Insulin Regimens to Treat Hyperglycemia in Hospitalized Patients on Nutritional Support: Systematic Review and Meta-Analyses

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Keywords

Nutritional support · Hospitalized patients · Insulin · Glycemic control

Abstract

Background: The best insulin regimen to treat hyperglycemia in hospitalized patients on nutritional support (NS) is unclear. **Methods:** We searched electronic databases to identify cohort studies or randomized clinical trials in order to evaluate the efficacy of different insulin regimens used to treat hyperglycemia in hospitalized patients on NS on diverse outcomes: mean blood glucose (MBG), hypoglycemia, length of stay in hospital, and mortality. **Results:** Seventeen studies from a total of 5,030 were included. Enteral Group included 8 studies; 1,203 patients using rapid, glargine, NPH, or Premix insulin; MBG 108–225 mg/dL; hypoglycemia 0–13%. In indirect meta-analyses, NPH insulin ranked best for glucose control (MD 95% CI –2.50 mg/dL [2.65 to –2.35]). Parenteral Group included 4 studies; 228 patients using regular and glargine or NPH insulin; MBG 137–202 mg/dL; hypoglycemia 0–40%. In meta-analyses comparing regular insulin added to parenteral nutrition bag with glargine, MBG (MD 95% CI –3.78 mg/dL [–11.93 to 4.37]; $I^2 = 0\%$) or hypogly-

emia frequency (RR 95% CI 1.37 [0.43–4.32]; $I^2 = 70.7\%$) did not differ. The description related to hospital length of stay and mortality was inconsistent between groups. **Conclusions:** The best insulin regimen to treat hyperglycemia in hospitalized patients on NS has not been established; best results using insulin regimens with NPH in enteral nutrition do not seem to be clinically relevant.

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Introduction

Hyperglycemia is a costly and common health care problem in hospitalized patients with and without diabetes. The risk of hospital complications increases with illness severity and also in patients without a previous history of diabetes [1]. The mechanism underlying hyperglycemia during acute illness is complex and includes the release of counter-regulatory hormones (corticosteroids and catecholamines) and proinflammatory mediators and administration of exogenous corticosteroids, vasopressors, and enteral and parenteral nutrition [2].

The objective of nutritional support (NS), including both enteral and parenteral nutrition, is to prevent the ef-

fects of starvation, such as increased risk of death and/or infection, and occasionally to alter favorably the natural course or treatment of a specific disease [3, 4]. Enteral nutrition, whenever possible, is preferred over parenteral nutrition because there are less associated complications, including hyperglycemia and costs [5].

The Van den Berghe et al. [6] seminal randomized clinical trial (RCT) conducted in critically ill surgical patients demonstrated that treatment of hyperglycemia by continuous intravenous insulin administration attaining strict glycemic control (80–110 mg/dL) reduced length of stay in morbidity intensive care unit (ICU) by 5 days, and surgical mortality in critically ill patients. Since then, the treatment of hyperglycemia in hospitalized patients has become an important target of clinical care. However, these results were not confirmed in the NICE-SUGAR multicenter study, where increased mortality occurred for ICU patients on strict glucose control using intensive insulin therapy and no reduction on length of stay in hospital was observed [7]. Subsequently, different strategies to reach glycemic control have been proposed for hospitalized patients inside and outside the ICU.

In general, up to 30% of hospitalized patients received some type of specialized NS [8]. Usually, a high frequency of hyperglycemia is observed in these patients. Depending on the definition of hyperglycemia, its prevalence varies from 44 to 90% [9] for patients receiving parenteral nutrition and around 40% [10] for patients on enteral nutrition. Clinical societies have different thresholds for hyperglycemia [11, 12]. According to the American Diabetes Association, insulin therapy should be initiated for treatment of persistent hyperglycemia starting threshold 180 mg/dL. Once insulin therapy is started, a target glucose range 140–180 mg/dL is recommended for the majority of critically and noncritically ill patients [12]. However, even considering the great number of patients who need to treat hyperglycemia and its associated complications in daily clinical practice, there are no guidelines to recommend the best regimen of insulin therapy to treat hyperglycemia in NS.

The aim of this study was to evaluate the effect of different insulin regimens used to treat hyperglycemia in hospitalized patients receiving NS – enteral, parenteral, or both – on pre-established outcomes: hyperglycemia, hypoglycemia, hospital length of stay, and mortality.

Methods

This systematic review was carried out using a protocol constructed according to the Cochrane Handbook recommendations [13] and reported in accordance with Preferred Reporting Items

for Systematic Reviews and Meta-Analyses statement [14]. The study protocol was registered in the PROSPERO International prospective register of systematic reviews (CRD42015015749).

