GUIDELINE

Insulin administration for the control of blood glucose in the adult ICU – an evidence-based guideline

Independent Nurse Educator (Critical Care), Cape Town
Roseanne E Turner, MSc Nursing

The South African Critical Care Nurses Forum identified the development of practice guidelines as an urgent priority. This guideline, which marks the beginning of this process, aims to present evidence-based recommendations for the administration of continuous infusions of intravenous insulin for the control of blood glucose in critically ill adult patients.

A wide range of databases was searched including Medline, CINAHL and the Cochrane database. Further references were obtained from the reference lists of relevant articles and Lilly Laboratories provided data relating to the stability of insulin in solution and storage recommendations. Expert knowledge and experience were also considered. The data were graded according to the strength of evidence and recommendations made for clinical practice.

These recommendations include using isotonic saline as the carrier, not preparing solutions in advance, remixing every 12 hours and priming the syringe and tubing before use. The use of a protocol is advisable but this is dependent on accurate measurement of blood glucose by properly trained staff. Capillary blood is adequate for most patients except for those who are in shock and on vasopressors. The signs of hypoglycaemia and hypokalaemia and the management of these complications are included.

Scope of guideline
South African critical care nurses in both the independent and public sectors.

Guideline purpose
To present evidence-based recommendations for the administration of continuous infusions of intravenous insulin for the control of blood glucose (BG) (4.5 - 6.1 mmol/l) in the critically ill adult patient.

Target population
Critically ill adult patients (medical and surgical) receiving continuous intravenous insulin infusions for glucose control.

Interventions and practices considered
1. What carrier solution (diluent) should be used?
2. How often should the solution be remixed?
3. How should solutions be administered?
5. How often should BG be measured?
6. Early detection and management of serious side-effects (hypokalaemia and hypoglycaemia).
7. The development of protocols.
8. South African Nursing Council (SANC) policy with regard to standing orders.

Background
A large number of critically ill patients will develop hyperglycaemia while in the intensive care unit (ICU). This hyperglycaemia, which is not related to a previous history of diabetes mellitus, is due to the hypermetabolic stress response associated with all major trauma or acute illness. In addition, the use of treatments like vasopressors, corticosteroids and nutrition (enteral and parenteral) is known to add to the risk of hyperglycaemia. High levels of hyperglycaemia on admission and prolonged duration of hyperglycaemia while in the ICU are thought to be predictors of poor outcome.

In 2001 Van den Berghe et al. reported that control of glucose resulted in: a 42% decrease in relative mortality; a reduction in patient complications, specifically severe infections and organ failure; a shorter ICU stay; less ventilator dependence and easier weaning of patients; and a 44% reduction in the risk of polyneuropathy. It is thought that the primary reasons for these improvements in outcome are related to the prevention of immune dysfunction, a reduction in systemic inflammation and the protection of endothelium and other cellular structures.

Since 2001 when Van den Berghe and colleagues demonstrated that the normalisation of BG levels in a large group of surgical ICU patients dramatically improved their clinical outcomes, there has been a worldwide trend to maintain strict glycaemic control in all critically ill patients. In 2004 the Surviving Sepsis Campaign included the maintenance of BG levels below 8.3 mmol/l in their guidelines for the management of severe sepsis and septic shock. In their more recent study looking at medical ICU patients Van den Berghe and colleagues demonstrate similar results but note an increased mortality in those medical patients who receive insulin therapy and who have a short ICU stay (less than 3 days). The reduction in morbidity and mortality rates in critically ill patients was shown to be associated with substantial cost saving when compared with conventional therapy.

Glycaemic control is now considered acceptable evidence-based practice in the care of certain groups of critically ill patients where skilled nurses and adequate medical equipment are available.

Methods
A wide range of databases was searched to gather evidence for the development of this guideline: Medline, CINAHL and the Cochrane database. In addition further references were obtained from the reference lists of relevant articles. Lilly Laboratories provided data relating to the stability of insulin in solution and storage recommendations. The data thus obtained were graded according to the strength of evidence presented, which in turn was based on the quality of study design. The recommendations, which appear at the end of each section, have been devised from the evidence. Practical aspects highlighted by clinical experts together with the experience of the author were also taken into consideration.

