Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Survey into blood glucose control in critically ill adult patients in the Netherlands

M.J. Schultz[1,2], J.M. Binnekade[1], R.E. Harmsen[1], M.J. de Graaff[1], J.C. Korevaar[3], F. van Braam Houckgeest[4], J.P. van der Sluijs[5], H. Kieft[6], P.E. Spronk[1,7*]

[1]Departments of Intensive Care, [2]Laboratory of Experimental Intensive Care and Anaesthesiology (LEICA), [3]Department of Clinical Epidemiology and Biostatistics, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands, [4]Department of Intensive Care, Tergooi Hospitals, location Hilversum, Hilversum, the Netherlands, [5]Department of Intensive Care Medicine, Medical Center Haaglanden, The Hague, the Netherlands, [6]Department of Intensive Care Medicine, Isala Clinics, location Sophia, Zwolle, the Netherlands, [7]Department of Intensive Care, Gelre Hospitals, location Lukas, Apeldoorn, the Netherlands, *corresponding author: tel.: +31 (0)20-566 25 09, e-mail: m.j.schultz@amc.uva.nl

ABSTRACT

Background: To study current clinical practice in blood glucose (BG) control in adult intensive care units (ICUs) in the Netherlands.

Methods: We performed a national survey focusing on blood glucose targets, insulin administration, BG control guidelines, and opinions regarding BG control aiming for normoglycaemia (known as intensive insulin therapy, IIT).

Results: The completed questionnaire was returned by 88/113 (78%) of the participating centres. In 98% (86/88) of the ICUs some sort of BG control was being practised. Half of the ICUs (42/86, 48%) used tight BG targets as with IIT; 28/86 (33%) and 13/86 (15%) used more liberal targets of 4.4 to 7.0 mmol/l and 4.4 to 8.0 mmol/l, respectively. Eighty-two (93%) reported having a local guideline on BG control (or IIT). The BG threshold to start insulin was 7.0±1.3 mmol/l *vs* 7.8±1.3 mmol/l in ICUs that practised IIT *vs* ICUs that practised less tight BG control, respectively (p=0.005). In 28/86 (33%) measurement of the BG values was done according to a strict time schedule (i.e., BG values were measured on predefined time points). While respondents were fairly agreed on the benefits of IIT, opinions regarding ease of implementation and time needed to apply this strategy varied. In addition, severe hypoglycaemia was considered a serious side effect of IIT.

Conclusion: Approximately half of the ICUs in the Netherlands reported having implemented IIT. However, the full guideline as used in the original studies on IIT was hardly ever implemented. Concerns about severe hypoglycaemia, at least in part, hampers implementation of IIT.

KEYWORDS

Glucose control; intensive insulin therapy; guideline; survey

INTRODUCTION

The optimal blood glucose target and best way to control blood glucose are currently undecided for adult critically ill patients. Although intensive insulin therapy (IIT, blood glucose control aiming at blood glucose levels of 4.4 to 6.1 mmol/l) improved the mortality and morbidity of adult critically ill surgical and medical patients in two randomised controlled trials,[1,2] the benefit of IIT was questioned in three recent studies[3-5] and one meta-analysis.[6] Concerns about severe hypoglycaemic events associated with implementation of IIT have been another reason to advise against implementing IIT and to accept higher blood glucose targets,[7-10] thereby potentially losing any benefit that is associated with IIT.[11-13] Other factors potentially impeding implementation of IIT may include the belief that this strategy is time consuming and costly, and the lack of a common guideline for IIT.

Understanding of current blood glucose control practice patterns, as well as beliefs and concerns surrounding blood glucose control, in particular IIT, is essential for development of (inter)nationally accepted guidelines for blood glucose control in adult critically ill patients. We hypothesised that IIT is far from being implemented in critically ill patients in the Netherlands, and if implemented that it differs significantly from the guideline

as originally described.[1,2] This postal survey amongst adult intensive care units (ICUs) in the Netherlands explored this hypothesis.

MATERIALS AND METHODS

This survey was conducted with the approval of the institutional review board of the Academic Medical Centre, Amsterdam, the Netherlands, which waived the need for informed consent. Respondents were told that consent for participation in the survey was implied if they answered and returned the questionnaire.

