Two-bag Versus One-bag Method for Adult and Pediatric Diabetic Ketoacidosis Management

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Study objective: We conducted a systematic review and meta-analysis to evaluate the safety and efficacy of the two-bag versus one-bag method in diabetic ketoacidosis (DKA) management in adult and pediatric populations.

Methods: The study was registered with the Prospective Register of Systematic Reviews, in adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A search was conducted across MEDLINE, EMBASE, and CENTRAL databases up to March 2025, with no restrictions on study design. Two reviewers independently assessed studies for bias using Cochrane Risk of Bias 2 (RoB2) tool and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I), extracted data, and synthesized findings using RevMan software. The Grading of Recommendations, Assessment, Development, and Evaluations tool was used to assess certainty of evidence. Main outcomes of interest were incidence of hypoglycemia and time to DKA resolution.

Results: Of 4,190 studies screened, 21 met inclusion criteria. These included 9 adult studies with 3,329 patient visits and 12 pediatric studies with 1,385 visits. Of these, one study was at critical risk of bias and was removed from meta-analysis. In both adult and pediatric populations, the two-bag method was associated with reduced incidence of hypoglycemia (risk ratio: 0.50, 95% confidence interval [CI] 0.41 to 0.59; I^2=51.8%) and time to DKA resolution (MD: −1.76 hours; 95% CI −2.80 to −0.71; I^2=61%). In adults only, the two-bag method was associated with a shortened duration of insulin infusion (MD: −3.74 hours, 95% CI −4.96 to −2.52; I^2=0%) and reduced incidence of hypokalemia (risk ratio: 0.84, 95% CI 0.76 to 0.93; I^2=47%).

Conclusion: The two-bag method is associated with reduced incidence of hypoglycemia and time to DKA resolution in both adult and pediatric populations. [Ann Emerg Med. 2026;87:346-364.]

Please see page 347 for the Editor's Capsule Summary of this article.

Keywords: Diabetic ketoacidosis, Hypoglycemia, One-bag method, Two-bag method.

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INTRODUCTION

Background

Diabetic ketoacidosis (DKA) is a critical, life-threatening condition frequently encountered in emergency departments and is a common cause of morbidity in patients living with diabetes mellitus.[1,2] This disease accounts for more than 500,000 hospital days per year, and as of 2017, the health care cost of treating DKA was $6.76 billion USD.[3-5]

The conventional one-bag method for DKA management uses an insulin infusion with a single electrolyte-containing intravenous fluid, later replaced with dextrose when glucose approaches normal levels, usually below 13.9 mmol/L.[1] Conversely, the two-bag method uses 2 fluid bags at onset of treatment, one with and one without dextrose, infused through a single line.[5] As blood glucose drops, the dextrose bag's rate increases, offering finer control over glucose and electrolytes, potentially enhancing quality of care, efficiency, and cost-effectiveness.[6]

Importance

Although promising, the safety and efficacy of this newer method in adult and pediatric populations require further investigation. Existing studies demonstrate conflicting results with respect to time to resolution of acidosis, incidence of hypoglycemia, and hypokalemia.[7-14] Review of the literature has revealed only a single meta-analysis on the efficacy and safety of the two-bag versus the one-bag method and was performed on pediatric and

Editor's Capsule Summary

What is already known on this topic

Both one-bag (a single nonglucose solution) and two-bag (one solution with and another without glucose) methods are initially used for emergency department management of diabetic keotacidosis (DKA).

What question this study addressed

Which method achieves the least later hypoglycemia and the quicker time to DKA resolution?

What this study adds to our knowledge

This systematic review and meta-analysis including 21 studies (4,714 patient visits) noted the two-bag method reports had a lower incidence of hypoglycemia and shorter time to DKA resolution than the one-bag method in adults and children.

How this is relevant to clinical practice

The two-bag method may allow faster and safer treatment but requires a confirmatory trial.

adolescent patients.[15] This is the first meta-analysis encompassing pediatric and adult patients.

Goals of This Investigation

The primary objective of this systematic review and meta-analysis was to investigate time to DKA resolution and incidence of hypoglycemia with use of the two-bag method compared to the one-bag method.

MATERIALS AND METHODS

Study Design

This was a systematic review and meta-analysis undertaken to investigate the safety and efficacy of using a two-bag fluid method to treat DKA in both adults (age $\geq$18 years) and pediatric patients (age $<$ 18 years), compared to the one-bag method. The protocol was registered on the Prospective Register of Systematic Reviews website (CRD42024541648) and adhered to the latest Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[16]

Study Eligibility Criteria and Definitions

Studies that were eligible included randomized controlled trials, case control studies, retrospective and prospective cohort studies, case reports, manuscript preprints, and conference abstracts.

We included any study investigating the safety and efficacy of the two-bag method in patients of any age in whom DKA was diagnosed in a hospital setting. Two-bag method was defined as the usage of insulin infusion alongside 2 bags of intravenous fluids with identical or similar electrolyte but differing dextrose concentrations in the treatment of DKA.[6] Concurrently, insulin infusion with the usage of a single bag of intravenous fluid with electrolytes was designated as a one-bag method.[6] Studies without a comparator group were excluded.

Each study included in our analysis required the diagnosis of DKA in all patients included, using that study's own diagnostic criteria.

Search Strategy

A comprehensive search of MEDLINE, EMBASE, and CENTRAL (through Ovid) was conducted for non-animal, English-language studies from inception to March 2025. An experienced clinical librarian (AI) developed the strategy using synonym-based queries, database-specific subject headings (eg, MeSH in MEDLINE and EMTree in EMBASE), and relevant keywords accounting for alternative spellings. Key topics included diabetic ketoacidosis, fluid/insulin therapy, and emergency or intensive care settings. Previously known studies helped refine the strategy. Results were exported to Covidence, which removed duplicates. Full details appear in Appendix E1 (available at http://www.annemergmed.com).

Study Selection Process and Data Collection

Two reviewers, AS and ARS, independently screened all titles and abstracts using Covidence. Potentially eligible studies were reviewed in full text, with discrepancies resolved through discussion or, if needed, with JWY. AS and ARS independently extracted data, including study location, design, patient characteristics, and interventions.

Authors were contacted for incomplete data, such as missing error measurements, qualitative summaries of quantitative data, or original values needed to assess skew before converting medians to means (Table 1).[8,10-13,17-22] Data were excluded from meta-analysis if the requested information was not obtained.

Risk of Bias Assessment and Sensitivity Analysis

Two reviewers independently conducted risk of bias assessment, resolving disagreements through discussion to reach consensus. The Cochrane the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool was used to assess risk of bias in nonrandomized trials, and the Cochrane Risk of Bias 2 (RoB2) tool for

Table 1. Authors contacted for clarification on methodology for risk of bias analysis, data collection, and individual data points.

Study ID	Reason For Contacting
Adams et al[17] (2024)	Clarification on methodology and data
Besli et al[18] (2024)	Providing mean (standard deviation) than median (quartile measures)
Castro et al[19] (2019)	Clarification on methodology and data
Cho et al[10] (2018)	Clarification on methodology
Haas et al[8] (2023)	Clarification on methodology
Hasan et al[20] (2021)	Clarification on methodology and data
Halfon et al[21] (2021)	Clarification on methodology and data
Merritt et al[22] (2021)	Clarification on methodology and data
Velasco et al[13] (2017)	Clarification on methodology and data
Veverka et al[12] (2016)	Clarification on methodology and data
Wolfgram et al[11] (2022)	Clarification on data

randomized controlled trials.[23-25] Risk of bias was deemed either "low," "moderate," "high," or "critical." Studies with critical risk were excluded from further review.[10]

Outcomes

Outcomes were defined a priori. The primary outcomes were the incidence of hypoglycemia, and the time to resolution of DKA. The incidence of hypoglycemia was defined as blood glucose less than 70 mg/dL (3.89 mmol/L), consistent with the definition by the American Diabetes Association.[26] Due to inconsistent definitions of time to DKA resolution between studies, we used the American Diabetes Association's definition of DKA when possible (defined as plasma glucose >200 mg/dL (11.1 mmol/L) or history of diabetes, β-hydroxybutyrate concentration >3.0 mmol/L, pH less than 7.3 and/or bicarbonate concentration less than 18 mmol/L in adults, and bicarbonate concentration less than 15 mmol/L in pediatrics), and reported the time to resolution of these variables.[5] When we could not use this definition in its entirety, we separately reported individual variables proxies for the time to DKA resolution, including time to bicarbonate >18 mmol/L in adults or 15 mmol/L in pediatrics, pH >7.3, or time to β-hydroxybutyrate normalization. These values were also reported individually. Time to anion gap closure was reported separately, but not as a proxy for time to resolution of DKA given its exclusion from the American Diabetes Association definition. Meta-regression was performed to identify if differing proxies contributed to heterogeneity.

Additional outcomes included duration of insulin infusion, incidence of hypokalemia (potassium less than 3.3 mmol/L), hospital length of stay (days), intravenous fluid bags used, time to first long-acting insulin (hours), incidence of cerebral edema (as defined by each individual study), hospital mortality and hospital charges (USD).