Grading of evidence in this way provides the reader with an indication of the author’s confidence that the guideline will produce the required outcome. The classification scheme presented by Shekelle et al. has been simplified to make it more accessible (Table I).

<table>
<thead>
<tr>
<th>Grading system</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grading of evidence</strong></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength of recommendation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>D</td>
</tr>
</tbody>
</table>

What carrier solution (dilutent) to use?
It used to be common practice to mix insulin for infusion in human albumin or stabilised human serum (SHS) as the presence of negatively charged proteins results in less adsorption of insulin to giving sets and containers. However, a subsequent study by Peterson et al. showed little discernible difference in the amount of insulin delivered when solutions containing albumin and those containing saline were used.
Human albumin and SHS are expensive especially as gelatin solutions (e.g. Haemacel) apparently have a similar effect, but it is not clear if the starch-based colloid also prevent insulin adsorption. Weisenfeld et al. recommend the addition of minute quantities (7 ml/500 ml) of human albumin to a saline carrier to prevent insulin loss. Kesher et al. reported that the addition of freshly drawn whole blood to the insulin solution was an effective means of preventing insulin adsorption. It can be argued that in practice the amount of insulin adsorbed is irrelevant as one is more concerned with the effect or BG level. Van den Berghe et al. and others use isotonic saline as the carrier for insulin in their protocols. Lilly Research Laboratories state that insulin may be diluted with normal saline 0.9% (personal communication). Dextrose solutions are not recommended as these in combination with insulin promote the passage of potassium out of the intravascular space and so increase the risk of hypokalaemia.

**Recommendation**: Isotonic saline should be used as the carrier for insulin in infusion. Level D.

**For how long is the solution stable?**

Insulin diluted to 10 IU/ml in normal saline is stable at room temperature for up to 24 hours (Lilly Research Laboratories) but no data could be found about the stability of lower concentrations of insulin, which are used for continuous infusions (i.e. 1 IU/ml). Lilly Research Laboratories state that they have not conducted stability studies to evaluate the stability of insulin in NS diluted to 1 IU/ml and so do not endorse this practice (personal communication). Weisenfeld et al. noted that at lower concentrations the adsorption of insulin into plastic is greater than at higher concentrations. There is also concern about the stability of insulin solution at room temperature for prolonged periods, especially as zinc used to stabilise insulin is also absorbed into plastic. Bradley reports that prepared infusions of insulin are stable for up to 12 hours.

**Recommendation**: Solutions should not be prepared before they are required and should be re-mixed every 12 hours or if patient insulin requirements increase unexpectedly. Level D.

**What administration set?**

Early studies by Weisenfeld et al. showed that the adsorption of insulin to infusion containers and tubing was considerable; in addition it appears that the lower the concentration of insulin, the longer the duration of contact with the adsorbing surface and the slower the flow rate, the greater the adsorption of insulin. In some instances as much as 70% of insulin was found to bind to binding sites in some giving sets. However once these binding sites are saturated it seems that further loss of insulin through adsorption is minimal. Peterson et al. therefore recommend that the entire infusion apparatus be flushed with 50 ml of insulin solution before commencement of the infusion. It is noted that priming of the administration set forms part of the Yale protocol described by Goldklang et al. for use in medical patients. Ling et al. found that the highest percentage loss of insulin occurred in infusion tubing, followed by IV bags, and that less adsorption occurred when polypropylene (syringes) and polyethylene (tubing) materials were used than when these were made of polyvinyl chloride (PVC) plastic. They also advocate priming the syringes, bags and administration sets to allow for the more accurate calculation of patient dose.

**Recommendations**: Where possible use 50 ml polypropylene (syringes) and polyethylene (tubing) materials. Avoid using PVC IV bags. In addition flush the entire administration set (syringe and tubing) with 50 ml of insulin solution prior to initial use. Level B.