Data Sources and Searches

We searched databases from Medline, Embase, ISI web of science, ClinicalTrials.gov register, Cochrane, and Scopus, up to March 2017, to identify studies that compared different insulin regimens in hospitalized patients receiving either enteral or parenteral NS. In addition, a manual search was performed in the reference lists of included articles. We contacted the authors by mail if essential data were not clearly described in a study.

The initial search strategy was defined by the following MESH terms: “Nutritional support”[Mesh] or “Enteral nutrition”[Mesh] or “Parenteral nutrition, Total”[Mesh] or “Parenteral nutrition, Solutions”[Mesh] combined with “Insulin”[Mesh] or “Insulin lente”[Mesh] or “Insulin ultralente”[Mesh] or “Insulin regular, human”[Mesh] or “Insulinlispro”[Mesh] or “Insulinaspart”[Mesh] or “Insulin shortactig”[Mesh] or “Insulin isophane”[Mesh] “Insulin detemir”[Mesh] or “Insulin long-acting, human”[Mesh]. Other types of insulin were also included in the search and the complete list of terms was described in the online supplementary material; for all online suppl. material, see www.karger.com/doi/10.1159/000481355. All potentially eligible studies were considered for review, regardless of the primary outcome, but limited to English, Spanish, French, or Portuguese language. A manual search was also performed in the reference lists of included articles and in recent reviews about the topic.

Study Selection

All citations retrieved from electronic databases were imported to the EndNote Program. Two reviewers (M.V.V. and L.V.V.) independently analyzed the titles and abstracts of every paper retrieved from the literature search to identify potentially eligible studies. All studies that did not meet the inclusion criteria were excluded. The full text of the remaining papers was obtained for further examination. Disagreements were resolved by a third reviewer (M.J.A.).

The inclusion criteria for the studies were RCTs and cohort studies that evaluated different insulin regimens in patients receiving enteral, parenteral, or both, NS. We excluded studies if patients were on an oral diet without enteral or parenteral support, or were using antihyperglycemic agents but insulin as the only treatment for hyperglycemia, or if they had no documented hyperglycemia.

Data Extraction and Quality Assessment

The data of included studies were independently extracted by the same 2 reviewers using a standardized data extraction form. Extracted data included the following information: first author's name, year of publication, number of participants, details of the study design (i.e., RCT or observational trial), study duration, and patient characteristics (age, gender, body weight, body mass index, severity of illness score, frequency of patients with diabetes, previous use of insulin or oral antihyperglycemic agents, corticosteroid use, reasons for admission (clinical or surgical), hospitalization setting (ward or ICU), mean baseline blood glucose, and presence of renal replacement therapy. The type of insulin therapy, as well the criteria adopted to initiate insulin therapy, total insulin dose, daily insulin units per body weight, and description of NS were recorded. Total energy, macronutrients, and fiber content were

also extracted when available. The preestablished evaluated outcomes were glycemic control, hypoglycemia, hospital length of stay, and mortality. Glycemic control targets and hypoglycemia were defined by each study's authors and this information was extracted.

Direct meta-analyses were performed in Stata and indirect meta-analysis was performed in R 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

The methodological quality of all included studies was independently assessed (M.V.V. and A.L.J.T.). We used a score based on the Cochrane Collaboration tool to assess risk of bias for RCTs [15] and the Newcastle-Ottawa Scale (NOS) for observational studies [16]. According to the Cochrane Collaboration, biases were classified into 6 domains: selection, performance, detection, attrition, and reporting [17]. The risk of bias for each domain was classified as high, low, or unclear. Regarding the NOS, each study is judged on 8 items and categorized into 3 groups: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest. Up to 9 stars were awarded for each quality item and served as a quick visual assessment [14].

The quality of the body of evidence of each meta-analysis was assessed by the GRADE [18] approach including factors that may decrease (e.g., methodological quality, directness of evidence, heterogeneity, precision of effect estimates, risk of publication bias) or increase (e.g., large magnitude of effect, reduction or spurious effect due to plausible confounding factors, dose-response gradient) the quality of evidence. Each evaluated factor was rated as high, moderate, low, or very low. Using this approach, we considered a serious risk of bias when an individual study had more than 3 unclear or high risk of bias and imprecision was defined as a meta-analysis confidence interval >0.5 .

Results

We identified 5,039 studies in our database search (Fig. 1). Of them, 4,885 were excluded based solely on title or abstract, leaving 154 for full text evaluation. From these 154 selected papers, 137 articles were also excluded after full text scrutiny mostly because they used the same regimens of insulin in both arms or due to the absence of a description of NS. Therefore, we included 17 studies (6 RCTs and 11 cohort studies) providing data from 3,260 patients. Clinical trials were heterogeneous in patient populations and there was lack of information on blood glucose variability, duration of blood glucose in target range, caloric and protein intakes, and timing of initiation of nutrition therapy preventing the need for most meta-analysis. Most of the patients ($n = 2,657$) were studied in the ICU. Enteral feeding was the only NS used in 8 studies, parenteral nutrition in 4, and mixed (enteral plus parenteral) in 5.