Study population

A questionnaire was sent to ICU physicians and/or ICU nurses in the Netherlands. Neonatal and paediatric ICUs were excluded from the survey. The medical directors of all adult ICUs were contacted and asked to appoint one ICU physician and/or one registered ICU nurse engaged in blood glucose control to complete the questionnaire, after which these participants were contacted.

Definitions

In the survey 'blood glucose control (with insulin)' was defined as any strategy aiming at a certain blood glucose level or range (with insulin); IIT was defined as blood glucose control aiming at the tight blood glucose targets of 4.4 to 6.1 mmol/l.[1,2] Hypoglycaemia is defined as blood glucose level between 2.2 to 4.4 mmol/l, severe hypoglycaemia as ≤2.2 mmol/l.

The questionnaire

A first draft of the questionnaire was developed at an informal meeting with ICU physicians and ICU nurses from four Dutch hospitals. This first draft was sent for review to two ICU physicians, four ICU nurses and one expert in informatics. They independently reviewed the text and added comments and new questions. The second draft was sent to the same experts, who all approved the questionnaire.

Questionnaire items

The questionnaire started with questions regarding demographic data, i.e., type of organisation, size and volume of responding ICU. This was followed by questions on blood glucose control and IIT. Four different aspects of blood glucose control and IIT were surveyed: 1) the availability of a guideline for blood glucose control or IIT; 2) rules for insulin administration and blood glucose targets; 3) specific measures surrounding blood glucose control or IIT; 4) opinions and behaviour in relation to IIT. The questionnaire ended with itemised statements on IIT, to which the respondents were asked to respond on a visual analogue scale (VAS, ranging from 1 for complete disagreement, to 10 for complete agreement).

Questionnaire format and pretesting

A printed questionnaire was first tested in a small subset of three ICU physicians and three ICU nurses in the Academic Medical Centre, Amsterdam, the Netherlands, to ensure that each question and statement was clear. Unclear questions and statements were rephrased with the help of these caregivers. Finally, the questionnaire was printed in an A5-format booklet.

Administration of the questionnaire

We sent the questionnaire to the selected respondents for self-administration. To maximise the response rate, we enclosed a postage-paid return envelope, and after three weeks a postal reminder was sent, and reminder phone calls were made. After a two-month response-free period, the survey was considered to be complete.

Data management and statistical analysis

Descriptive statistics of dichotomous or ordinal variables are proportions. Continuous variables are expressed by the mean ± standard deviations (SD), medians and interquartile ranges (IQR), or the odds ratio and 95% confidence interval. We determined the significance of differences between variables with χ^2 analysis (for categorical variables) and independent t-test (for continuous variables). A p value of <0.05 was considered to be significant. Effect sizes of dichotomous data or data aggregated into dichotomous data were expressed as relative risks. Multiple factors considered to be modifiers for dichotomous dependent variables were analysed by multivariate logistic regression analysis. If suitable we expressed statistical uncertainty as 95% confidence limits. Analysis were performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

Response rate

Of 113 adult ICUs, 88 returned a completed questionnaire (response rate 78%). Questionnaires were returned for 68% (60/88) by an ICU physician and 32% (28/88) by an ICU nurse.

ICU characteristics

The characteristics of responding ICUs are given in *table 1*.

Availability of guidelines for blood glucose control or IIT

In 98% (86/88) of the responding ICUs some sort of blood glucose control was being practised. Approximately half of these ICUs (42/86, 48%) used the tight blood glucose

Table 1. *Characteristics of responding ICU*

	N = 88
Type of hospital*, N (%)	
• Academic centres	12 (14%)
• Non-academic training centres	47 (53%)
• Non-academic nontraining centres	27 (31%)
Type of ICU (organisation)**, N (%)	
• Closed-format	79 (90%)
• Open-format	8 (10%)
Type of ICU (specialities), N (%)	
• Mixed medical-surgical	81 (92%)
• Surgical	6 (7%)
• Neurosurgery	1 (1%)
Number of ICU beds available for mechanical ventilation, N (%)	
• >20 beds	13 (15%)
• 15-20 beds	5 (6%)
• 5-15 beds	48 (55%)
• <5 beds	21 (24%)
Number of admissions per year***, N (%)	
• >2000	8 (9%)
• 1500-2000	7 (8%)
• 1000-1500	18 (20%)
• 500-1000	39 (44%)
• <500	9 (10%)
Staffing, median (IQR)	
• Board-certified ICU physicians	3.7 (2-5) FTE
• Board-certified ICU nurses	34 (24-55) FTE
• ICU fellows (13 academic or training ICU)	6 (2-10)
• Number of patients a physician attended for during office hours	6 (4-8)
• Number of patients a physician attended for during the evening/weekend	9 (6-12)
• Number of nurses per bed per 24 hours	3 (2-3)