**Capillary versus whole blood?**

The ability to achieve tight control of BG is dependent on the reliability and accuracy of the BG monitoring. Sharp highlights the many potential problems associated with bedside BG monitoring and that nurses may obtain inaccurate results because of incorrect timing, insufficient blood sampling and the incorrect use of equipment. It is therefore vital that nurses responsible for the bedside measurement of BG are properly trained in the correct use of the monitoring equipment.

Critically ill patients are often hypoperfused, on vasopressor medications and have significant peripheral oedema, all of which compromise peripheral circulation and interfere with capillary blood samples (finger prick). Sylvain et al. found the accuracy of finger-prick measurements in hypotensive patients unacceptable and these resulted in a statistically significant underestimation of serum glucose measurements. Kanji et al. went further and evaluated the reliability of BG readings in a group of critically ill patients with poor peripheral circulation (on vasopressors) and with significant peripheral oedema, and compared results from capillary blood measured with a glucometer, arterial blood measured with a glucometer and arterial blood measured on a blood gas machine. These results were also compared with laboratory results. Clinical agreement occurred when paired test readings would result in the same clinical action occurring (e.g. decrease of insulin rate). Kanji et al. demonstrated that clinical agreement with the laboratory was best when arterial blood was measured on the blood gas machine (76.5%); when using a glucometer the clinical agreement was better with arterial blood (70%) than with capillary blood (57%).
the presence of hypoglycaemia these differences were even more noticeable as clinical agreement was only 26% with capillary blood and 65% with arterial blood. In both capillary and arterial samples the glucometer provided higher values than those recorded in the laboratory. By contrast Maser et al.18 found that capillary BG sampling tended to underestimate the BG while arterial sampling tended to overestimate BG.

Nurses also need to be aware that if patients are receiving medications which contain maltose, e.g. immunoglobulins, there is a risk that bedside monitors will over-read the BG level.9

**Recommendations:** Properly trained personnel must do BG evaluation. Capillary samples are adequate for most patients. Arterial and not capillary blood must be used to monitor BG in patients in shock, those on vasopressors and those who have peripheral oedema. Level C.

**How often is BG monitoring required?**

It is important that the monitoring of BG is done at close enough intervals to ensure patient safety through the early detection of hypoglycaemia (BG less than 4.4 mmol/l). Frequent monitoring can markedly increase the nursing workload. Aragon19 calculated that the hourly monitoring and glycaemic control of a single critically ill patient could add as much as 2 nursing hours in a 24-hour period. In the initial protocol presented by Van den Berghe et al.3 BG levels are measured every 1 - 2 hours until stable and then 4-hourly. Goldberg et al.13 recommend that BG be checked hourly until stable for 3 consecutive hours (i.e. levels within target range), then 2-hourly for 12 - 24 hours and then 4-hourly. If the patient’s condition deteriorates, insulin, vasopressor and/or steroid therapy is changed or if the nutrition intake alters then hourly checks should be reinstated until the patient is once again stable.

**Recommendations:** All patients should have hourly BG levels done until they are stable for 3 hours; then the interval can be increased to 2- and later 4-hourly. Hourly monitoring must be re-introduced if the patient's condition changes. Level D.

**Early recognition and treatment of hypoglycaemia**

Hypoglycaemia (BG < 4.4 mmol/l) is a serious complication of insulin therapy, which can result in devastating neurological consequences. The incidence of hypoglycaemia during insulin therapy is reportedly as high as 16% in some cases20 especially if the target range for glucose levels is relatively tight (4.5 - 6.1 mmol/l). Lower levels of hypoglycaemia have been reported when the target levels are slightly higher (4.5 - 8.3 mmol/l). In addition the detection of hypoglycaemia is often difficult in the sedated critically ill patient and the nurse has to be particularly vigilant and rely on BG levels as well as physical signs that include tachycardia, diaphoresis and seizures.21 Vriesendorp et al.22 report a number of independent factors that may predispose patients to hypoglycaemia. These factors include diabetes mellitus, sepsis, female gender, use of bicarbonate dialysis, use of vasopressors and a reduction of nutrition rate without the concurrent reduction of insulin. Other factors predisposing to hypoglycaemia may include the use of beta-blockers, liver failure and the tapering of steroids. Patients should never be given insulin if they are not receiving some form of glucose supplementation (i.e. either nutrition or a dextrose infusion). If the BG falls below 4.4 mmol then the insulin infusion must be stopped and the patient given a bolus of 50% glucose intravenously. It is advisable to use 10 - 20 ml 50% glucose, re-check the level after 15 minutes and then give more glucose if necessary. If too large an initial dose of 50% glucose is used it is often difficult to regain control of blood glucose.