Effect Measures and Statistical Analysis

For continuous pooled data, the mean difference (MD) for each study was calculated, followed by an inverse variance and random-effects meta-analysis, where applicable, to estimate the overall intervention effect. When studies presented continuous data as median and interquartile ranges (IQR), these values were converted to means and standard deviations using the methods described by Wan et al[27] to effectively pool data for meta-analysis.[28]

For pooling of categoric data, the risk ratio (RR) for each study was calculated and reported with confidence intervals (CIs). This was followed by analysis using the Mantel–Haenszel method, a fixed-effects model, employed to calculate an overall effect.[29]

Data analysis was conducted using Cochrane RevMan software (Review Manager [RevMan], The Cochrane Collaboration, 2022, Copenhagen, Denmark).

When data were not appropriate for meta-analysis as per Cochrane guidelines, narrative synthesis was performed.[29]

Subgroup Analysis

We planned for 2 subgroup analyses: (1) age (adults ≥18 years) and pediatrics (less than 18 years) and (2) DKA severity (mild [pH: 7.25-7.30], moderate [pH: 7.00-7.24], and severe [pH less than 7.00]).

Strategy for Heterogeneity and Sensitivity Analysis

Pooled data for each outcome underwent a χ^2 test (with p less than 0.10 indicating significance) and an I^2 statistic was calculated. As per Cochrane guidelines, an I^2 statistic of 0% to 40% was classified as negligible, 30% to 60% as "potentially moderate," 50% to 90% as "potentially substantial," and more than or equal to 75% as considerable heterogeneity.[29] Visual inspection of forest plots was also used to determine heterogeneity.[29,30] A random-effects model was applied to address both statistical and visual heterogeneity, following Cochrane guidelines.[29]

Publication Bias

Publication bias was assessed using generation of funnel plots with Egger's test when outcomes included more than 10 studies. For outcomes with fewer than 10 studies, visual inspection of funnel plot symmetry was used.

Certainty Assessment

The certainty of the evidence obtained in this meta-analysis was assessed using the The Grading of

Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[30-32]

RESULTS

Study Selection Process and Study Characteristics

The systematic search identified a total of 4,535 studies (Figure 1). Screening of titles and abstracts led to 68 studies for full-text review, where we further excluded 47 studies due to duplication, incorrect intervention, lack of comparator group, or data reused in subsequent studies. This resulted in 21 studies included in the final review: 4 randomized controlled trials, 16 retrospective cohort studies, and one prospective, quality improvement study (Table 2).[6-14,17-22,33-38] Of these, 5 were conference abstracts, and the remaining were full-length peer-reviewed journal articles.[17,19,22,34,35] The studies included 9 on adults, and 12 on pediatric patients.[6-14,17-22,33-39] The one- and two-bag composition was largely similar between studies, with minor variations in electrolyte concentrations (Table 3). Finally, studies did not stratify outcomes based on DKA severity; therefore, that subgroup analysis was not performed.

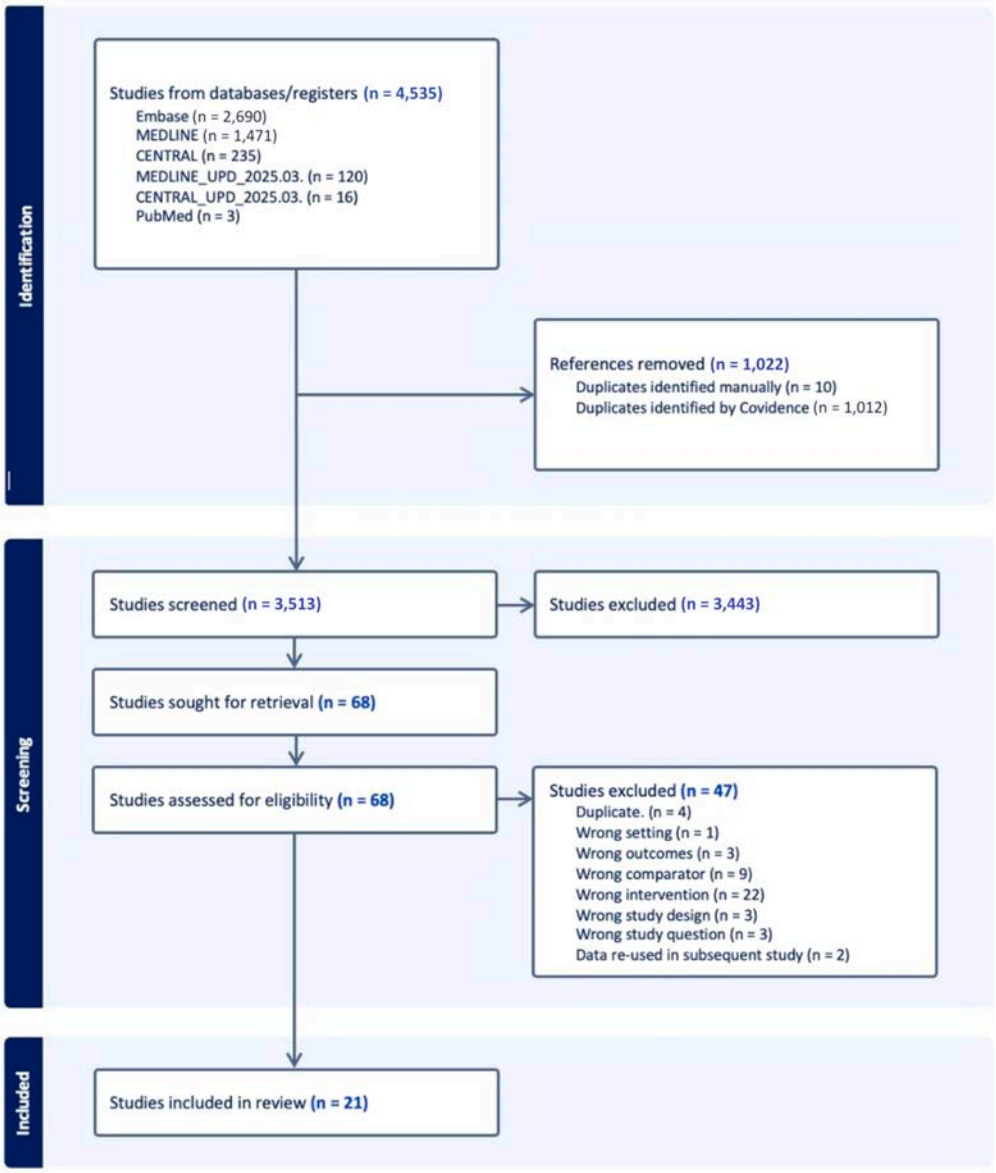

Figure 1. Systematic review flowchart.

Risk of Bias Assessment

Of the 21 studies reviewed, 4 were randomized controlled trials— 2 with a low risk of bias and 2 with an unclear risk due to limited available information (Figure 2).[14,19,33,34] Sixteen studies in this review were nonrandomized and retrospective in nature, and the one remaining was a quality improvement study (Figure 2). The retrospective studies inherently carry a high risk of bias within the domain concerning the presence of confounding variables, unless addressed with regression analysis or other statistical methods such as stratification.[8,10-12,18,21,36-38] Only 5 studies used such adjustments, yielding a moderate risk of bias for that domain.[6,7,9,13,20] Nine studies had high risk of bias, and 3 had unclear information pertaining to that domain (Figure 2).[8,10-12,17,18,21,22,35-38] Additionally, 3 studies were particularly susceptible to selection bias as their hospitals had not fully transitioned to the two-bag method, allowing physicians to choose between the one-bag and two-bag methods based on clinical judgment or available resources.[10,12,36] Of these studies, the study by Cho et al[10] showed baseline differences in the reported outcomes and had a critical risk of bias due to deviations from intended interventions, as it lacked a standardized DKA order set, leading to variations in infusion rates and fluid contents that may have influenced the final data.

Overall, most domains across the 21 studies had low risk of bias. Nine studies had at least one high-risk domain, with the large study by Cho et al[10] having 2 high-risk domains and 1 critical risk domain. Therefore, data from Cho et al[10] were removed from meta-analyses and narrative synthesis. Finally, the unclear domains were due to conference abstracts with limited information, and when authors could not be successfully contacted for clarification or further data.

Publication Bias

Egger's test showed no evidence of publication bias for hypoglycemia (Figure E1, available at http://www.annemergmed.com) or hypokalemia (Figure E2, available at http://www.annemergmed.com). Publication bias was suspected for time to DKA resolution (overall and pediatric subgroups) based on asymmetry in funnel plots (Figure E3, available at http://www.annemergmed.com). No publication bias was observed by visual inspection of the remaining outcomes (Figures E1-E4, available at http://www.annemergmed.com).