*** two missing values; ** one missing value, *** seven missing values.**

targets as in the original studies on IIT by Van den Berghe *et al.* (i.e., 4.4 to 6.1 mmol/l);[1,2] 28/86 (33%) and 13/86 (15%) of responding ICUs used more liberal targets of 4.4 to 7.0 mmol/l and 4.4 to 8.0 mmol/l, respectively. One ICU reported accepting blood glucose values up to 10 mmol/l. Three ICUs did not use a range, but aimed for a blood glucose level of 6.5 mmol/l.

Six out of 86 ICUs (7%) reported that they did not have a (written or electronic) guideline on blood glucose control or IIT (two academic, three non-academic teaching and one non-academic nonteaching ICUs; all closed-format ICUs); 56 (65%) reported having both a physician- and a nurse-based guideline on blood glucose control or IIT; 7% (6/86) and 21% (18/86) said that the guideline on blood glucose control or IIT was either physician-based or nurse-based, respectively. Availability of a guideline was not statistically different between the different ICU types (p=0.97). Within ICUs that practised IIT the availability of a guideline was similar compared with ICUs that practised less tight blood glucose control (p=0.31).

Rules for insulin administration

The mentioned blood glucose threshold to start insulin was 7.4±1.3 mmol/l (range 6 to 12 mmol/l). ICUs that practised IIT said that they started insulin at a lower blood glucose value than ICUs that practised less tight blood glucose control (7.0±1.3 mmol/l *vs* 7.8±1.3 mmol/l, p=0.005).

The majority of respondents, 73% (64/86), said that they applied blood glucose control in all patients, irrespective of the referring speciality. This was not different for centres using IIT and less tight blood glucose control; there were no differences between medical and surgical ICUs either. In 24% (21/88) of the ICUs blood glucose control was not initiated in patients who were expected to stay on the ICU <3 days. Diabetes mellitus or no need for mechanical ventilation were only seldom a reason for not applying blood glucose control (2/80 and 10/77, respectively).

ICU physicians and ICU nurses were allowed to initiate insulin in similar frequencies (51% (45/86) and 64% (56/86), respectively), with no differences between ICUs that applied IIT and ICUs that aimed for less tight blood glucose levels (p=0.89). The same applied for insulin dose adjustments; dosing adjustments were made in 63% (55/86) and 75% (66/86) by ICU physicians and ICU nurses, respectively. ICU physicians were reported to have the exclusive legal responsibility for insulin dosing in 31/86 (35%) ICUs, while this responsibility was exclusively with ICU nurses in 28/86 (11%) and with both in 28/86 (32%); in 13/86 (15%) of the responding ICUs this was not mentioned. There were no differences between ICUs that practised IIT and ICUs that aimed for less tight blood glucose levels (p=0.65).

In most ICUs (66%, 49/88) adjustments in insulin dosing were made as a consequence of blood glucose values and according to a flow chart. In other ICUs, the insulin dose was adjusted with the help of specially developed software (6%, 6/88), or a calculation formula (14%, 12/88).

Specific measures surrounding blood glucose control or IIT

In the majority of ICUs timing of blood glucose measurement was unclear and/or highly variable. Measurement of the blood glucose values was only done according to a strict time schedule (i.e., blood glucose values were measured at predefined time points, usually in addition to the possibility to measure them in between) in approximately one third of ICUs (34%, 28/86). Of the ICU physicians, 86% (76/88) individually determined the time of the next blood glucose measurement, while for the ICU nurses this was 80% (71/88).

There were no differences between ICUs that practised IIT and ICUs that aimed for less tight blood glucose targets (p=0.65).