**Recommendations:** Nurses must be trained to recognise patients at greater risk of developing hypoglycaemia, to recognise the physical signs of hypoglycaemia and administer treatment according to the local protocol. Patients with physical signs of hypoglycaemia should be treated even if the bedside glucose level appears to be within normal limits. Level D.

**Early recognition and treatment of hypokalaemia**

Hypokalaemia (serum potassium < 3.5 mEq/l) is another life-threatening complication of insulin therapy. Hypokalaemia occurs as a result of potassium shifts into the cells. Symptoms of hypokalaemia include weakness, fatigue, respiratory difficulty, paralytic ileus and leg cramps. Hypokalaemia can also be suggested by the ECG changes, which include U waves, t-wave flattening, ST-segment changes and arrhythmias.22 Patients already at risk of developing hypokalaemia from gastrointestinal (diarrhoea) and renal loss (diuretics, penicillin, amphotericin B) and those suffering from malnutrition or alkalosis are at increased risk of developing hypokalaemia while on insulin therapy, as are those patients receiving adrenaline and other sympathometrics. In addition hypokalaemia potentiates digitalis toxicity.22 Potassium replacements are given according to medical prescription. The safest way to correct potassium is by oral or nasogastric replacement. If the situation is life threatening, intravenous potassium can be administered at a rate not exceeding 20 mmol/h.22 Intravenous potassium should where possible be given via a central line and an infusion pump or rate controller must always be used.
Recommendations: Nurses must be trained to recognise patients at greater risk of developing hypokalaemia and to recognise the physical signs of hypokalaemia. Serum potassium levels should be checked daily in all patients and twice daily in those patients at high risk of developing hypokalaemia. Level D.

Interaction with other drugs

Insulin infusions should ideally be given via a dedicated intravenous line. There are very few published data about the compatibility of insulin with other drugs although it has been established that insulin is incompatible with dopamine, magnesium, phenitoin and ranitidine. These drugs must therefore never be given via the same intravenous line as insulin. Many antibiotics, heparin, furosemide and potassium are physically compatible and can be administered via the same line as insulin saline. However it must be noted that intermittent infusions (antibiotics, potassium, furosemide) and those with fluctuating infusion rates should never be given via the same line as continuous infusions even when venous access is limited. When intensive insulin therapy is given, all medications should be mixed with saline and not dextrose as this ensures more stable BG.

Recommendation: Insulin infusions may be given via the same line as other compatible medications provided the infusion rate is stable. Other medications should be mixed with saline. Level D.

The development of protocols

Since 2001 there have been a number of reports in the literature describing the implementation of various insulin infusion protocols, which are safe, effective and practical to use. Maintaining tight BG levels is labour intensive, and studies report the problems associated when nurses follow individual, intuitive criteria to manage the BG. These problems include higher incidence of severe hypoglycaemia, the more frequent need for rescue dextrose therapy and underlin the need for a protocol which is sophisticated enough to allow for the control of glucose yet simple and practical enough to be implemented in units without expert supervision or the need for frequent deviations from the protocol. Kanji et al. found that with a protocol they were able to achieve glycaemic control more rapidly and so improved the efficiency of the insulin therapy. Another advantage of a good protocol is the reduction in nursing time, as less frequent monitoring is required and less time required instituting rescue therapy. Most nurses endorse tight glycaemic control but the time required adds to the already burdensome workload of the critical care nurse. Protocols improve efficiency and safety of BG control in critically ill patients.

Recommendation: All units should develop or adopt nurse-driven protocols for the standardisation of intravenous insulin therapy. Level C.