Certainty Assessment

Most of the meta-analyzed data had low to very low certainty because of the retrospective, nonrandomized design, and issues such as imprecision or inconsistency, where point estimates varied widely across studies and/or CIs showed minimal overlap (Tables 4 and 5). The only exception was the incidence of hypoglycemia in adults, which, despite most evidence coming from nonrandomized studies, was rated up to a high level of certainty due to a particularly large effect size, consistent results across studies, lack of publication bias (Figure E1) and substantial overlap in CIs indicating consistency and precision, whereas incidence of hypoglycemia in combined analysis was rated as moderate certainty given the lack of large effect size (RR less than 0.50) (Figure 3).[30,32]

Main Outcomes

Incidence of hypoglycemia. Incidence of hypoglycemia was reported in 14 studies, with 12 demonstrating an association between the two-bag method and a reduced risk of hypoglycemia.[7-9,11,13,14,17,18,20-22,35,37,38] Among 1,975 patients in the one-bag group, 473 (23.9%) experienced hypoglycemia, compared to 215 out of 2,345 patients (9.2%) in the two-bag group. This translates to the two-bag method being associated with a reduction of 50% in the incidence of hypoglycemia (RR: 0.50, 95% CI 0.41 to 0.59; I^2=51.8%) (Figure 3).

In adults, the two-bag method was associated with a 54% risk reduction in incidence of hypoglycemia (RR: 0.46, 95% CI 0.38 to 0.57; I^2=45%), and in pediatrics, a 38% reduction was observed (RR: 0.62, 95% CI 0.44 to 0.87; I^2=59%) (Figure 3).

Time to DKA resolution. Time to DKA resolution was meta-analyzed over 11 studies yielding a total of 1,640 patients in the one-bag group, and 1,646 patients in the two-bag group.[7-9,12-14,18,21,34,36,37] Pooled analysis revealed that the two-bag method was associated with a 1.76-hour reduction in time to DKA resolution compared to the one-bag method across all age groups (MD: –1.76 hours; 95% CI –2.80 to –0.71; I^2=61%) (Figure 4). Within our subgroup analysis, there was a similar statistically significant reduction in the adult population of 2.19 hours, (MD: –2.19 hours; 95% CI –3.99 to –0.40; I^2=76%) and in the pediatric population by 1.61 hours (MD: –1.61 hours; 95% CI –3.10 to –0.13; I^2=42%). Separate analysis of time to bicarbonate correction yielded no differences in the pooled analysis, but among adults, the two-bag method was associated with a shorter time to bicarbonate correction by 1.98 hours (MD: –1.98 hours; 95% CI –3.97 to –0.00; I^2=85%) (Figure E5, available at http://www.annemergmed.com). Time to pH>7.3 was only reported in 2 pediatric studies, both yielding no differences between

Table 2. Study characteristics and outcomes.

Study ID	Country	Study Design	Age Group	Primary Outcomes	Secondary Outcomes
Adams et al[17] (2024)	United States of America	Retrospective cohort study	Adults	Time to anion gap closure	Incidence of hypokalemia, hypoglycemia
Besli et al[18] (2024)	Turkey	Retrospective cohort study	Pediatric	Correction time of acidosis and ketosis, correction rates of bicarbonate and blood ketones	Duration of intravenous insulin infusion, the number of intravenous fluid bags used, hypokalemia, hypophosphatemia, hypernatremia, hyperchloremia, hyperchloremic acidosis, hypoglycemia, hypocalcemia, cerebral edema
Castro et al[19] (2019)	United States of America	Retrospective cohort study	Adults	Time to anion gap closure	N/A
Cho et al[10] (2018)	United States of America	Retrospective cohort study	Adults	Time to anion gap closure	Hospital length of stay, insulin infusion duration, time to bicarbonate >18 mmol/L
Dhochak et al[14] (2018)	India	Randomized controlled trial	Pediatric	Blood glucose variability	Incidence of cerebral edema, incidence of hypokalemia, hypoglycemia, time to acidosis resolution
Ferreira et al[34] 2014	Argentina	Randomized controlled trial	Pediatric	Time to acidosis resolution	N/A
Gilchrist et al[37] (2023)	United States of America	Retrospective cohort study	Adults	Time to anion gap closure, β-hydroxybutyrate normalization	Hospital length of stay, insulin infusion duration, incidence of hypoglycemia
Grimberg et al[6] (1999)	United States of America	Retrospective cohort study	Pediatric	Insulin infusion duration, fluid bags used, hospital charges	N/A
Haas et al[8] (2023)	United States of America	Retrospective cohort study	Adults	Time to bicarbonate >18 mmol/L	Mortality, incidence of hypokalemia, hypoglycemia, hospital length of stay, fluid bags used, insulin infusion duration
Halfon et al[21] (2021)	Unclear	Retrospective cohort study	Adults	Incidence of hypoglycemia, hyperkalemia, and hypokalemia	DKA resolution, rebound hyperglycemia, hospital length of stay
Hone et al[38] (2025)	United States of America	Retrospective cohort study	Pediatrics	Blood glucose decline	Hospital length of stay, fluid bags used, acidosis correction, DKA complications, ICU stay
Hasan et al[20] (2021)	United States of America	Retrospective cohort study	Pediatric*	Time to anion gap resolution	Hypokalemia, hypoglycemia
Merritt et al[22] (2021)	United States of America	Retrospective cohort study	Pediatric	PICU costs	Acidosis correction, insulin drip duration, hypoglycemia
Moorhouse et al[35] (2024)	United States of America	Pre-post study	Adults	Time to anion gap resolution	ICU and hospital length of stay, insulin infusion duration, time to BG $\leq$ 250 mg/dL
Munir et al[9] (2016)	United States of America	Retrospective cohort study	Adults	Time to anion gap resolution	BG<250 mg/dL, HCO_3>18 mol/L, hospital stay
Nahle et al[7] (2024)	United States of America	Retrospective cohort study	Adults	Incidence of hypoglycemia (BG<70 mg/dL)	Anion gap closure, Insulin infusion duration, HCO_3 correction, hypokalemia

Table 2. Continued.

Study ID	Country	Study Design	Age Group	Primary Outcomes	Secondary Outcomes
Poirier et al[33] (2004)	United States of America	Randomized controlled trial	Pediatric	Glucose decline rate	Bicarbonate correction, insulin therapy duration, fluid bags used, cerebral edema
So et al[37] (2009)	United States of America	Retrospective cohort study	Pediatric	Bicarbonate or glucose correction rate	Insulin infusion duration, hospital length of stay, time to pH correction, time to ketone normalization
Velasco et al[13] (2017)	United States of America	Retrospective cohort study	Pediatric*	Incidence of hypoglycemia (BG<70 mg/dL)	Bicarbonate correction >15 meq/L, pH correction >7.3, PICU discharge
Veverka et al[12] (2016)	United States of America	Retrospective cohort study	Pediatric	Time to acidosis normalization (bicarbonate>15 mmol/L)	Intravenous fluid changes, insulin therapy duration, fluid bag waste, DKA management complications
Wolfgram et al[11] (2022)	United States of America	Plan-do-study-act cycles	Pediatric	Incidence of hypoglycemia (BG<80 mg/dL)	Hospital length of stay, emergency department length of stay, time to acidosis resolution, admission rates

BG, blood glucose; *DKA*, diabetic ketoacidosis; *N/A*, not applicable; *PICU*, pediatric intensive care unit.
*Studies that defined age less than 21 years old as pediatrics.

groups.[13,36] Time to β-hydroxybutyrate normalization was reported in one adult study that showed a 10-hour reduction with usage of the two-bag method, and 2 pediatric studies which yielded no significant differences.[18,36,37] Given low number of studies and inconsistent results, both variables were not suitable for meta-analysis due to risk of poorly estimated inconsistency, heterogeneity, and potential for misleading conclusions.[29] Individual study data are summarized in Table 6.

Meta-regression to analyze the degree to which the proxy definitions contributed to heterogeneity revealed an R^2 of 39.3% (P = NS).

Time to anion gap closure was reported in 5 adult studies and 1 pediatric study, totaling 1,321 patients in the one-bag group and 623 patients in the two-bag group.[7,9,17,19,37,38] With pooled analysis, there was no difference in time to closure of anion gap between the one- and two-bag method (MD: –1.17 hours; 95% CI –2.52 to 0.18; I^2=86%) (Figure E6, available at http://www.annemergmed.com), and there was high directional heterogeneity.