The studies included in the current systematic review were classified into 3 groups according to the type of NS

Fig. 1. Flow diagram of literature search to identify studies evaluating different insulin regimens to treat hyperglycemia in hospitalized patients on nutritional support.

received by patients: Enteral NS Group, Parenteral NS Group, and Mixed NS Group.

General features of studies, adopted definitions of hyperglycemia and hypoglycemia, type of insulin regimens, data on mean blood glucose (MBG), and hypoglycemia, besides other studied outcomes for each included study are presented in Table 1 according to the types of NS. The report on outcomes as well as the description or definition of studied variables were not uniform. Mortality was described only in seven studies [19–25] and hospital length of stay in 6 [20–22, 24, 26, 27]. MBG was described in all but one study [28]. The presence of hypoglycemia in the studies was differently reported: number of events, percentage of events, or number of patients with hypoglycemia. Total energy, macronutrients, and fiber content of administered NS were not reported in most of the studies. Details of insulin regimens and available NS information of included studies are presented as online supplementary Table 1.

Enteral NS Group: eight studies [19–21, 28–32] evaluated different insulin regimens for glycemic control in patients receiving enteral support (Table 1a). Two RCTs and 6 cohort studies comprising 1,203 patients were reviewed. Patients' mean age was 64.8 years, 57% were men, BMI ranged from 28 to 30 kg/m², and 64% had diabetes.

Table 1. General characteristics of studies included in the systematic review

Author, years	Study and patients characteristics	Main outcomes definitions	Insulin regimens	Mean blood glucose significance between interventions	% of hypoglycemia events statistical significance between interventions	Other outcomes statistical significance between interventions
a Enteral nutrition						
<i>Randomized control trials</i>						
Korytkowski et al. [29], 2009	<i>n</i> = 50 Age = 65 years Male = 30 (60%) DM = 50 (100%) BMI = 28 kg/m ² ICU = none Ward = 50 (100%) Follow-up = 6±2.2 days	Glycemic target 100–180 mg/dL Hypoglycemia <70 mg/dL	Intervention 1 (<i>n</i> = 25): sliding scale regular insulin Intervention 2 (<i>n</i> = 25): insulin glargine plus sliding scale regular insulin	Intervention 1 160.2±28.8 mg/dL Intervention 2 165.8±28.8 mg/dL <i>p</i> = 0.71	Intervention 1 1.1% Intervention 2 1.3% <i>p</i> = 0.35	Hospital LOS: NA Hospital mortality: NA
Leelarathna et al. [30], 2013	<i>n</i> = 24 Age = 60.5 years Male = 18 (75%) DM = 11 (46%) BMI = 27.45 kg/m ² ICU = 24 (100%) Ward = none Follow-up = 48 h	Glycemic target 108–144 mg/dL Hypoglycemia <40 mg/dL	Intervention 1 (<i>n</i> = 12): fully automated IV regular insulin Intervention 2 (<i>n</i> = 12): IV sliding scale regular insulin	Intervention 1 142 (133–148) mg/dL Intervention 2 164 (150–234) mg/dL <i>p</i> = 0.001	Intervention 1 0% Intervention 2 0% <i>p</i> = ns	Hospital LOS: NA Hospital mortality: NA
<i>Cohort studies</i>						
Grainger et al. [31], 2007	<i>n</i> = 52 Age = 67.5 years Male = 26 (50%) DM = 36 (69%) BMI = 29 kg/m ² ICU = 52 (100%) Ward = none Follow-up = maximum 21 days	Glycemic target 80–140 mg/dL Hypoglycemia <79 mg/dL	Intervention (<i>n</i> = 28): glargine and lispro insulin Control (<i>n</i> = 24): preprandial insulin	Intervention 148±51.4 mg/dL Control 225±72 mg/dL <i>p</i> < 0.0001	Intervention 4.1% Control 1.7% <i>p</i> = 0.02	Hospital LOS: NA Hospital mortality: NA
Chase et al. [39], 2008	<i>n</i> = 784 Age = 64 years Male = 479 (61%) DM = 133 (17%) BMI = NA ICU = 784 (100%) Ward = none Follow-up = NA	Glycemic target 72–108 mg/dL Hypoglycemia <40 mg/dL	Intervention (<i>n</i> = 371): Specialized Relative Insulin Nutrition Tables (SPRINT) protocol (IV insulin) Control (<i>n</i> = 413): variety of s.c. insulin sliding scales	Intervention 108±28.8 mg/dL Control 129±43.2 mg/dL <i>p</i> < 0.01	Intervention 2.8% Control 1.2% <i>p</i> < 0.01	Hospital LOS: NA Hospital mortality: (categorized by length of ICU stay) Intervention 20.6–26.3% Control 27.4–34.4%
Cook et al. [32], 2009	<i>n</i> = 159 Age = 68.5±12.8 years Male = 77 (48.4%) DM = 54 (40%) BMI = NA ICU = NA Ward = NA Follow-up = NA Retrospective	Glycemic target: 80–110 mg/dL Hypoglycemia: NA	Intervention 1 (<i>n</i> = 31): s.c. insulin as part sliding scale Intervention 2 (<i>n</i> = 52): NPH insulin sliding scale every 4 h Intervention 3 (<i>n</i> = 76): NPH insulin sliding scale every 6 h	Intervention 1 156 (153–161) mg/dL Intervention 2 134.7 (133–137) mg/dL Intervention 3 133.7 (132–135) mg/dL <i>p</i> < 0.01 (1 vs. 2 or vs. 3) <i>p</i> = 0.41 (2 vs. 3)	Intervention 1 0.7% Intervention 2 1.36 % Intervention 3 0.9% <i>p</i> = 0.03 (1 vs. 2) <i>p</i> = 0.25 (1 vs. 3) <i>p</i> = 0.16 (2 vs. 3)	Hospital LOS: NA Hospital mortality: NA

