Towards a feasible algorithm for tight glycaemic control in critically ill patients: a systematic review of the literature

CRD summary
The authors concluded that glycaemic control in critically ill patients is best achieved using a dynamic scale protocol with continuous insulin infusion and frequent blood gas (BG) measurements, with the last two BG values determining the insulin rate. Poor reporting and methodological problems of the review, as well as differences between the studies, mean that these conclusions may not be reliable.

Authors' objectives
To determine a feasible and reliable protocol for achieving tight glycaemic control in critically ill patients.

Searching
PubMed, EMBASE and the Cochrane Library were searched; the search terms were reported. It appears that the 'related articles' features of these databases were also checked, and that unpublished studies and those published only in abstract form were excluded.

Study selection
Studies of glycaemic control strategies that targeted or achieved a blood glucose (BG) of a maximum of 10 mmol/L were eligible for inclusion. Studies using glucose-insulin-potassium (GIK) protocols were included if they met the other inclusion criteria. Those using an experimental closed-loop intervention were excluded. The studies in the review utilised either a sliding scale algorithm (i.e. depending on the BG, a predetermined amount of insulin is given) or a dynamic scale algorithm (i.e. depending on the BG, the current insulin dose is adjusted by a predetermined amount). In the included studies, the target minimum BG ranged from 3.3 to 8.3 mmol/L and the target maximum ranged from 6.1 to 11.1 mmol/L. The frequency of BG testing varied from every 15 minutes to every 4 hours. Most studies administered insulin by continuous intravenous (IV) infusion plus bolus injections, others largely by subcutaneous injection, while others used continuous IV GIK infusions (with or without IV boluses).

The participants in eligible studies were critically ill patients. Studies of patients undergoing only minor surgery were excluded. The review included studies of patients in surgical and medical intensive care units (ICUs), undergoing cardiac or general surgery, or with acute myocardial infarction or stroke. The patients in most studies, other than those based in ICU settings, had a history of diabetes mellitus.

It was unclear whether studies were required to report specific outcomes in order to qualify for inclusion. The following outcomes were reported in the review: the proportion of BGs in the required range, mean or median BG, and the frequency of episodes of hypoglycaemia. Hypoglycaemia was defined as less than 2.2 to 3.8 mmol/L.

There were no inclusion criteria with respect to the study design, except that a clear description of the study protocol was required. In the review, only study arms treated using an insulin/glucose protocol were included. The results in control groups were not reported.

Two reviewers evaluated studies for selection; it was not stated whether they made decisions independently, or how any disagreements were resolved.

Assessment of study quality
The authors did not state that they assessed validity

Data extraction
Descriptive data were extracted from the primary studies in the form of percentages for binary data and mean or medians for continuous data. The authors did not state how the data were extracted for the review, or how many
reviewers performed the data extraction

**Methods of synthesis**

All of the studies were presented in a table, grouped by study setting. Selected studies were combined in a narrative, grouped according to the mode of administration and/or by the type of glycaemic protocol utilised (sliding scale, GIK or dynamic scale). Clinical differences between the studies were discussed in the text.

**Results of the review**

Twenty-four studies (n=3,425) were included. Their designs were not reported.

Subcutaneous insulin (3 studies, n=867).

Subcutaneous therapy (with IV insulin as needed) achieved glycaemic control in only two thirds of ICU patients. One study (n=37) used a sliding scale and achieved reasonable control with a mean BG of 7.2 (± 1.2) mmol/L in 19 patients receiving subcutaneous insulin and a similar BG (7.3 ± 1.1 mmol/L) in 18 patients in a comparison group receiving IV insulin. Another study (n=30) achieved glycaemic control in only 40% of the group; it was unclear whether a sliding or dynamic scale was used. A third study (n=800) of subcutaneous insulin plus IV boluses on a sliding scale achieved glycaemic control in 70% of patients. BG was measured from 1 to 4 hourly in these studies and rates of hypoglycaemia ranged from 0.34 to 5.6% of patients.

Continuous insulin with sliding scale protocol (4 studies, n=261).

