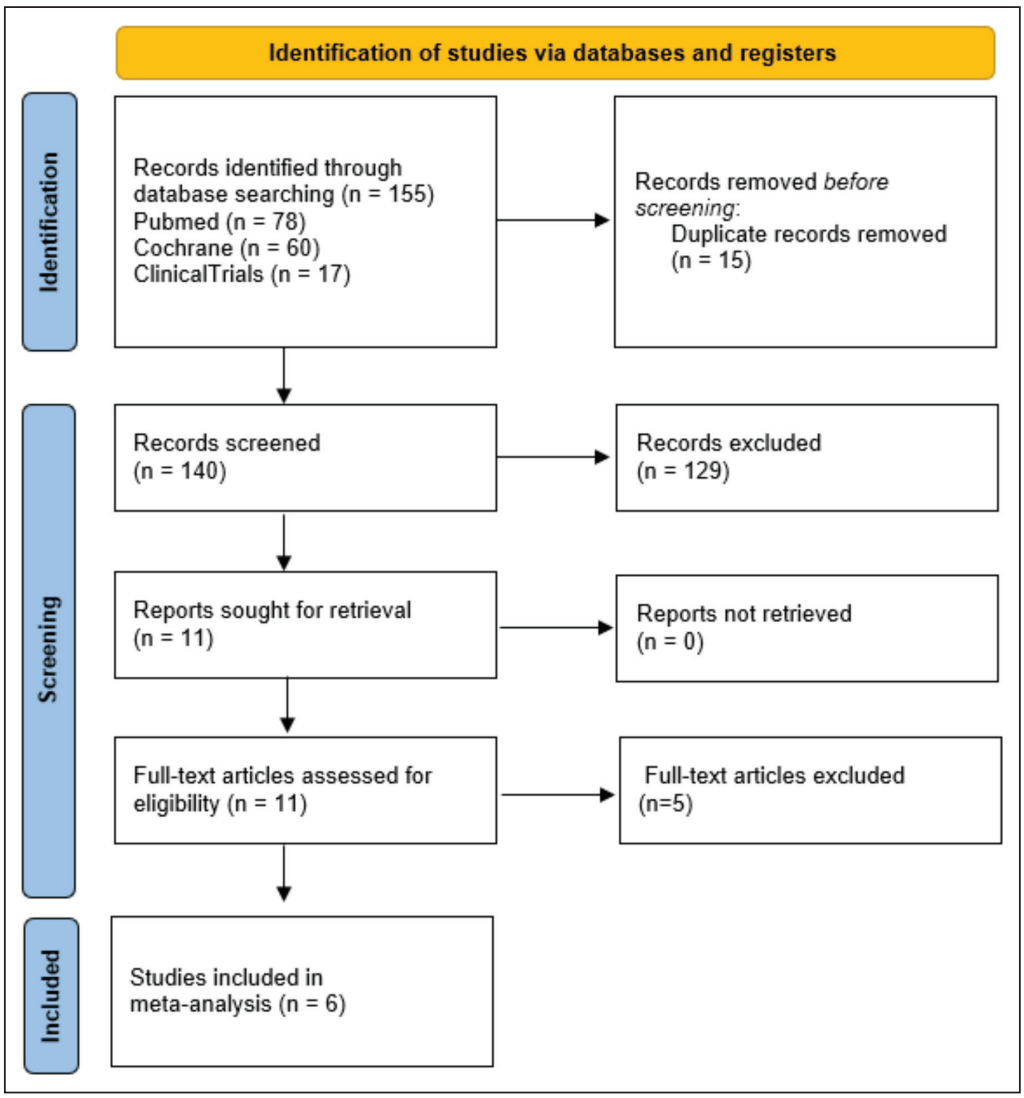

Figure 1. *Prisma flow diagram.*

Table 1. *Study characteristics of the included studies.*

First Author and Study Year	Study location	Study Design	Groups	No. of Participants (n)	Sex	Age (Years) Mean ± SD/ Median (IQR)	HbA1c (%) Mean ± SD	Glucose (mg/dL) Mean ± SD/ Median (IQR)	Bicarbonate (mg/dl)	pH Mean ± SD/ Median (IQR)	Anion gap Mean ± SD/ Median (IQR)
Thammakosol 2023	Thailand	Single-Centre, Open-Label, Randomized Controlled Trial	Glargine	n=30	M = 13 F = 17	54.2 ± 14.3	12.77 ± 2.72	601.5 ± 210.2	10.3 ± 5.1	7.20 ± 0.15	26.2 ± 5.6
			Control	n=30	M = 11 F = 19	58.2 ± 18.5	11.54 ± 3.64	554.6 ± 193.5	12.8 ± 5.2	7.31 ± 0.16	24.0 ± 5.6
Doshi 2015	USA	Prospective Randomized Trial	Glargine	20	M = 14 F = 6	38.5 (31.5–45.5)	NA	640.5 (476.0–700.0)	12.5 (8.0, 14.5)	7.2 (7.1–7.3)	18.5 (17.5–26.0)
			Control	20	M = 10 F = 10	41.5 (29.0–50.5)	NA	542.0 (426.0–676.0)	13.0 (8.5–14.0)	7.1 (7.1–7.3)	19.5 (17.5–21.5)
Houshyar 2015	Iran	Randomized Clinical Trial	Glargine	20	M = 9 F = 11	29.65±13.60	12.31 ± 2.40	30±11.6	6.51±3.34	7.09±0.15	NA
			Control	20	M = 9 F = 11	29.25±15.69	12.78 ± 2.41	27.63±5.7	6.37±3.49	7.09±0.14	NA
Hsia 2012	USA	Prospective Randomized Trial	Glargine	30	M = 18 F = 12	42.7±15.5	9.7 ± 2.7	NA	NA	NA	NA
			Control	31	M = 20 F = 11	43.4 ± 15.4	10.1 ± 2.7	NA	NA	NA	NA
Assaad-Khalil 2011	Egypt	Randomized Prospective Pilot Study	Glargine	15	NA	20.1 ± 4.9	41.1 + 5.7	634.4 ± 106	6.3 ± 3.3	7.12 ± 0.10	41.1 ± 5.7
			Control	15	NA	21.2 ± 4.4	40.9 ±9.1	626.2 ± 212	7.1 ± 3	7.13 ± 0.11	40.9 ± 9.1
Shanker 2007	USA	Retrospective Study	Glargine	12	M = 7 F = 5	13.3 ± 3.5	NA	590 ± 263	NA	7.11 ± 0.09	NA
			Control	59	M = 19 F = 40	12.5 ± 2.7	NA	583 ± 262	NA	7.07 ± 0.11	NA

quality assessment of the only non RCT study was done via the Newcastle Ottawa scale shown in Supplementary Table 3. We did not conduct a publication bias assessment since the total number of included studies is less than the required criteria of 10.