Table 1. (continued)

Author, years	Study and patients characteristics	Main outcomes definitions	Insulin regimens	Mean blood glucose significance between interventions	% of hypoglycemia events statistical significance between interventions	Other outcomes statistical significance between interventions
Hsia et al. [28], 2011	<i>n</i> = 22 Age = 23–68 years Male = NA DM = 22 (100%) BMI = NA ICU = none Ward = 100% Follow-up = 72 h Retrospective	Glycemic target: 140–180 mg/dL Hypoglycemia: <70 mg/dL	Intervention 1 (<i>n</i> = 8): basal/bolus glargine/lispro Intervention 2 (<i>n</i> = 8): premixed insulin 70/30 twice daily Intervention 3 (<i>n</i> = 6): premixed insulin 70/30 three times daily	Intervention 1* 24% Intervention 2* 22% Intervention 3* 69% * % of BG values in the target range <i>p</i> < 0.01	Intervention 1 5.4% Intervention 2.1% Intervention 3 1.4% <i>p</i> = 0.07 (1 vs. 2 vs. 3)	Hospital LOS: NA Hospital mortality: NA
Dickerson et al. [20], 2013	<i>n</i> = 66 Age = 58 years Male = 17 (25%) DM = 37 (56%) BMI = 30 kg/m ² ICU = 66 (100%) Ward = none Follow-up = 7 days Retrospective	Glycemic target 70–148 mg/dL Hypoglycemia <40 mg/dL	Intervention 1 (<i>n</i> = 32): continuous IV regular insulin infusion therapy Intervention 2 (<i>n</i> = 34): supplemental intermittent IV regular insulin therapy	Intervention 1 125±11 mg/dL Intervention 2 133±14 mg/dL <i>p</i> < 0.01	Intervention 1* 9% Intervention 2* 9% * Percentage of patients with any hypoglycemic event <i>p</i> = NA	Hospital LOS: Intervention 1 41±27 days Intervention 2 39±28 days <i>p</i> = ns Hospital mortality: Intervention 1 3.2% Intervention 2 13.3% <i>p</i> = ns
Murphy et al. [21], 2014	<i>n</i> = 46 Age = 74.8 years Male = 27 (58.6%) DM = 46 (100%) BMI = NA ICU = NA Ward = NA Follow-up = over 40 days Retrospective	Glycemic target NA Hypoglycemia <72 mg/dL	Intervention 1 (<i>n</i> = 18): premixed insulin 70/30 Intervention 2 (<i>n</i> = 13): short acting s.c. insulin before each feed plus Glargine insulin at night Intervention 3 (<i>n</i> = 15): long acting analogue insulin	Intervention 1 227±97.3 mg/dL Intervention 2 225±76 mg/dL Intervention 3 218±90 mg/dL <i>p</i> = 0.46	Intervention 1* 4% Intervention 2* 0% Intervention 3* 7% * % hypoglycemia during feeding <i>p</i> = 0.004	Hospital LOS: Over 40 days for the 3 groups Hospital Mortality: Intervention 1 3 (16.7%) Intervention 2 4 (30.8%) Intervention 3 5 (33.8%) <i>p</i> = NA
b Parenteral nutrition						
<i>Randomized trials</i>						
Hakeam et al. [33], 2016	<i>n</i> = 67 Age = 58 years Male = 28 (42%) DM = 55 (82%) BMI = 27.7 kg/m ² ICU = none Ward = 67 (100%) Follow-up = NA	Glycemic target 140–180 mg/dL Hypoglycemia <70 mg/dL	Intervention (<i>n</i> = 35): Glargine insulin at night Control (<i>n</i> = 32): regular insulin added to parenteral nutrition	Intervention 136.8±39.6 mg/dL Control 148±37.8 mg/dL <i>p</i> = 0.39	Intervention* 5.7% Control* 6.25% * % of patients with hypoglycemia <i>p</i> > 0.1	Hospital LOS: NA Hospital Mortality: NA