Additional Outcomes

The incidence of hypokalemia in patients treated with the one-bag versus two-bag fluid method was reported in 5 adult studies and 4 pediatric studies.[7,8,12,14,17,18,21,35,38] Among 1,511 patients receiving the one-bag method, 721 cases of hypokalemia were observed (47.7%), compared to 354 cases in 1,601 patients treated with the two-bag method (22.1%), representing a 14% risk reduction with the two-bag approach (RR: 0.86; 95% CI 0.78 to 0.96; I^2=71%) (Figure 5). On subgroup analysis, this relative risk reduction only remained significant in the adult population (RR: 0.84; 95% CI 0.76 to 0.93; I^2=60%) (Figure 5). Pooled analysis for duration of insulin infusion included 3 adult studies and 5 pediatric studies, totaling 1,271 patients in the one-bag group and 1,206 in the two-bag group.[6-8,12,18,36-38] Meta-analysis of the pooled data showed a 1.81-hour decrease in duration of insulin infusion in the two-bag method (MD: –1.81; 95% CI –3.42 to –0.19; I^2=61%) (Figure 6). When stratified by age, this beneficial effect was maintained in the adult patients (MD: –3.74; 95% CI –4.96 to –2.52; I^2=0%), but not in pediatrics (MD: –1.05; 95% CI –3.03 to 0.94; I^2=60%) (Figure 6). The two-bag method was associated with a significant decrease in hospital length of stay (MD: –0.4 days; 95% CI –0.64 to –0.16; I^2=30%), with this effect maintained in the pediatric population (MD: –0.44 days; 95% CI –0.68 to –0.20; I^2=19%) but not in adults (MD: –0.19 days; 95% CI –0.79 to 0.42; I^2=51%)

Table 3. Protocol constituents per study, and number of patient visits per protocol.

Study ID	One-Bag Protocol	Two-Bag Protocol	No. of Patients in One-Bag System Cohort	No. of Patients in the Two-Bag System Cohort
Adams et al[17] (2024)	Fixed rate crystalloid fluid with no dextrose	Nondextrose+dextrose containing crystalloid	56	34
Besli et al[18] (2024)	NS bolus followed by fluid replacement/maintenance at steady rate. Insulin and potassium added per MD preference	Two bags, bag 1 with NS +20 mEq KCl and bag 2 with D30+20 mEq KPO_4	77	68
Castro et al[19] (2019)	ADA-guided intravenous fluids	Not explicitly provided	11	10
Cho et al[10] (2018)	Not explicitly provided	NaCl, KCl, KPO_4 + D10W	68	54
Dhochak et al[14] (2018)	Single bag, changing dextrose concentration	Two bags, only 1 bag with dextrose	15	15
Ferreira et al[34] 2014	Not explicitly provided	Two bags, bag 2 with D10W	6	6
Gilchrist et al[37] (2023)	NaCl+KCl, hypoglycemia managed as needed with dextrose addition	Two bags, bag 2 with D10W	59	84
Grimberg et al[6] (1999)	Intravenous electrolyte and dextrose (% not specified)	Two bags, Bag 2 with D10W	10	10
Haas et al[8] (2023)	Not explicitly provided	0.45% NaCl+KCl, D10W as needed	107	634
Halfon et al[21] (2021)	Variable saline solution and dextrose options ($^1/_2$ normal saline solution, $^1/_2$ normal saline solution + KCl, D5W, or D5W + KCl)	Two bags, simultaneous IVF infusion of of D10W + KCl and $^1/_2$ normal saline solution+KCl	204	401
Hone et al[38] (2025)	NaCl + KCl, dextrose added when BG<300	Two bags, one with D10W	52	57
Hasan et al[20] (2021)	0.9% NaCl with KCH_3CO_2 20 mEq/L, KPO_4 20 mEq/L	Two bags, one with 12.5% dextrose and 0.45% NaCl	94	100
Merritt et al[22] (2021)	Not explicitly provided	Not explicitly provided	47	27
Moorhouse et al[35] (2024)	Not explicitly provided	Not explicitly provided	61	43
Munir et al[9] (2016)	Normal saline solution + electrolytes	Two bags, one with D10W	249	134
Nahle et al[7] (2024)	NaCl±KCl, add D5 when BG<250	Two bags, one with D10W	842	242
Poirier et al[33] (2004)	Not explicitly provided	Two bags, different dextrose concentrations	16	17
So et al[36] (2009)	Varied fluids, commonly saline solution or lactated ringers	Two bags, one with $^1/_2$ normal saline solution + 20mEq/L KCl or 20 mEq/L KPO_4 and one with D10 $^1/_2$ NS and the same electrolyte composition	9	22
Velasco et al[13] (2017)	Not explicitly provided	Two bags, different dextrose concentrations	38	23
Veverka et al[12] (2016)	Normal saline solution bolus, repeated as needed	Bag 1 with $^1/_2$ normal saline solution+KCH_3CO_2+KPO_4 and Bag 2 with $^1/_2$ normal saline solution+D10W+ KCH_3CO_2+KPO_4	73	46
Wolfgram et al[11] (2022)	Electrolyte-only fluids	Two bags, one with D10W	92	465

ADA, American Diabetes Association; *BG*, blood glucose; *IVF*, intravenous fluid; *MD*, mean difference; *NS*, normal saline solution.

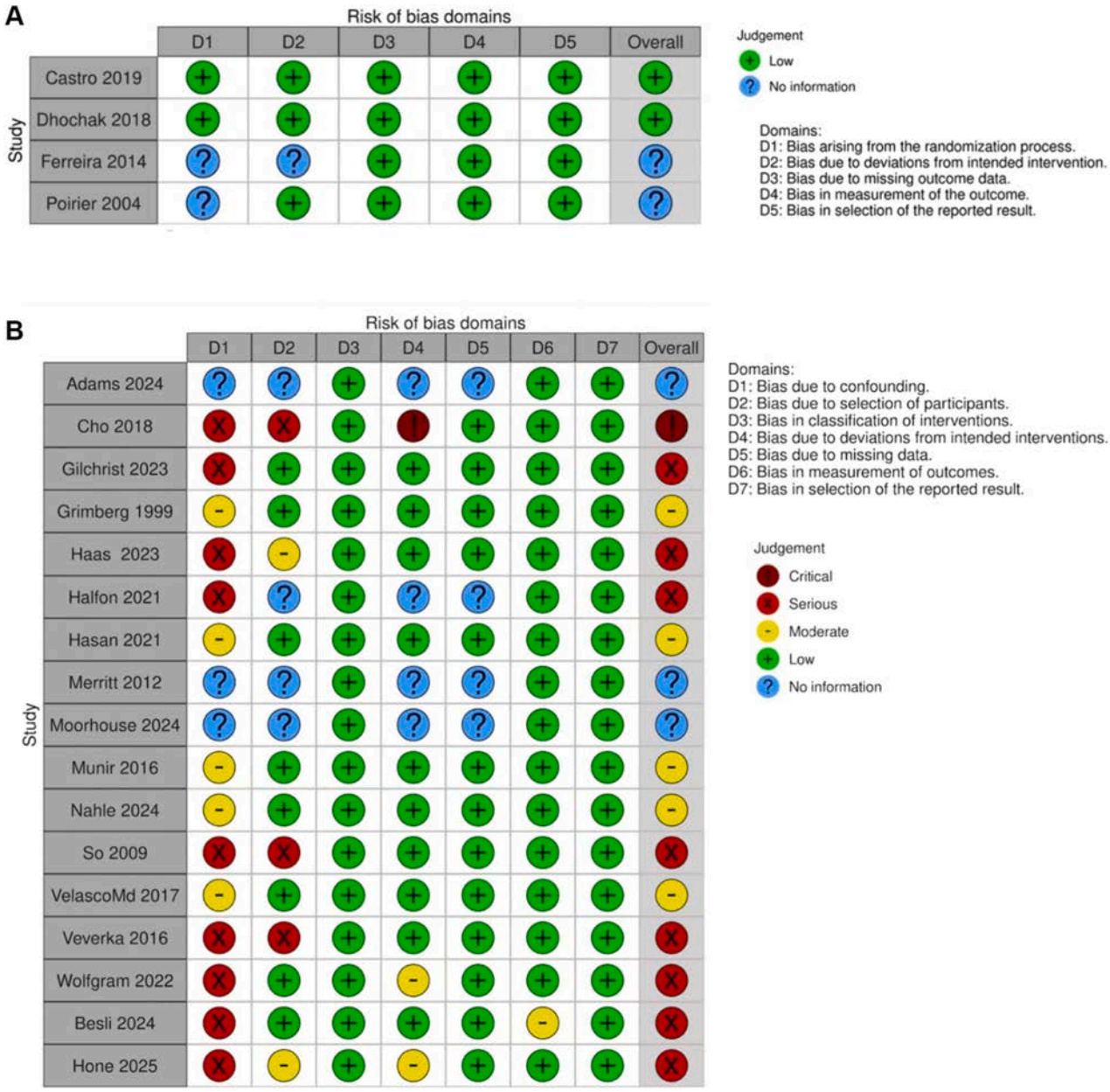

Figure 2. A, Risk of Bias Assessment using the Rob2 tool for randomized controlled trials. B, ROBINS-I tool for nonrandomized studies.