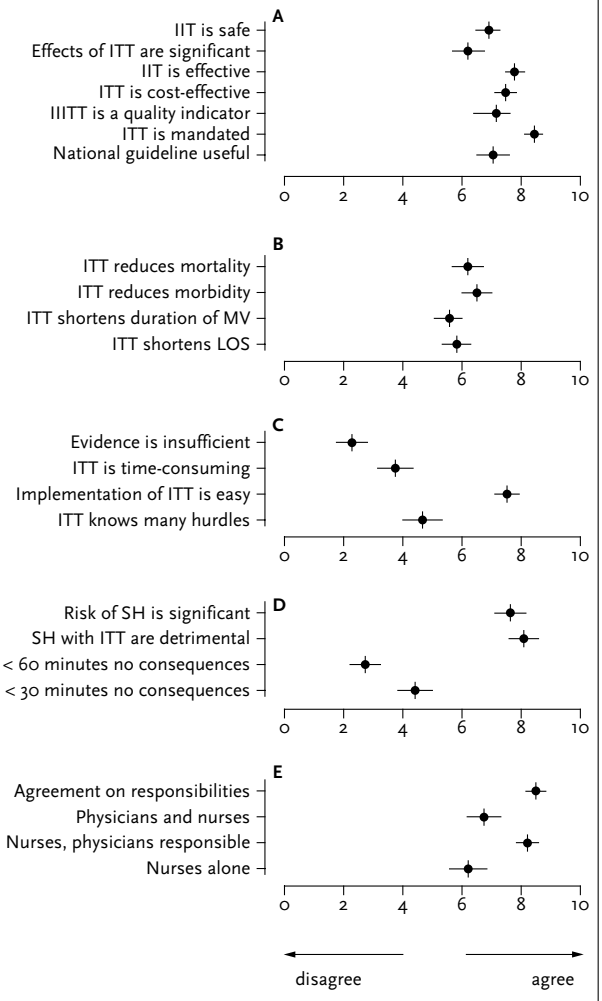
Guidelines provided adjustments for insulin dosing when patients received parenteral or enteral nutrition in 46% (40/86) of participating ICUs; corticosteroid therapy

(18/86; 21%) or the presence of diabetes mellitus was mentioned in 17/86 (19%) of the responses. Of the local guidelines, 53% (47/88) indicated that (tight) blood glucose targets should no longer be aimed for if patients were on oral feeding. Blood glucose control was to be discontinued if the patient was transferred to a step-down facility in 78% (69/86) of cases. Surprisingly, blood glucose control was also to be stopped if patients were in the predefined blood glucose ranges for two days or longer (38%, 33/86). Severe hypoglycaemia was seldom reported as a reason to stop blood glucose control (3%, 3/86).

Opinions and behaviour in relation to IIT

Figure 1 shows responses to the itemised statements regarding IIT. Most respondents agreed on the statements that IIT is safe and (cost)-effective. In agreement with this, most respondents thought of IIT as a mandatory ICU strategy and application of IIT as an indicator of ICU quality. While respondents were fairly agreed on the benefits of IIT, opinions regarding ease of implementation and time needed to apply IIT varied. In addition, severe hypoglycaemia was considered a serious side effect of IIT. Finally, there was good agreement on responsibilities regarding starting and dosing insulin. In contrast to what was practised in the original studies on IIT, the responsibility of ICU nurses varied widely across ICUs in the Netherlands.

Figure 1. *Responses to itemised statements on IIT (A: general statements; B: effects of IIT; C: implementation aspects; D: risks of hypoglycaemia; E: statements on responsibilities surrounding IIT). Respondents were asked to respond on a visual analogue scale (VAS), ranging from 1 for complete disagreement, to 10 for complete agreement. Data are means + 95% confidence intervals. IIT = intensive insulin therapy; LOS = length of stay; MV = mechanical ventilation; SH = severe hypoglycaemia; 60 (or 30) minutes no consequences: severe hypoglycaemia <60 (or 30) minutes is without clinical consequences.*



DISCUSSION

In this survey into blood glucose control and IIT we showed fair but incomplete implementation of IIT in ICUs in the Netherlands. Indeed, while approximately half of the ICUs mentioned that they used IIT and a fast majority stated that they had a guideline on glucose control, insulin was started at much higher blood glucose values than in the original studies by Van den Berghe *et al.*[1,2] Also, in contrast to the studies from Leuven, insulin was started and its dose adjusted by both ICU physicians and ICU nurses, rather than by ICU nurses alone. This survey demonstrates the need for a clear (inter)nationally accepted guideline on blood glucose control.