South African Nursing Council (SANC) policy with regard to standing orders

Standing orders do not comply with the SANC requirements for a legally valid prescription, i.e. it is not an individualised, written instruction by a medical practitioner for a medication or treatment. SANC recognises that there are times when nurses need to use standing orders or prescriptions and makes the following recommendations to eliminate risk to the nurse. Protocols for the tight control of BG fall into this domain.

In order to be legally valid a copy of the standing prescription, which displays the patient’s name and hospital number, must be attached to the prescription chart and this copy must be signed and dated by the prescribing doctor as soon as possible.

BG control in critically ill adults

Please note that a glucose control protocol is a medical prescription and must comply with the SANC regulations. Units should develop protocols from the evidence presented above, taking into consideration the patient profile and the available resources. The protocol given below is based on these guidelines and intended only as an example.

Patient monitoring

1. All new admissions must have BG checked.
2. Monitor and chart BG level every 4 hours for all ICU patients.
3. When patient is on insulin infusion, monitor BG hourly until stable.
4. Monitor serum potassium at least daily. Monitor twice daily in patients at increased risk of developing hypokalaemia.
5. Use a correctly calibrated and serviced glucometer to monitor BG.
6. Check accuracy daily by comparing ward glucose level with a laboratory sample.
7. Use capillary blood (finger prick) unless patient is in shock, on inotropes or has peripheral oedema.
8. Use arterial blood if the patient is in shock, on inotropes or has peripheral oedema.
9. If the BG level is over 8.3 mmol/l commence insulin infusion as outlined below.
Commencing insulin infusion

1. Mix regular insulin (Actrapid or Humulin R) in NaCl.
2. Mix 1 IU per 1 ml of normal saline (i.e. solution = 1 IU insulin/ml).
3. Mix in a 50 ml syringe and administer via syringe pump.
4. Mix infusion immediately prior to use and re-mix every 12 hours.
5. Flush 50 ml of solution through all the IV tubing (to saturate the binding sites).
6. Make sure patient is receiving either enteral feeds or glucose IV.
7. Commence insulin protocol with IV bolus dose of regular soluble insulin and commence infusion according to the BG level.\(^1\)
   a. < 10 mmol/l – no bolus, start infusion at 2 ml/h
   b. 10 - 15 mmol/l – 1 IU bolus dose and start at 2.5 ml/h
   c. 15 - 20 mmol/l – 2 IU bolus dose and start at 3 ml/h
   d. > 20 mmol/l – 3 IU bolus dose and start at 3.5 ml/h.

Changing the rate of insulin infusion

1. Check BG hourly till BG stable for 3 consecutive samples, then 2-hourly.
2. Maintain BG between 4.5 and 8.3 mmol/l.
3. If BG is within target range, maintain infusion at current rate.
4. If BG falls to < 4.4 mmol STOP insulin infusion and give bolus dose of 10 - 20 ml 50% glucose IV. Recheck BG in 15 minutes and give more glucose if necessary. Recomence infusion as per protocol if necessary.
5. If BG remains > 8.3 mmol but < 15 mmol, increase insulin infusion by 2 ml/h.
6. If BG > 15 mmol, give a bolus of 2 IU insulin and increase rate by 2 ml/h.

NOTE
- If BG remains high, consider remixing the infusion.
- Ensure that IV glucose-containing solutions are given at a constant rate to maintain stability. Use normal saline for drug boluses.
- Patients must be receiving an IV glucose infusion or an enteral feed at all times.

Special thanks to: Lilly Research Laboratories, Jane Roe (Nurse Specialist, St George’s Hospital, London), Rencia Gillespie and Lance Michell.

GUIDELINE STATUS

Date developed: October 2006 (Review in 4 years – 2010)

Developed by: R E Turner (MSc Nursing)

Guideline committee: Critical Care Nurses Forum with input from critical care specialists in private and public sectors.

Endorsed by: Critical Care Society of Southern Africa (CCSSA)

Conflict of interest: Nil, this guideline was not commercially funded.