(Figure E7, available at http://www.annemergmed.com). The two-bag method was associated with a significant decrease in number of intravenous fluid bags used in 1 adult and 2 pediatric studies, whereas no differences were noted in 3 other pediatric studies (Table 7).[6,8,12,18,20,33] However, data for number of intravenous fluid bags was not suitable for meta-analysis given heterogeneity and inconsistency in data. In adults, Grimberg et al[6] showed that the two-bag method was associated with reduced hospital costs, and Haas et al[8] revealed no differences in time to first subcutaneous insulin between the 2 methods. Incidence of cerebral edema was reported in 4 pediatric studies, totaling 3 out of 156 patients in the one-bag group and 1 out of 135 in the two-bag method (Table 8).[12,14,20,33]

Table 4. GRADE certainty assessment in safety outcomes.

Two-bag Method Compared to One-bag Method in DKA Treatment Patient or Population: DKA Treatment Setting: Intervention: Two-bag Method Comparison: One-bag Method						
	Anticipated Absolute Effects* (95% CI)					
Outcomes	**Risk With One-bag Method**	**Risk With Two-bag Method**	**Relative Effect (95% CI)**	**No of Participants (Studies)**	**Certainty of the Evidence (GRADE)**	**Comments**
Incidence of hypoglycemia in adults	27 per 100	12 per 100 (10 to 15)	RR 0.46 (0.38 to 0.57)	3,150 (7 nonrandomized studies)	⨁⨁⨁⨁ High†	Two-bag system results in large reduction in incidence of hypoglycemia in adults.
Incidence of hypoglycemia in pediatrics	26 per 100	16 per 100 (10 to 22)	RR 0.62 (0.38 to 0.84)	970 (7 nonrandomized studies)	⨁⨁◯◯ Low†,‡	Two-bag system may reduce incidence of hypoglycemia in pediatrics slightly.
Incidence of hypoglycemia in all age groups	24 per 100	12 per 100 (10 to 15)	RR 0.50 (0.42 to 0.61)	4,320 (14 nonrandomized studies)	⨁⨁⨁◯ Moderate†	Two-bag system likely reduces incidence of hypoglycemia in all age groups.
Incidence of hypokalemia in adults	52 per 100	44 per 100 (40 to 49)	RR 0.84 (0.76 to 0.93)	2,624 (5 nonrandomized studies)	⨁⨁◯◯ Low†,‡	Two-bag system may reduce incidence of hypokalemia in adults slightly.
Incidence of hypokalemia in pediatrics	9 per 100	8 per 100 (5 to 13)	RR 0.88 (0.53 to 1.46)	488 (4 nonrandomized studies)	⨁◯◯◯ Very low†,‡	Two-bag system may have little to no effect on incidence of hypokalemia in children but the evidence is very uncertain.
Incidence of hypokalemia in all age groups	48 per 100	40 per 100 (36 to 44)	RR 0.84 (0.76 to 0.93)	3,112 (9 nonrandomized studies)	⨁⨁◯◯ Low†,‡	Two-bag system may reduce incidence of hypokalemia in all age groups slightly.
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. **Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.						

CI, confidence interval; *RR*, risk ratio.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

†Some included studies have at least 1 domain categorized as high risk of bias.

‡Substantial statistical and directional heterogeneity led to rating down for serious inconsistency.

Table 5. GRADE certainty assessment in efficacy outcome.

Outcomes	Risk With Two-Bag Method Compared to One-Bag Method	No. of Participants (Studies)	Certainty of the Evidence (GRADE)	Comments
Time to DKA resolution in adults	MD 2.19 hours lower (3.99 lower to 0.4 lower)	2,888 (5 nonrandomized studies)	⨁⨁◯◯ Low*,†,‡	Two-bag system may reduce time to DKA resolution in adults slightly.
Time to DKA resolution in pediatrics	MD 1.61 hours lower (3.1 lower to 0.13 lower)	398 (6 nonrandomized studies)	⨁◯◯◯ Very low*,†,‡,§	Two-bag system may reduce/have little to no effect on time to DKA resolution in pediatrics but the evidence is very uncertain.
Time to DKA resolution in all age groups	MD 1.76 hours lower (2.8 lower to 0.71 lower)	2,866 (11 nonrandomized studies)	⨁◯◯◯ Very low*,†,‡,‖	Two-bag system may reduce/have little to no effect on time to DKA resolution in all age groups but the evidence is very uncertain.
Duration of insulin infusion in adults	MD 3.74 hours lower (4.96 lower to 2.52 lower)	1,968 (3 nonrandomized studies)	⨁⨁◯◯ Low*,¶,#	The evidence suggests two-bag system results in a slight reduction in duration of insulin infusion in adults.
Duration of insulin infusion in pediatrics	MD 1.06 hours lower (3.03 lower to 0.91 higher)	509 (5 nonrandomized studies)	⨁◯◯◯ Very low*,**,††	The evidence is very uncertain about the effect of two-bag system on duration of insulin infusion in pediatrics.
Duration of insulin infusion in all age groups	MD 1.82 hours lower (3.42 lower to 0.21 lower)	2,477 (8 nonrandomized studies)	⨁◯◯◯ Very low*,#,**,††	Two-bag system may reduce/have little to no effect on duration of insulin infusion in all age groups but the evidence is very uncertain.

CI, Confidence interval; *GRADE*; Grading of Recommendations, Assessment, Development, and Evaluations.

*Some included studies have at least 1 domain categorized as high risk of bias.

†Although statistical heterogeneity is substantial, and visual inspection of forest plots indicates minimal inconsistency.

‡Rated down for indirectness, as individual proxy variables were collated to achieve final result.

§Due to the small number of included studies (less than 10), formal tests for publication bias (eg, Egger's test) were not performed, as they lack statistical power. However, visual inspection of the funnel plot revealed clear asymmetry, suggesting potential publication bias.

‖Visual inspection of the funnel plot reveals obvious asymmetry. Rated down 1 level for strongly suspected publication bias.

¶Imprecision was present despite a precise summary estimate, as individual study CIs overlapped thresholds of clinical importance, reducing confidence in the consistency of the effect.

#Because of the small number of included studies (less than 10), formal tests for publication bias (eg, Egger's test) were not performed, as they lack statistical power. However, visual inspection of the funnel plot revealed no asymmetry. Therefore analysis was not rated down for publication bias.

**Moderate-substantial statistical and visual heterogeneity, leading to rating down for inconsistency.

††Downgraded for imprecision due to CI overlap with the threshold of clinical relevance.

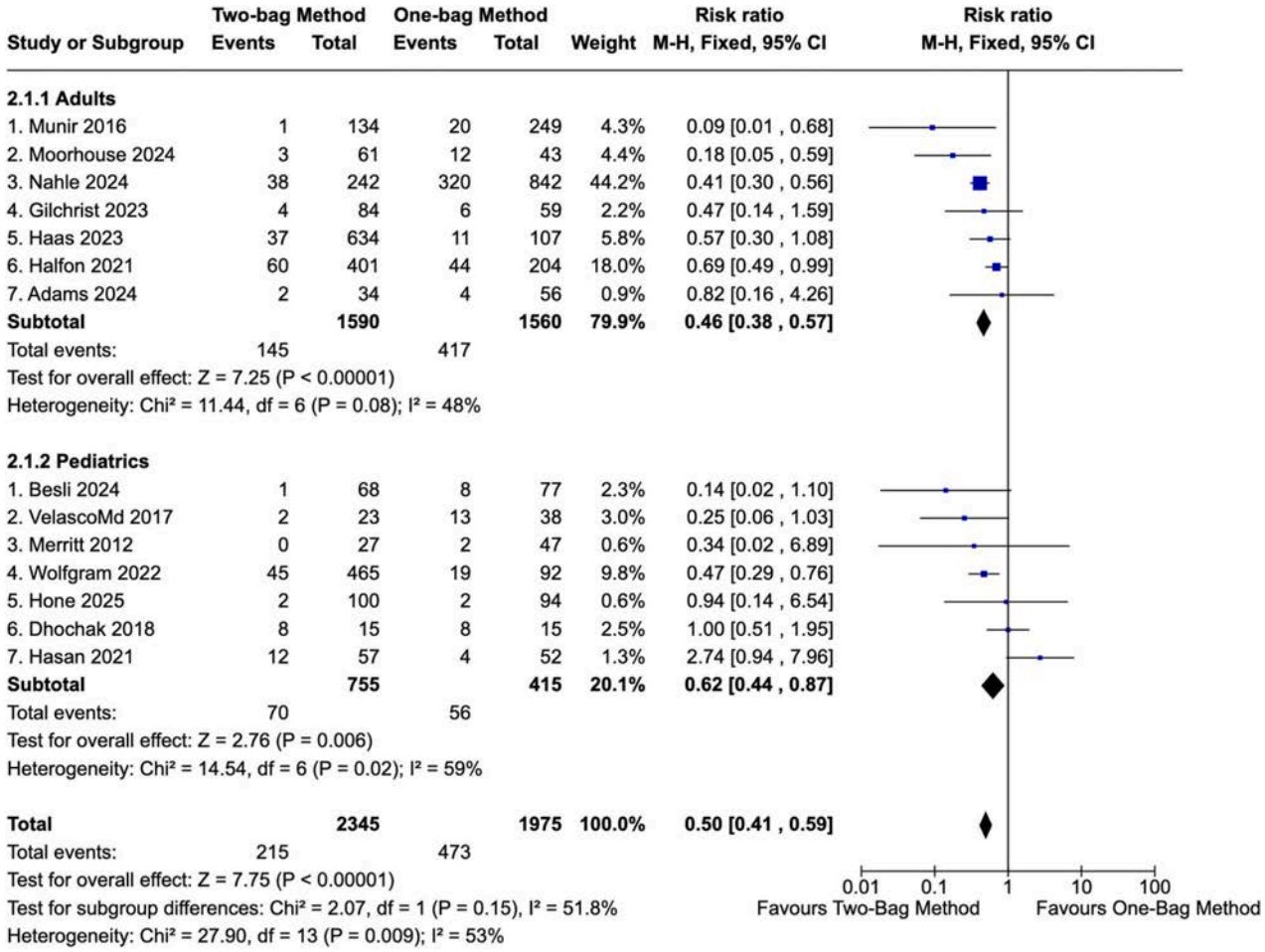

Figure 3. Forest plot of studies reporting incidence of hypoglycemia. Subgroup analysis involves adult patients versus pediatric patients.