Implementation of a guideline is a complex process, involving numerous successive steps.[14,15] One of the first steps is an environmental scan, such as (regional and/or local) surveys into current practice, behaviour and potential hurdles (including concerns and (mis)beliefs) for adopting a certain guideline. Surveys also allow insight into translational errors of complex guidelines. We demonstrated several differences between guidelines on blood glucose control and the guideline as used by Van den Berghe *et al.*[1,2] The guideline in Leuven combined a simple set of rules on blood glucose control, next to targeting at tight blood glucose levels of 4.4 to 6.1 mmol/l: a) start of insulin is advised even with low blood glucose levels, even when within targets (thus at fairly low blood glucose levels); b) initiation and dose adjustment of insulin is done solely by ICU nurses (and never by ICU physicians, who are in fact banned from blood glucose control in Leuven); c) blood glucose measurements are to be performed at predefined time points (i.e., every four hours, but measurements can be done in between if needed; the decision is left to the discretion of the attending ICU nurse), d) although

severe hypoglycaemia is clearly stated as a potentially dangerous side effect, (mild) hypoglycaemia is not a reason for stopping insulin and infusing glucose, but a reason to be more careful and take more frequent blood glucose measurements to adjust the dose of insulin when the risk of severe hypoglycaemia increases or persists. The present survey clearly shows that these aspects are not translated into the currently used guidelines on blood glucose control. Although it is difficult, if not impossible, to determine whether all the above-mentioned aspects add to the success of IIT in the two original studies on IIT,[1,2] it is our belief that if we want to implement true IIT we should implement what was practised in these two positive studies. The results from this survey, therefore, have been used in an implementation project aiming for complete implementation of IIT in four hospitals in the Netherlands, which we will report on after completion of the project.[16]

The benefit of IIT in adult critically ill patients has been questioned recently.[3,4,6] Indeed, three recent randomised controlled trials did not confirm the beneficial effects of IIT.[3-5] It must be mentioned, however, that in all three trials blood glucose control in the intervention group was less tight than in the original studies in Leuven.[1,2] Also, compared with the control groups of the two original studies there was improved blood glucose control in the control groups, further decreasing the contrast between the study arms of these three negative studies. In addition, the first two confirmation studies may have been (severely) underpowered, one study due to the fact that it was stopped prematurely because the safety board considered the higher incidence of severe hypoglycaemia to be significant and dangerous.[3] A meta-analysis of randomised controlled trials by Wiener *et al.* showed that hospital mortality did not differ between blood glucose control and usual care overall; also, mortality was not influenced when stratified by blood glucose targets or ICU settings.[6] However, in our view Wiener *et al.* incorrectly meta-analysed the results from all the studies, including those in which IIT was said to be practised but actually not achieved.[3,4] The most recent meta-analysis on IIT by Griesdale *et al.*[17] showed that particularly surgical patients may benefit from IIT by lower mortality (RR=0.63; CI=0.44 to 0.91), confirming the original findings by Van den Berghe. The difference with the meta-analysis of Wiener *et al.* is predominantly explained by the inclusion of a recent Chinese study performed in a surgical ICU.[18] One recent paediatric study adds to the evidence on the benefit of IIT in critically ill subjects.[19] This randomised controlled trial showed IIT to improve short-term outcome of patients in a paediatric ICU. Of note, in this study exactly the same guideline, though with different (age-adjusted, lower) blood glucose targets, was used as in the two former studies from Leuven.[1,2]

It seems that blood glucose control is not a completely nurse-driven strategy in many ICUs, in contrast to what is practised in Leuven. Indeed, starting insulin as well as making dose adjustments were reported to be done by both ICU physicians and nurses. This may be a misconception: in particular the continuous presence of ICU nurses at the bedside may prevent deterioration of glucose control. For instance, changes in feeding, the most important cause of severe hypoglycaemia with IIT,[20] are recognised earlier by ICU nurses allowing them to adjust the insulin dose more swiftly. Similarly, giving full control of insulin dosing to those carers, who are constantly present (i.e., ICU nurses), allows shorter durations of both hyperglycaemia and hypoglycaemia.