Most studies of sliding scale protocols achieved moderate to poor glycaemic control, despite 1 to 4 hourly BG measurement. Mean BGs of 8.2 to 10.3 mmol/L were reported in 3 studies (n=93). A fourth study (n=168) reported that glycaemic control was achieved in 61% of the sample. Rates of hypoglycaemia ranged from 0.2 to 7.1% of BG samples, where stated.

GIK infusion (3 studies, n=114).

GIK infusions achieved variable rates of glycaemic control. One study (n=17) of a GIK infusion using a dynamic scale reported a mean BG of 10.1 mmol/L. Another (n=25) reported that 68% of patients achieved a mean BG of less than 7mmol/L, and a third (n=72), achieved a mean BG of 7.7 (± 0.2) mmol/L; it was unclear whether a sliding or dynamic scale was used. BG was measured from 1 to 2 hourly in these studies; only one clearly reported the rate of hypoglycaemia, which was 1 out of 25 patients.

Continuous infusion with dynamic scale protocol (11 studies).

Studies using a dynamic scale generally achieved better glycaemic control than those using predefined targets, and reported fewer hypoglycaemic episodes than those using sliding scale protocols. They used tight glucose targets, with the insulin rate determined by the last two BG measurements. Six studies, all conducted in ICUs, had BG targets within a range of 4.0 to 7.7 mmol/L. One (n=765) achieved a mean BG of 5.7 (± 1.1) mmol/L and another (n=50) reported achieving glycaemic control for a mean of 11.5 (± 3.7) hours daily. Two (n=20 and n=27) reported mean and median BGs of 7.8 and 6.6 mmol/L, respectively, and two others (n=118 and n=52) reported achieving glycaemic control in 73% and 66% of patients, respectively. BG was measured from 1 to 4 hourly in these studies. Rates of hypoglycaemia ranged from nil to 5.1% of patients in these studies.

Five studies (n=879) that appeared to use dynamic scale protocols had BG targets within a range of 6.7 to 11.1 mmol/L. Four (n=802) reported mean BGs of 6.9 to 9.7 mmol/L; the fifth reported that 62% of patients had BGs of 3.5 to 15 mmol/L. BG was measured from 0.5 to 4 hourly in these studies; rates of hypoglycaemia ranged from 2 out of 77 patients to 18% of patients, where reported.

Three studies (n=272) apparently used different types of protocol, with mixed results.

**Authors’ conclusions**

Tight glycaemic control and low frequency of hypoglycaemia in critically ill patients is best achieved using a dynamic
scale protocol with continuous insulin infusion combined with frequent BG measures, using the last two BG values to determine the insulin infusion rate.

CRD commentary
The objective was clear but the inclusion criteria were wide and imprecise, with no stated inclusion criteria relating to the study design. Three databases were searched but other relevant sources were not consulted, and the restriction to published studies means that the review may be subject to publication bias. The search dates were not reported. There was no indication that studies were assessed for risk of bias, and it was not stated whether steps were taken to minimise reviewer error and bias during the data extraction, such as decisions being made independently by more than one reviewer. Insufficient detail was provided about the primary studies, in particular with respect to study design and glycaemic protocol. For most of the data measures of variance were not reported. The narrative synthesis addressed only some of the primary studies, without providing any rationale for this, and did not adequately address the heterogeneity. The lack of reporting of review methods, the clinical heterogeneity of the studies, the exclusion of control groups from the analysis, and the selective reporting of results in the text make it difficult to interpret the data presented. These methodological problems and the wide variation among the studies mean that the authors’ conclusions may not be reliable.

Implications of the review for practice and research
Practice: The authors stated that a feasible glycaemic protocol for critically ill patients should include a BG target of 4 to 8 mmol/L (depending on current BG levels and local resources); a dynamic scale protocol with 1 to 4 hourly BG tests using the last 2 BGs to determine the insulin infusion rate; continuous enteral feeding; and nursing acceptance of the protocol. The review did not consider evidence on enteral feeding or nursing attitudes.

Research: The authors did not state any implications for further research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.