LIMITATIONS

This meta-analysis has several limitations. First, some extracted data were reported as medians and interquartile ranges (IQR), requiring conversion to means and standard deviations (SD) for pooling. We used a highly validated method for this conversion.[27,28]

Moreover, although we defined pediatrics as patients less than 18 years, 2 studies defined pediatrics as age less than 21 years.[13,20] We retained them, as the mean ages were still below 18 (13.24±3.90 and 15.6±3.79) years and comparable to other pediatric studies. Nonetheless, including participants aged more than 18 years remains a limitation. We attempted to contact the authors to exclude those aged more than 18, but the necessary data were unavailable.

Several included studies had moderate to high risk of bias, mainly due to unadjusted confounders in retrospective designs. Five abstracts had unclear bias due to limited information but were still included.[17,22,33-35] We contacted authors, but data were only obtained for one study. Most studies were also nonrandomized and retrospective, reducing the certainty of conclusions. To address this, we applied a random-effects model and used GRADE to assess certainty of evidence.[31] Finally, although several outcomes showed high statistical heterogeneity, visual inspection of forest plots for hypoglycemia incidence and DKA resolution time showed minimal inconsistency or directional heterogeneity.[30] We also used various proxies for "time to DKA resolution," introducing indirectness. We accounted for this using GRADE and meta-regression, which showed proxies explained some, but not all, heterogeneity.

DISCUSSION

To our knowledge, this is the first meta-analysis to assess and compare the safety and efficacy of the two-bag versus one-bag method for DKA in both adult and pediatric

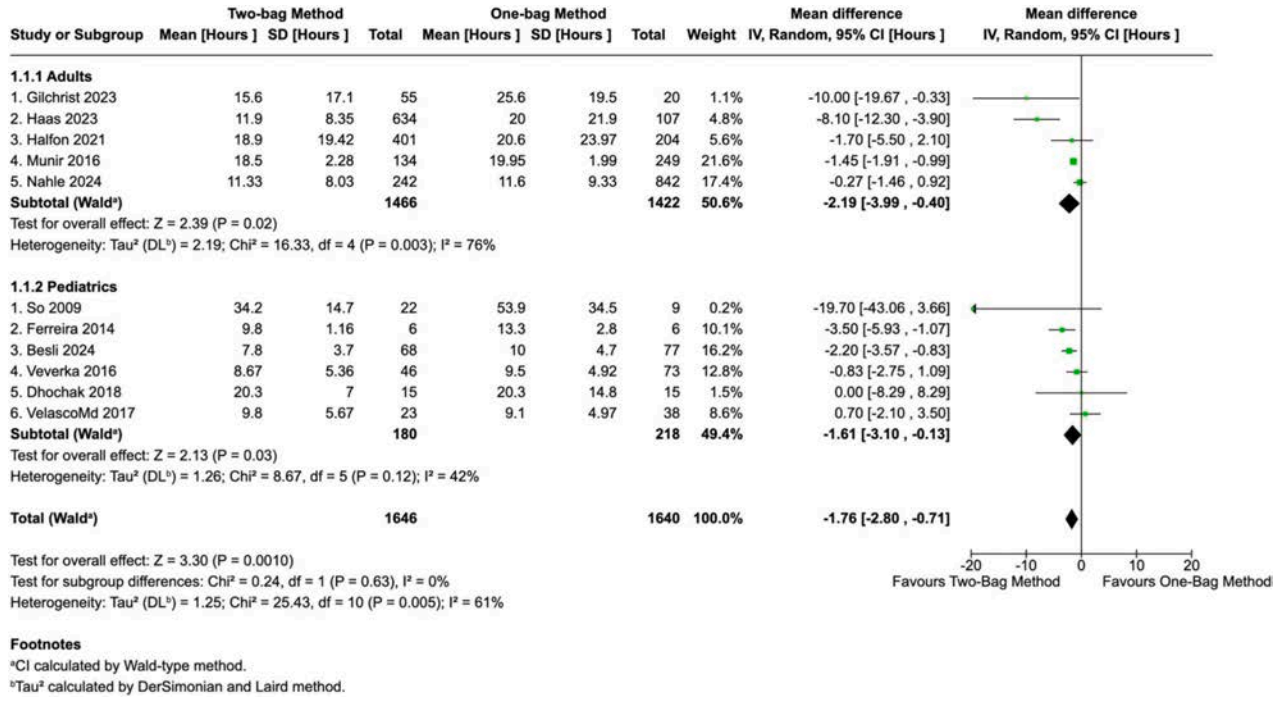

Figure 4. Forest plot of studies reporting Time to DKA resolution (in hours). Subgroup analysis involves adult patients versus pediatric patients.

populations. Our findings show that the two-bag method is associated with benefits in incidence of hypoglycemia, hypokalemia, time to resolution of DKA, and duration of insulin infusion, when compared to the one-bag method.

Although it has been a long-speculated benefit of the two-bag method, our review is the first to identify a strong association between it and the reduction in hypoglycemia in both adults and pediatrics. The two-bag method is designed to enable more efficient glycemic control by allowing fluid rate adjustments in response to changes in serum glucose, rather than requiring complete fluid bag changes. Our analysis found a significantly lower incidence of hypoglycemia in the two-bag group, supporting this theoretical advantage. Notably, this contrasts with the earlier pediatric-focused meta-analysis by Nasser et al,[15] which showed no differences. However, the former study included only 8 pediatric studies, whereas our updated review incorporates 12 pediatric studies within a broader data set of 21 total studies. This suggests that with strict adherence to standardized protocols, the two-bag method can achieve tighter glucose control and, consequently, reduce the risk of hypoglycemia more reliably across both pediatric and adult populations.

Our meta-analysis revealed that the two-bag method was also associated with a reduction in time to DKA resolution, albeit with low to very low certainty of evidence. Although the design of the two-bag method does not inherently guarantee faster resolution, the improved efficiency of this method likely contributes to this outcome. Several studies have specifically highlighted these efficiency gains, underlining a significantly shorter response time to fluid changes following placement of order by the physician.[6,33,38] Accordingly, the two-bag method may be indirectly improving time to DKA resolution by eliminating the delays associated with pharmacy-prepared bags and the need to interrupt insulin infusions during bag changes. Although studies included in the current review did not track the number of insulin infusion interruptions, it is plausible that maintaining continuous insulin delivery contributed to the shorter time to DKA resolution observed in the two-bag cohort.

Although anion gap has historically been used to monitor DKA resolution, it has been removed from the most recent American Diabetes Association diagnostic criteria due to its lack of specificity and variability across patient conditions and laboratory methods.[5] Factors such as renal failure, lactic acidosis, hypoalbuminemia, and the recovery phase hyperchloremic metabolic acidosis can all confound the anion gap, leading to either falsely elevated or normalized values in the context of true DKA.[2,5,40] Despite this, we analyzed anion gap closure separately due to its longstanding clinical use, finding no significant differences between groups.

Table 6. Time to DKA resolution and related parameters for OB method versus TB method*.