Our survey suggests concern about severe hypoglycaemia is one reason to accept higher blood glucose values, which is a frequently mentioned barrier to implementation of IIT.[21,22] It seems contradictory that the respondents indicated IIT in itself to be safe, but when specifically asked for their opinion pertaining to severe hypoglycaemia, their replies indicated concerns about a higher occurrence and potential safety issues. This is an interesting contradiction, but might be explained by the fact that the respondents did not directly link the occurrence of severe hypoglycaemia to IIT per se. Indeed, opinion leaders sturdily point to the high incidence of (severe) hypoglycaemia as (one) reason not to aim for normoglycaemia.[7-10] Moreover, several large trials have even been stopped due to a high incidence of (severe) hypoglycaemia although predefined endpoints had not yet been reached.[3,23] Consequently, implementation of IIT is far from complete, and frequently local guidelines still accept higher blood glucose levels than those accepted in the original studies on IIT.[1,2] Severe and prolonged hypoglycaemia can indeed cause complications and mortality.[24,25] Although hypoglycaemia occurs more often in patients who are most severely ill and have a long stay on the ICU, this association does not suffice to conclude that severe hypoglycaemia actually causes death. Solid evidence for a causal relationship between short-lasting IIT-induced severe hypoglycaemia in the ICU setting and risk of death is lacking. A retrospective nested case-control study that was carefully matched for type and severity of illness as well as duration of ICU stay and thus for exposure time to insulin infusions, however, suggested no causal relationship between severe hypoglycaemia and mortality.[26] Moreover, experimental data showed that glucose reperfusion, rather than hypoglycaemia itself, is the cause of neuronal damage.[27]

Results from our survey are different from results from three surveys in Canada,[28] the United Kingdom[21] and Australia/New Zealand.[22] First, we found that insulin is started at lower blood glucose levels. Indeed, McMullin *et al.* reported thresholds for hyperglycaemia to be remarkably high: the median threshold was 10 mmol/l (IQR 9 to 11 mmol/l), with ICU nurses acting on 0.5 mmol/l higher blood glucose levels.[28] Of interest, in

the survey by McMullin *et al*. blood glucose control was judged not to be important for surgical patients, the targeted patients in the first study on IIT in ICU patients by Van den Berghe *et al*. Our survey showed that ICUs practise blood glucose control or IIT in all patient groups, irrespective of the referring speciality. Second, the level of IIT implementation is higher than in the UK and Australia/New Zealand. Mackenzie *et al*.[21] reported that only 25% of ICUs aimed for blood glucose levels similar to those used in the studies by Van den Berghe *et al*. Mitchell *et al*. also found that only a few ICUs have adopted blood glucose control.[22] The majority of the ICU nurses in the UK (82%) reported having concerns regarding severe hypoglycaemia in the patients receiving blood glucose control, although a clear reasoning for these feelings was lacking.[21] In the survey in Australia/New Zealand, reasons for not implementing IIT were also concerns about the risk of severe hypoglycaemia, but also doubts about the external validation of the original study by Van den Berghe *et al*.[22] Our results are, at least in part, in line with a recent survey by Hishberg *et al*. on stated blood glucose control practice in North American ICUs.[29] In this survey, 83% of adult ICU physicians preferred a target blood glucose level between 4.4 and 6.1 mmol/l, which is even higher than in our survey. In the North American survey many ICU clinicians (60%) mentioned hypoglycaemia to be more dangerous than hyperglycaemia, which seems in line with opinions in our survey.

Several limitations to our survey should be mentioned. Most important, the response from participating ICUs could be either by ICU physicians and/or nurses. However, responses from different care providers in centres from which we received both a response from an ICU physician and an ICU nurse were not different. Second, although the response rate is very high (78%), institutions that did not respond to the survey could potentially be less likely to be convinced of the benefits of IIT and/or less likely to practise IIT. This may have influenced the results, but we consider this unlikely because both academic and non-academic hospitals were broadly represented in the survey. Third, one questionnaire per participating centre may not be an adequate way of interpreting the standard of care pertaining to IIT in the participating centres. Nevertheless, we think that in general the responses were a reflection of department policies, because in an accompanying letter, the medical directors were specifically asked to reply in such a manner. Fourth, a survey only asks for current policy, and does not test whether a certain strategy is truly (and correctly) applied. For instance, one report on IIT in Finland showed that while it was implied that IIT was performed, the median blood glucose level of 6.2 mmol/l with 53% of blood glucose measurements above target suggested that implementation of IIT was rather 'loose'.[30] Finally, it can be questioned whether our findings are relevant to other countries.