Table 1. (continued)

Author, years	Study and patients characteristics	Main outcomes definitions	Insulin regimens	Mean blood glucose significance between interventions	% of hypoglycemia events statistical significance between interventions	Other outcomes statistical significance between interventions
Oghazian et al. [26], 2015	<i>n</i> = 42 Age = 56.1 years Male = 26 (43%) DM = 0 BMI = 23.5 kg/m ² ICU = 100% Ward = none Follow-up = NA	Glycemic target 110–180 mg/dL Hypoglycemia <700 mg/dL	Intervention (<i>n</i> = 21): Glargine insulin Control (<i>n</i> = 21): regular insulin added to parenteral nutrition bag	Intervention 140±19 mg/dL Control 142±15 mg/dL <i>p</i> = 0.741	Intervention* 19 % Control* 0% * % of patients with hypoglycemia <i>p</i> = 0.107	Hospital LOS: Intervention 37 days Control 37 days Survival to hospital discharge: NA
<i>Cohort studies</i>						
Jakoby et al. [34], 2012	<i>n</i> = 48 Age = 58.5 years Male = 21 (43.8%) DM = 16 (33.3%) BMI = NA ICU = 10 (20.8%) Ward = 38 (79.1%) Follow-up = NA Prospective	Glycemic target 140 mg/dL Hypoglycemia: <80 mg/dL	Intervention (<i>n</i> = 22): insulin doses based on carbohydrate delivery (regular insulin in parenteral nutrition bag and NPH) Control (<i>n</i> = 26): ad hoc insulin management (NPH, glargine, etc.)	Intervention 138±37 mg/dL Control 159±46 mg/dL <i>p</i> < 0.0001	Intervention* 3% Control* 1% * Number of glycemic events <40 mg/dL <i>p</i> = 0.12	Hospital LOS: NA Hospital mortality: NA
Neff et al. [22], 2014	<i>n</i> = 53 Age = 68 years Male = 30 (56.6%) DM = 18 (33.9%) BMI = 27 kg/m ² ICU = none Ward = 53 (100%) Follow-up = NA Retrospective	Glycemic target 72–180 mg/dL Hypoglycemia <72 mg/dL	Intervention (<i>n</i> = 32): IV insulin protocol Control (<i>n</i> = 21): individually prescribed s.c. insulin supplemental scales (basal + rapid acting analogues)	Intervention 173±37 mg/dL Control 202±48 mg/dL <i>p</i> = 0.009	Intervention* 40% Control* 29% * Percentage of patients with any hypoglycemic event <i>p</i> = 0.19	Hospital LOS: Intervention 61±49 days Control 43±35 days <i>p</i> = 0.08 Survival to hospital discharge: Intervention 77% Control 67% <i>p</i> = 0.2
c Mixed nutritional support						
<i>Randomized trials</i>						
Holzinger et al. [23], 2004	<i>n</i> = 40 Age = 54.5 years Male = 27 (67.5%) DM = none BMI = 26.2 kg/m ² ICU = 40 (100%) Ward = none Follow-up = 9±4.5 days	Glycemic target: NA Hypoglycemia: NA	Intervention (<i>n</i> = 20): low dose continuous IV insulin (1 IU/h) Control (<i>n</i> = 20): placebo	Intervention 131±39 mg/dL Control 128±30 mg/dL <i>p</i> = ns	Intervention 0% Control 0% <i>p</i> = ns	Hospital LOS: NA Hospital mortality: Intervention 5 (25%) Control 6 (30%) <i>p</i> = ns

Table 1. (continued)