Study ID	Time to DKA Resolution Mean [H]±SD	Time to Anion Gap Closure Mean [H]±SD	Time to Bicarbonate >18 mmol/L (or >15 mmol/L in Pediatrics) Mean [H]±SD	Time to β-Hydroxybutyrate Correction Mean [H]±SD	Time to pH Correction Mean [H]±SD
Adams et al[17] (2024)		OB: 10.1 ± 6.85 TB: 12.2 ± 6.73	–	–	–
Besli et al[18] (2024)†,§	OB: 10 ± 4.7 TB: 7.8 ± 3.7	–	OB: 10 ± 4.7 TB: 7.8 ± 3.7	OB: 11 ± 4.3 TB: 8.4 ± 3	–
Castro et al[19] (2019)†	–	OB: 12.01 ± 6.68 TB: 13.54 ± 7.73	–	–	–
Dhochak et al[14] (2018)‡	OB: 20.3 ± 14.8 TB: 20.3 ± 7	–	–	–	–
Ferreira et al[34] 2014‡	OB: 13.3 ± 2.8 TB: 9.8 ± 1.16	–	–	–	–
Gilchrist et al[37] (2023)§	OB: 25.6 ± 19.5 TB: 15.6 ± 17.1	OB: 16.9 ± 11 TB: 12.7 ± 5.8	–	OB: 25.6 ± 19.5 TB: 15.6 ± 17.1	–
Grimberg et al[6] (1999)	–	–	–	–	–
Haas et al[8] (2023)‡,§	OB: 20 ± 21.9 TB: 11.9 ± 8.35	–	OB: 20 ± 21.9 TB: 11.9 ± 8.35	–	–
Halfon et al[21] (2021)†,‡	OB: 20.6 ± 23.97 TB: 18.9 ± 19.42	–	–	–	–
Hone et al[38] (2025)†	–	OB: 9.53 ± 5.35 TB: 8.17 ± 4.67	–	–	–
Hasan et al[20] (2021)	–	–	–	–	–
Merritt et al[22] (2021)	–	–	–	–	–
Moorhouse et al[35] (2024)	–	OB: 11 (no SD) TB: 13 (no SD)	–	–	–
Munir et al[9] (2016)§	OB: 19.95 ± 1.99 TB: 18.5 ± 2.28	OB: 13.57 ± 1.75 TB: 10.95 ± 1.63	OB: 19.95 ± 1.99 TB: 18.5 ± 2.28	–	–
Nahle et al[7] (2024)†,§	OB: 11.6 ± 9.33 TB: 11.33 ± 8.03	OB: 9.54 ± 6.16 TB: 8.78 ± 4.91	OB: 11.6 ± 9.33 TB: 11.33 ± 8.03	–	–
Poirier et al[33] (2004)	–	–	–	–	–
So et al[37] (2009)§	OB: 53.9 ± 34.5 TB: 34.2 ± 14.7	–	–	OB: 53.9 ± 34.5 TB: 34.2 ± 14.7	OB: 9.7 ± 4.3 TB: 9.1 ± 7.4
Velasco et al[13] (2017)§	OB: 9.1 ± 4.97 TB: 9.8 ± 5.67	–	OB: 9.1 ± 4.97 TB: 9.8 ± 5.67	–	OB: 10.2 ± 6.03 TB: 10 ± 5.36
Veverka et al[12] (2016)†,§	OB: 9.5 ± 4.92 TB: 8.67 ± 5.36	–	OB: 9.5 ± 4.92 TB: 8.67 ± 5.36	–	–
Wolfgram et al[11] (2022)‡	OB: 8.28 (no SD) TB: 8.28 (no SD)	–	–	–	–

OB, One bag; *TB*, two bag; *SD*, standard deviation.
*Data not reported indicated with dash (–).
†Data originally reported as median (interquartile range) in the source manuscript, converted to mean (SD) for consistency in present manuscript or original data points obtained through email from source authors.
‡,§"Time to DKA resolution" is reported either as defined by the original study‡; when not explicitly defined, presented as a proxy variable§ (eg, time to bicarbonate, ketone, or pH correction) selected by the current authors to align with the American Diabetes Association definition of DKA resolution, excluding anion gap closure. In studies reporting multiple such endpoints, time to bicarbonate correction was prioritized a priori to reduce interstudy variability, followed by time to β-hydroxybutyrate normalization.

Additionally, pooled analysis found that insulin infusion duration was shorter with the two-bag method in adults. However, this outcome is not a direct surrogate for DKA resolution, as insulin therapy often extends beyond physiologic resolution until patients transition to oral intake.[41,42] In fact, across all studies, time to DKA

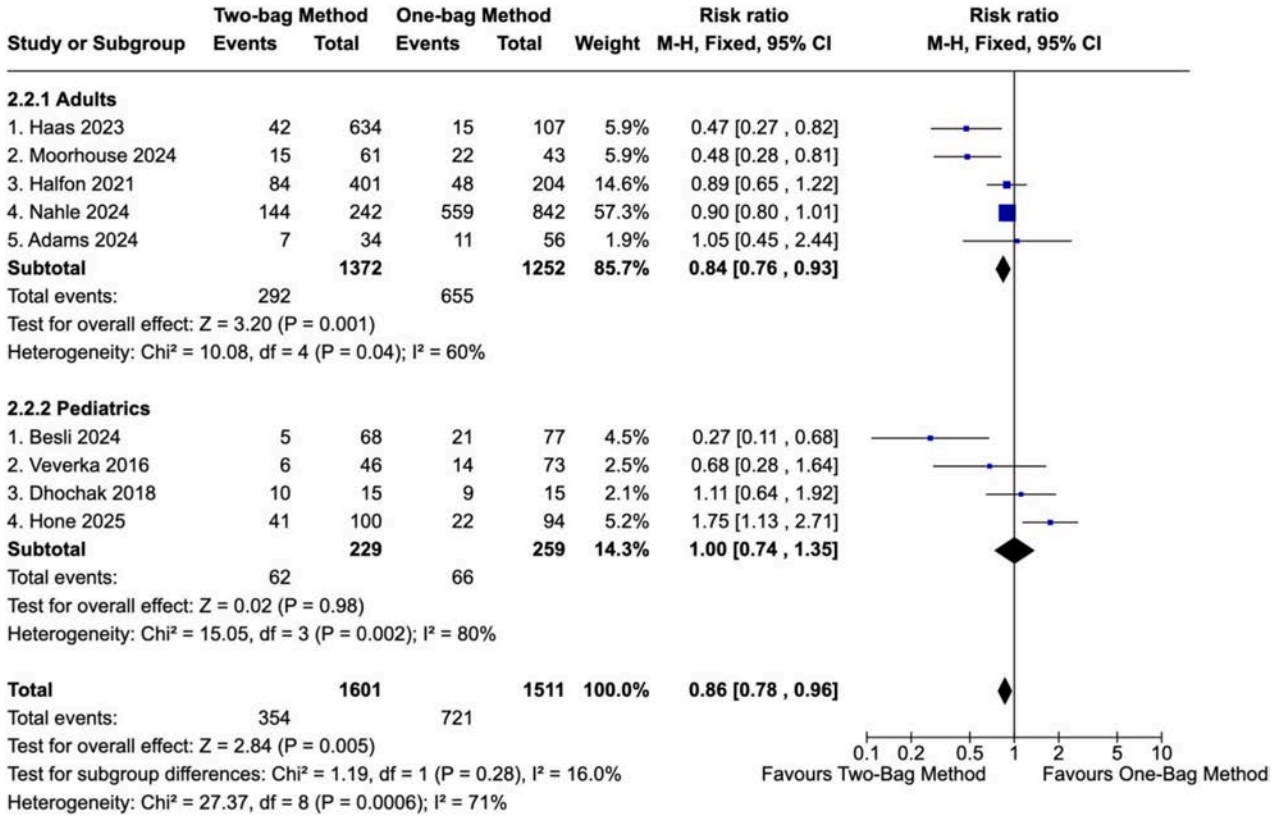

Figure 5. Forest plot of studies reporting incidence of hypokalemia. Subgroup analysis involves adult patients versus pediatric patients.

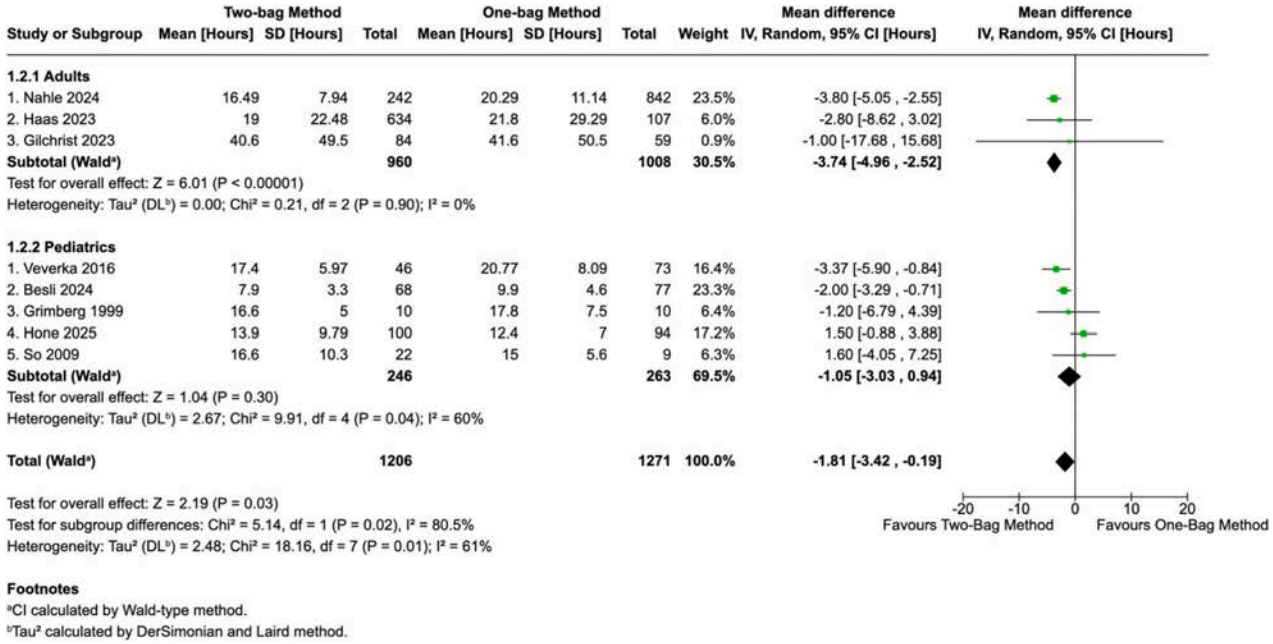

Figure 6. Forest plot of studies reporting duration of insulin infusion. Subgroup analysis involves adult patients versus pediatric patients.