Time to DKA resolution

All the included studies except Hsia et al. [15] reported this outcome. The pooled result found that co-administration of insulin glargine was significantly better than standard IV insulin infusion in the hours it took to DKA resolution [MD: -4.17, 95% CI: (-6.16 to -2.17); p= 0.03, I2= 64%], Figure 2.

Hospital length of stay

Four of the included studies analyzed this outcome [16,17,19,20]. The meta-analysis based on the random-effects model demonstrated that SC glargine co-administration resulted in significantly lesser length of hospital stay than the participant group who received IV insulin infusion alone [MD: -1.15, 95% CI: (-2. 60 to –0.30); p= 0.02, I2= 69%], Figure 3.

Hypoglycemia

All studies reported incidences of hypoglycemia incurred due to insulin administration during the duration of admission except the study by Shanker et al. [19]. After applying the random effects model, the analysis deemed the risk ratio between the two groups to be insignificant [RR: 1.05, 95% CI: (0.51 to 2.19); p= 0.76, I2= 0%], Figure 4.

Hypokalemia

Only two studies reported this outcome [16,20]. The pooled result showed no significant difference in terms of incidence of hypokalemia between the two groups [RR: 1.51, 95% CI: (0.49 to 4.70); p= 0.16, I2= 49%], Figure 5.

Discussion

This updated systematic review and meta-analysis evaluated the effectiveness of SC basal insulin glargine co-administration with IV insulin in the management of both children and adults presenting to the emergency department with DKA, according to the pooled results, the glargine co-administration resulted in significantly faster DKA resolution, and a significantly shorter length of hospital stay, furthermore, both the intervention and control groups were associated with similar rates of hypoglycemia and hypokalemia.