Author, years	Study and patients characteristics	Main outcomes definitions	Insulin regimens	Mean blood glucose significance between interventions	% of hypoglycemia events statistical significance between interventions	Other outcomes statistical significance between interventions
Van Herpe et al. [24], 2013	<i>n</i> = 300 Age = 63.5±14.5 years Male: 181 (60%) DM = 64 (21.3%) BMI = 27.7±5.15 kg/m ² ICU = 300 (100%) Ward = none Follow-up = 14 days	Glycemic target 80–110 mg/dL Hypoglycemia <40 mg/dL	Intervention 1 (<i>n</i> = 149): algorithm guided IV insulin Intervention 2 (<i>n</i> = 151): nurse-directed IV insulin	Intervention 1 106±9 mg/dL Intervention 2 107±11 mg/dL <i>p</i> = 0.36	Intervention 1 0% Intervention 2 6 (0.1%) <i>p</i> = 0.015	Hospital LOS: Intervention 1 16 (10–33) days Intervention 2 14 (9–27) days <i>p</i> = 0.24 Hospital mortality: Intervention 1 19 (12.8%) Intervention 2 10 (6.6%) <i>p</i> = ns
<i>Cohort studies</i>						
Thomas et al. [35], 2005	<i>n</i> = 891 Age = 51.4 years Male = 458 (56%) DM = NA BMI = NA ICU = 891 (100%) Ward = none Follow-up = NA Retrospective	Glycemic target: maximum 128 mg/dL Hypoglycemia: <50 mg/dL	Control (<i>n</i> = 288): no protocol Intervention 1 (<i>n</i> = 502): protocol-IV insulin Intervention 2 (<i>n</i> = 101): modified protocol of IV insulin	Control: 131±32.4 mg/dL Intervention 1: 118±28.8 Intervention 2: 111.6±23.4 <i>p</i> = NA	Control* 1 Intervention 1* 13 Intervention 2* 6 * <i>Number of hypoglycemic events</i> <i>p</i> = NA	Hospital LOS: NA ICU mortality: Control: 76 (26%) Intervention 1: 125 (25%) Intervention 2: 27 (27%) <i>p</i> = NA
Dortch et al. [25], 2008	<i>n</i> = 552 Age = 41 years Male = 391 (71%) DM = 40 (7.2%) BMI = NA ICU = 552 (100%) Ward = none Follow-up = NA	Glycemic target: 80–110 mg/dL Hypoglycemia: <40 mg/dL	Intervention (<i>n</i> = 243): IV insulin computerized protocol Control (<i>n</i> = 309): paper-based IV insulin protocol	Intervention 116±37 mg/dL Control 120±37 mg/dL <i>p</i> < 0.001	Intervention 0.54 % Control 0.23% <i>p</i> < 0.001	Hospital LOS: NA Hospital mortality: Intervention 33 (13.6%) Control 51 (16.5%) <i>p</i> = 0.4
Dickerson et al. [27], 2014	<i>n</i> = 46 Age = 68 years Male = 38 (82.6%) DM = 20 (43.5%) BMI = 33±8.5 kg/m ² ICU = 46 (100%) Ward = none Follow-up = 7 days	Glycemic target 150–180 mg/dL Hypoglycemia <40 mg/dL	Intervention 1 (<i>n</i> = 21): former protocol Intervention 2 (<i>n</i> = 25): new protocol	Intervention 1 145±10 mg/dL Intervention 2 133±14 mg/dL <i>p</i> < 0.001	Intervention 1 0.35% Intervention 2 0% <i>p</i> = 0.005	Hospital LOS: Intervention 1 38±26 days Intervention 2 44±35 days <i>p</i> = ns Hospital mortality: NA

BMI, body mass index; DM, diabetes mellitus; ICU, intensive care unit; IV, intravenous; NA, not available; LOS, length of stay; ns, not significant; s.c. = subcutaneous. Data are shown as mean ± SD; median (interquartile range).

Fig. 2. Forest plot (indirect meta-analysis, random-effect model) of rapid insulin sliding scale (RISS), NPH, Premix, Glargine + Lispro insulin regimen effects on mean blood glucose (mg/dL) in hospitalized patients on enteral support.

Half of the studies were conducted in ICU settings and 3 studies did not inform the patients' setting. Glycemic targets and hypoglycemia definitions were heterogeneous: the glycemic target ranged from 70 to 180 mg/dL and hypoglycemia was defined as capillary glucose less than 40 mg/dL in 3 studies [19, 20, 30], less than 70 mg/dL in 3 [21, 28, 29] and less than 79 mg/dL in one [31]. Only one study had no definition for hypoglycemia [32]. Only one study in this category presented data about hospital length of stay [20] and 3 described hospital mortality [19–21]. MBG control ranged from 108 to 225 mg/dL and was <180 mg/dL in 62.5% of the studies (5 out of 8) in both control and intervention groups. The percentage of hypoglycemia varied from 0 to 9%. The most used insulin regimen to control glucose was sliding scale insulin [19, 29, 31, 32]. Regarding enteral support, 4 studies [19, 20, 31, 32] used special formulas (online suppl. Table 1a).

Figure 2 summarizes the results of the indirect meta-analysis [21, 31, 32] comparing all evaluated insulin regimens. NPH insulin ranked as the best regimen to reduce MBG level (SMD 95% CI): NPH, -2.50 mg/dL (-2.65 to -2.35); Premix, -1.21 (-1.53 to -0.89), and Glargine + Lispro, -1.23 (-1.41 to -1.05) mg/dL as compared to sliding scale rapid insulin regimen. There was no difference between Premix and Glargine + Lispro insulin regimens.