Table 7. Additional outcomes for OB method versus TB method*.

Study ID	Duration of Insulin Mean [H]±SD	Hospital Length of Stay Mean [D]±SD	Time to First Long-Acting and/or Subcutaneous Insulin Mean [H]±SD	No. of Fluid Bags Used Mean [No. of Bags]±SD	Hospital Charges Mean [US Dollars $]±SD
Adams et al[17] (2024)	–	–	–	–	–
Besli et al[18] (2024)†	OB: 9.9 ± 4.6 TB: 7.9 ± 3.3	–	–	OB: 8.6 ± 3.6 TB: 4.9 ± 1.9	–
Castro et al[19] (2019)	–	–	–	–	–
Cho et al[10] (2018)	OB: 28.3 ± 19.0 TB: 29.9 ± 17.0	OB: 5.52 ± 4.63 TB: 4.88 ± 2.72	–	–	–
Dhochak et al[14] (2018)	–	–	–	–	–
Ferreira et al[34] 2014	–	–	–	–	–
Gilchrist et al[37] (2023)	OB: 41.6 ± 50.5 TB: 40.6 ± 49.5	OB: 4 ± 6.67 TB: 6 ± 8.148	–	–	–
Grimberg et al[6] (1999)	OB: 17.8 ± 7.5 TB: 16.6 ± 5	–	–	OB: 8.6 ± 1.2 TB: 4.8 ± 0.3	OB: 1,092 ± 147 TB: 622 ± 40
Haas et al[8] (2023)	OB: 21.8 ± 29.29 TB: 19 ± 22.48	OB: 3.4 ± 4.49 TB: 3.8 ± 7.07	OB: 21.6 ± 25.33 TB: 16.7 ± 8.99	OB: 29.7 ± 19.53 TB: 5.3 ± 5.14	–
Halfon et al[21] (2021)†	–	OB: 4.6 ± 2.99 TB: 4.1 ± 2.9	–	–	–
Hone et al[38] (2025)†	OB: 12.4 ± 7 TB: 13.9 ± 9.79	–	–	–	–
Hasan et al[20] (2021)	OB: 12.43 ± 7 TB: 13.9 ± 9.79	–	–	–	–
Merritt et al[22] (2021)	–	–	–	–	–
Moorhouse et al[35] (2024)	OB: 19 (no SD) TB: 15 (no SD)	OB: 3.7 (no SD) TB: 4.0 (no SD)	–	–	–
Munir et al[9] (2016)	–	OB: 4.86 ± 3.63 TB: 4.33 ± 2.53	–	–	–
Nahle et al[7] (2024)†	OB: 20.29 ± 11.14 TB: 16.49 ± 7.94	–	–	–	–
Poirier et al[33] (2004)	–	–	–	OB: 3.2 ± 0.42 TB: 4.1 ± 0.6	–
So et al[36] (2009)	OB: 15 ± 5.6 TB: 16.6 ± 10.3	OB: 3.9 ± 1.8 TB: 3.8 ± 1.4	–	–	–
Velasco et al[13] (2017)	–	OB: 2.0 ± 0.93 TB: 1.2 ± 0.64	–	–	–
Veverka et al[12] (2016)†	OB: 20.77 ± 8.09 TB: 17.4 ± 5.97	OB: 2.67 ± 0.76 TB: 2.33 ± 0.77	–	OB: 4 ± 1.51 TB: 4 ± 1.53	–
Wolfgram et al[11] (2022)	–	OB: 1 (no SD) TB: 0.756 (no SD)	–	–	–

OB, One bag; *TB*, two bag; *SD*, standard deviation.
*Data not reported indicated with dash (–).
†Data originally reported as median (interquartile range) in the source manuscript, converted to mean (SD) for consistency in present manuscript or original data points obtained through email from source authors.

resolution was consistently shorter than insulin infusion duration, reinforcing the need for precise measurements when assessing treatment efficacy. A shorter duration of insulin infusion reflects more efficient resource utilization, as many hospitals restrict insulin infusions to the ICU, potentially reducing the need for, or duration of ICU admission.

Similarly, we found that the two-bag method was associated with a reduction in the incidence of hypokalemia in adults, but not in pediatric patients.

Table 8. Safety outcomes for OB method versus TB method*.

Study ID	Incidence of Hypoglycemia Events/Total (N/n)	Incidence of Hypokalemia Events/Total (N/n)	Incidence of Cerebral Edema Events/Total (N/n)
Adams et al[17] (2024)	OB: 4/56 TB: 2/34	OB: 11/56 TB: 7/34	–
Besli et al[18] (2024)	OB: 8/77 TB: 1/68	OB: 21/77 TB: 5/68	–
Castro et al[19] (2019)	–	–	–
Cho et al[10] (2018)	–	–	–
Dhochak et al[14] (2018)	OB: 8/15 TB: 8/15	OB: 9/15 TB: 10/15	OB: 0/15 TB: 0/15
Ferreira et al[34] (2014)	–	–	–
Gilchrist et al[37] (2023)	OB: 6/59 TB: 4/84	–	–
Grimberg et al[6] (1999)	–	–	–
Haas et al[8] (2023)	OB: 11/107 TB: 37/634	OB: 15/107 TB: 42/634	–
Halfon et al[21] (2021)	OB: 44/204 TB: 60/401	OB: 48/204 TB: 84/401	–
Hone et al[39] (2025)	OB: 4/52 TB: 12/57	–	OB: 1/52 TB: 0/57
Hasan et al[20] (2021)	OB: 2/94 TB: 2/100	OB: 22/94 TB: 41/100	–
Merritt et al[22] (2021)	OB: 2/47 TB: 0/27	–	–
Moorhouse et al[35] (2024)	OB: 12/43 TB: 3/61	OB: 22/43 TB: 15/61	–
Munir et al[9] (2016)	OB: 20/249 TB: 1/134	–	–
Nahle et al[7] (2024)	OB: 320/842 TB: 38/242	OB: 559/842 TB: 144/242	–
Poirier et al[34] (2004)	–	–	OB: 0/16 TB: 0/17
So et al[37] (2009)	–	–	–
Velasco et al[13] (2017)	OB: 13/38 TB: 2/13	–	–
Veverka et al[12] (2016)	–	OB: 14/73 TB: 6/46	OB: 2/73 TB: 1/46
Wolfgram et al[11] (2022)	OB: 19/92 TB: 45/465	–	–

OB, One bag; *TB*, two bag.
*Data not reported indicated with dash (–).

Although the certainty of evidence for this outcome was also classified as low, this finding highlights a potential difference in how fluid and electrolyte management affect these populations, though the exact reasons remain speculative. Several physiologic and protocol-related differences may contribute to this discrepancy. Pediatric patients have distinct fluid requirements and follow weight-based fluid infusion rates due to their higher risk of cerebral edema.[41,43-45] Additionally, insulin boluses are contraindicated in pediatric DKA management, unlike in adults.[41,43] Differences in glycogen reserves, insulin sensitivity, and overall metabolic responses between children and adults may also play a role in influencing intracellular potassium shifts during treatment.[44,45]

Ultimately, the effectiveness of the two-bag method depends on strict adherence to established protocols, as its safety and efficiency require timely, appropriate adjustments during treatment. Notably, multiple studies

reviewed herein emphasized that successful implementation requires targeted education and training for physicians and nurses, along with an adjustment period of several months before evaluating the true efficacy of the two-bag method. Given prior findings of significant variability in DKA protocol adherence globally, structured onboarding and reinforcement of guidelines are critical to realizing the full benefits of this approach.[46]

In conclusion, this meta-analysis reveals that the two-bag method is strongly associated with a reduced incidence of hypoglycemia in both adult and pediatric populations. Although the strength of evidence is weak, our findings suggest that the two-bag system is associated with faster DKA resolution in both populations. It is also linked to a shorter duration of insulin infusion, a lower overall incidence of hypokalemia, and these benefits were maintained in the adult subgroup analysis.

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All authors attest to meeting the four ICMJE.org authorship criteria:(1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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