In conclusion, many ICUs have adopted some form of blood glucose control, in half of the ICUs even with the tight blood glucose targets as used in the original studies on IIT. However, not all aspects of the original guideline, as used in Leuven, are fully appreciated. One reason for not implementing IIT seems concerns about severe hypoglycaemia, although it is questionable whether this fear is rational.

ACKNOWLEDGEMENTS

MJS is supported by a restricted grant of the Netherlands Organisation for Health Research and Development (ZonMW); NOW-VENI grant 2007 [project number 80-007028-98-07301].

REFERENCES

1. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. N Engl J Med. 2001:345:1359-67.
2. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006:354:449-61.
3. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med. 2008:358:125-39.
4. De la Rosa GD, Donado JH, Restrepo AH, et al. Strict glycemic control in patients hospitalized in a mixed medical and surgical intensive care unit: a randomized clinical trial. Crit Care. 2008:12:R120.
5. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009:360:1283-97.
6. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008:300:933-44.
7. Polderman KH, Girbes AR. Intensive insulin therapy: of harm and health, of hypes and hypoglycemia. Crit Care Med. 2006:34:246-8.
8. Malhotra A. Intensive insulin in intensive care. N Engl J Med. 2006:354:516-8.
9. Russell JA. Management of sepsis. N Engl J Med. 2006:355:1699-1713.
10. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008:36:296-327.
11. Van den Berghe G, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med. 2003:31:359-66.
12. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. JAMA. 2003:290:2041-7.
13. Schultz MJ, de Graaff MJ, Kuiper MA, Spronk PE. The new Surviving Sepsis Campaign recommendations on glucose control should be reconsidered. Intensive Care Med. 2008:34:779-80.
14. Grol R, Grimshaw J. From best evidence to best practice: effective implementation of change in patients' care. Lancet. 2003:362:1225-30.
15. Cook DJ, Montori VM, McMullin JP, Finfer SR, Rocker GM. Improving patients' safety locally: changing clinician behaviour. Lancet. 2004:363:1224-30.
16. http://www.onderzoekinformatie.nl/en/oi/nod/onderzoek/OND1326385/.
17. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ. 2009:180:821-7.

18. He W, Zhang TY, Zhou H, et al. [Impact of intensive insulin therapy on surgical critically ill patients]. Zhonghua Wai Ke Za Zhi. 2007:45:1052-4.

19. Vlasselaers D, Milants I, Desmet L, et al. Intensive insulin therapy for patients in paediatric intensive care: a prospective, randomised controlled study. Lancet. 2009:373:547-56.

20. Vriesendorp TM, van Santen S, DeVries JH, de Jonge E, Rosendaal FR, Schultz MJ, et al. Predisposing factors for hypoglycemia in the intensive care unit. Crit Care Med. 2006:34:96-101.

21. Mackenzie I, Ingle S, Zaidi S, Buczaski S. Tight glycaemic control: a survey of intensive care practice in large English hospitals. Intensive Care Med. 2005:31:1136.

22. Mitchell I, Finfer S, Bellomo R, Higlett T. Management of blood glucose in the critically ill in Australia and New Zealand: a practice survey and inception cohort study. Intensive Care Med. 2006:32:867-74.

23. http://clinicaltrials.gov/show/NCT00107601 [accessed May 2009].

24. Bates DW. Unexpected hypoglycemia in a critically ill patient. Ann Intern Med. 2002:137:110-6.

25. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. Diabetes Care. 2003:26:1902-12.

26. Vriesendorp TM, DeVries JH, van Santen S, et al. Evaluation of short-term consequences of hypoglycemia in an intensive care unit. Crit Care Med. 2006:34:2714-18.

27. Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. J Clin Invest. 2007:117:910-8.

28. McMullin J, Brozek J, Jaeschke R, et al. Glycemic control in the ICU: a multicenter survey. Intens Care Med. 2004:30:798-803.

29. Hirshberg E, Lacroix J, Sward K, Willson D, Morris AH. Blood glucose control in critically ill adults and children: a survey on stated practice. Chest. 2008:133:1328-35.

30. Kaukonen KM, Rantala M, Pettila V, Hynninen M. Severe hypoglycemia during intensive insulin therapy. Acta Anaesthesiol Scand. 2009:53:61-5.