The effectiveness of adding SC glargine to the standard IV infusion in reducing time to DKA resolution could be explained by the associated pharmacokinetics of insulin glargine, its ability to provide a peak free basal insulin coverage for up to 24 hours not only decreases the requirement and the duration of IV insulin infusion but also helps in a smoother transition from continuous infusion to maintenance therapy [10,15,20]. The results from our study further confirm the results from the only previously published meta-analysis [10] on this topic except, regarding the outcome of the duration of hospital stay, which in our study is found to be significantly shorter with the co-administration of SC insulin, which is in congruence with the lesser time taken to DKA

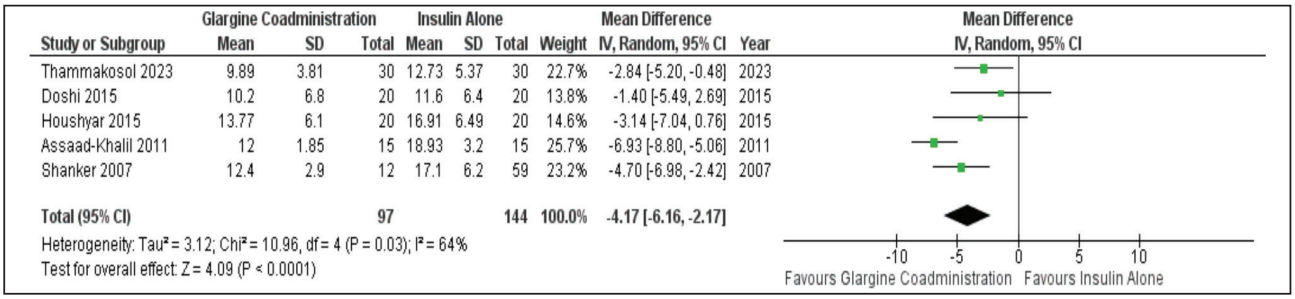

Figure 2. *Forest plot for Time to DKA resolution.*

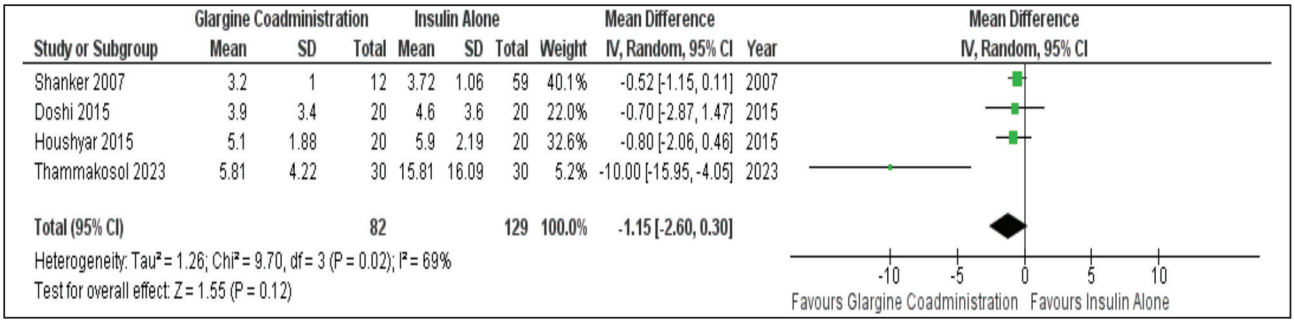

Figure 3. *Forest plot for Length of hospital stay.*

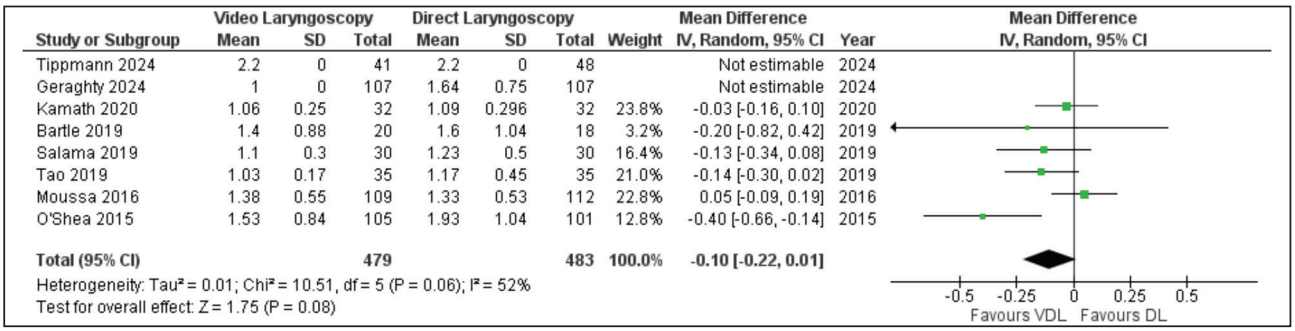

Figure 4. *Forest plot for risk of hypoglycemia.*

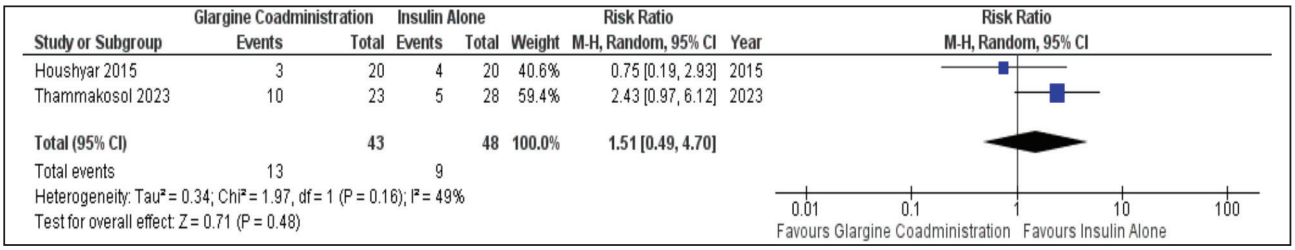

Figure 5. *Forest plot for risk of hypokalemia.*

resolution. The associated moderate to high heterogeneity in the results could be explained by the lesser number of included studies and smaller sample sizes, along with the different study designs; hence, more powered studies need to be conducted to further confirm our results. Subgroup analysis to find out the cause of heterogeneity was not possible due to incomplete data.

Moreover, the misconception behind the unsatisfactory systemic absorption of insulin administered via the subcutaneous route in patients with DKA due to the state of shock and dehydration has been removed by a number of recent trials demonstrating the opposite [10,20].

The effect of co-administration on the phenomenon of rebound hyperglycemia was reported by only three of the included studies [15,16,20], two of which showed significant reduction in rebound hyperglycemia with insulin glargine [15,16], interestingly, this effect is not only limited to patients with DKA; another study [21] conducted focusing on non-DKA hyperglycemic patient management demonstrated significantly less rebound hyperglycemia with co-administration of basal insulin analogues (glargine, detemir, degludec), without increased rates of hypoglycemia. However, the most recent study by Thammakosol et al. [20] did not find a significant difference in terms of rebound hyperglycemia, which they reported could be due to a smaller sample size; hence, more such studies need to be conducted to form a consensus regarding this effect.

The rates of hypoglycemia and hypokalemia were found to be similar between the two groups in our study; however, the smaller number of studies reporting on this complication associated with the management of DKA and the smaller sample sizes need further confirmation by newer, robust studies with larger populations.