Parenteral NS Group: four studies [22, 26, 33, 34] evaluated different insulin regimens for glycemic control in parenteral support (Table 1b). Two RCTs and 2 cohort studies comprising 228 patients were reviewed. Mean age was 60.7 years, BMI 23.5–27.7 kg/m², and 40% of the patients had diabetes. One study was conducted exclusively in an ICU setting [26], 2 studies included exclusively ward patients [22, 33], and one study included patients from ICU and ward settings [34]. Glycemic targets and hypoglycemia definitions were heterogeneous in these studies:

the maximum glycemic target ranged from 140 to 180 mg/dL and hypoglycemia was defined as glucose less than 80 mg/dL in 2 studies and around 70 mg/dL in 2 others. MBG ranged from 137 to 173 mg/dL in the intervention group and from 142 to 202 mg/dL in the control group. The percentage of hypoglycemia varied from 3 to 40% in the intervention group and from 0 to 29% in the control group. MBG was <180 mg/dL both in control and intervention groups, except in one study [22].

RCTs compared subcutaneous insulin glargine with regular insulin added to the parenteral nutrition bag [26, 33]. Meta-analyses did not demonstrate differences in MBG (SMD 95% CI -3.78 mg/dL [-11.93 to -4.37]; $I^2 = 0\%$) or frequency of hypoglycemia (RR 95% CI 2.48 [0.61–10.10]; $I^2 = 45.6\%$) between the 2 insulin regimens (Fig. 3a, b).

Mixed NS Group (enteral plus parenteral): five studies [23–25, 27, 35] evaluated different insulin regimens for glycemic control in mixed (parenteral plus enteral) NS (Table 1c). Two RCTs and 3 cohort studies comprising 1,829 patients were reviewed. All studies were conducted in the ICU. One study was conducted exclusively with patients with acute kidney failure [27] and one study excluded patients with diabetes [23]. The mean age was 50.5 years, BMI 25.7–27 kg/m², and 18% of patients had diabetes. Glycemic targets and hypoglycemia definitions were diverse: the maximum glycemic target ranged from 80 to 180 mg/dL and hypoglycemia was defined as glucose less than 40 mg/dL in 3 studies [24, 25, 27]. MBG ranged from 106 to 145 mg/dL in the intervention group and from 107 to 133 mg/dL in the control group. Hypoglycemic events varied from zero to less than 1% in the included studies. In all studies, MBG was lower than 180 mg/dL.

Three studies compared computer-based protocols with standard protocols for hyperglycemia control (one RCT and 2 cohort studies) [24, 25, 35]. The RCT [24] protocol took into account several variables (patient profile at admission, blood glucose, insulin dose, nutrition, and steroid medication) and was not comparable to cohort study protocols. A meta-analysis of cohort studies [25, 35] demonstrated that the MBG value was higher in paper-based than computer-based protocols (MD 95% CI 5.41 [1.40–9.40]; $I^2 = 0\%$). Descriptions of hypoglycemic events were not comparable in studies.

Quality Evaluation

Individual quality of RCTs revealed a low risk of bias for most evaluated domains, except performance (bias for most of studies; online suppl. Table 2). For observational studies, NOS scored moderate (4–7 stars out of 9; online suppl. Table 3).

Fig. 3. Forest plots (meta-analyses, random-effects models) of the effect of different insulin regimens on mean blood glucose (**a**) and on the frequency of hypoglycemia in parenteral nutrition support (**b**).

The GRADE quality of evidence for systematic review was evaluated (online suppl. Table 4). In the indirect meta-analysis of the insulin regimens used to treat hyperglycemia in patients on enteral support, the GRADE score evidence was considered very low due to the indirect nature of the comparison and small number of studies. The quality of direct meta-analyses of insulin regimens on parenteral nutrition support was moderate both for MBG and frequency of hypoglycemia events. The quality of evidence was also low for meta-analysis of MBG of insulin-based protocol regimens in mixed NS.

Discussion

This systematic review included 17 studies, 6 RCTs, and 11 cohort studies, designed to evaluate diverse insulin regimens used to treat hyperglycemia and comprised 3,260 hospitalized patients receiving enteral, parenteral,

or mixed NS. MBG ranged from 106 to 225 mg/dL and frequency of hypoglycemia from 0 to 40%. Taking into account the type of administered NS, we performed some direct or indirect meta-analyses. These comparisons allowed us to demonstrate that in patients on enteral support, the MBG was lower with NPH insulin than with sliding scale insulin, Premix, or Glargine + Lispro regimens (indirect meta-analysis). On the other hand, for parenteral nutrition support, the reduction patterns of hyperglycemia did not differ when insulin was added to the parenteral nutrition bag or with subcutaneous insulin glargine use. Lastly, for hyperglycemic patients on mixed NS insulin regimens using computer-based protocols seemed to promote more MBG reduction than paper protocols. Hypoglycemia could be compared only in patients on parenteral nutrition in whom hyperglycemia was treated using regular insulin added to the parenteral nutrition bag or with subcutaneous insulin glargine and no difference was observed between these insulin regimens.

However, regardless of the insulin regimen used, there was only a small, not clinically significant, reduction in MBG.

Hyperglycemia in critically ill patients may be an adaptive response to spare glucose to brain, erythrocytes, and injured tissues, although the benefits of this response may be outweighed by detrimental effects over the long term [36]. Hence, there is still some controversy about the degree of glycemic control in hospitalized patients, especially in ICU settings [6, 7]. Most critical care and endocrinology societies nowadays endorse a random glucose value below 180 mg/dL [4, 30] as the target for hospitalized patients. In our systematic review, there was a great variability in glycemic target even within the nutritional categories; however, in most studies (76%), MBG values were in agreement with current recommendations. This MBG goal was reached irrespective of the insulin regimen used to treat hyperglycemia. Only in 4 studies, 3 conducted in ICU settings, the target of strict glucose control was less than 110 mg/dL [19, 24, 25, 32], but MBG reached this goal only in half of them [19, 24]. Actually the differences between MBG reductions of insulin interventions were lower than 6 mg/dL. This small difference in MBG would require a very large study to show a clinical benefit. Therefore, it should be emphasized that although our results on glucose control were statistically significant, there is no clinical relevance.

A post hoc analysis of the NICE-SUGAR trial revealed that hypoglycemia was strongly associated with mortality [37] and guidelines recommend that insulin infusion programs have to be coordinated with NS intervention to minimize the risk of both hyperglycemia and hypoglycemia [11]. In this sense, severe hypoglycemia, defined as blood glucose lower than 40 mg/dL [38], is the most feared adverse effect related to insulin treatment. Therefore, the choice of insulin regimen should also be based on the absence of harmful effects. From the total of 17 included studies, only 6 [20, 24, 25, 27, 30, 39] reported data on severe hypoglycemia and its frequency varied from 0 to 2.8%. Moreover, in the current systematic review, the definition of hypoglycemia was heterogeneous and unclear in most studies. We could compare only the frequency of hypoglycemia in 2 studies [26, 33] conducted in patients on parenteral nutrition and there was no difference in hypoglycemic events.

Our systematic review had some limitations even though we have performed a comprehensive search and detailed data extraction strictly following all current recommended guidelines [14, 15, 40]. It was not possible to compare most of the studies due to their methodological

differences, unclear or different outcomes definitions, or even missing data. The quality of included studies was moderate and most of them were observational. Very few studies evaluated mortality and hospital length of stay and, therefore, these outcomes could not be compared. Heterogeneity of insulin regimens did not allow us to perform direct comparisons for other predetermined outcomes. The differences among the individual studies are likely to be important. The type of patients (medical, surgical) and the place where the studies occurred (ICU or ward) differed significantly and this might influence the optimal glycemic target. Lack of clinical outcomes could have been attributed to heterogeneity in patient population between studies, differing populations whereby benefit from level of glycemic control may be different, blood variability, hours/day in target blood glucose range, caloric and protein intakes, and timing of initiation of nutrition therapy. Also, samples with diverse characteristics, such as patients with or without diabetes, were studied together. The possible influence of this heterogeneity on our results is unknown, since sensitivity analyses were not allowed due to the characteristics of these studies. Lastly, NS was heterogeneous even within the same category and poorly described and this might be a potential confounder factor.

According to our systematic review, studies comparing different insulin regimens to treat hyperglycemia in hospitalized patients requiring NS are heterogeneous. Our best results on reduction of MBG obtained by insulin regimens using NPH in enteral nutrition or rapid insulin computer-based protocols in mixed NS were not clinically relevant. Additional RCTs, with focus on hard outcomes and severe hypoglycemia, beyond hyperglycemia per se, are needed. Possibly, the best choice might be the less expensive insulin regimen with less associated hypoglycemia events. However, until now it has not been feasible to establish the best insulin regimen to treat hyperglycemia in hospitalized patients on NS.

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Disclosure Statement

The authors declare no conflicts of interest.

Author Contribution

Study concept and design: M.V.V., L.V.V., and M.J.A. Literature search and data extraction: M.V.V., L.V.V., and A.L.T. Assessment of methodological quality: M.V.V. and A.L.T. Statistical

analysis: L.V.V. and M.V.V. Manuscript drafting: all authors. Critical revision of the manuscript for important intellectual content: all authors.

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