Limitations

Our study has a few limitations that need to be addressed. First, the quality of the included studies was questionable as all the studies were deemed to be of unclear to high risk, and all the studies were open label in design, which confers biasness to the observed results. Furthermore, significant heterogeneity came across in the pooled results of the outcomes of Time to DKA resolution, length of hospital stays, and incidence of hypokalemia. This variability between studies could be due to several factors, such as the diverse age population, including children to adults, the variation in study designs, and patients with varied severity of DKA across studies. Subgroup analysis to find out the cause of this heterogeneity was not possible due to a lack of substantial data. Lastly, this meta-analysis consists of very few studies with small sample sizes; hence, it is necessary to conduct large-scale trials with sufficient statistical power.

Conclusion

Initiating a combination of long-acting basal insulin glargine with IV insulin infusion in the management of DKA may result in quicker resolution of DKA and shorter length of hospital stay, without elevating the risks of hypoglycemia and hypokalemia. This approach could also potentially alleviate the economic strain associated with hospitalization for DKA. Therefore, early subcutaneous administration of insulin glargine in DKA management warrants consideration.

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Ethical Approval and consent to participate
This study did not require ethical approval or participant consent, as it does not involve human subjects or identifiable data.

Consent to Publication
Not applicable, as no individual data requiring consent for publication were included.

Data Availability statement
All data underpinning the findings presented in this manuscript are provided within the main text or accompanying supplementary files.

Conflict of interest
The authors affirm that they have no financial interests or personal affiliations that could be perceived as potential conflicts or as having influenced the conduct or reporting of this research.

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Author Contribution
Each author has made substantial intellectual and practical contributions to the research, including conceptualization, study design, data collection, analysis, and interpretation. All authors were involved in manuscript preparation, critical revisions, and approved the final version for submission. Furthermore, all authors consent to the chosen journal and accept full responsibility for the integrity of the work.

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Supplementary content (If any) is available online.

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