Management of Parenteral Nutrition Associated Hyperglycaemia: A Comparison of Subcutaneous and Intravenous Insulin Regimen

Abstract:

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Abstract

PN is associated with significant hyperglycaemia, which may be detrimental to clinical outcome. There are few data on the management of this phenomenon outside of intensive care units. In our unit, we studied the efficacy of protocol-based intravenous insulin delivery as compared to subcutaneous insulin prescribed individually outside of the critical care setting. In a retrospective review over a two-year period, we compared patients with PN-associated hyperglycaemia who had received both modes of insulin therapy. A total of 122 who developed PN-associated hyperglycaemia were identified. Those on the intravenous insulin regimen were within glycaemic target for more time than those on the subcutaneous regimen (62% Vs 43%, p=0.008). We therefore conclude that outside of the critical care setting, intravenous insulin delivers better glycaemic control and should therefore be considered optimum therapy for patients with PN-associated hyperglycaemia.

Introduction

Parenteral nutrition (PN) is used in a wide variety of clinical scenarios, and it is widely accepted that adequate nutritional support is an essential part of successful recovery from critical illness[1,2]. However, PN has been associated with hyperglycaemia in patients with and without diabetes[1-3]. Up to 88% of PN recipients develop hyperglycaemia[4-6]. This effect is particularly evident in patients with acute pancreatitis, where the addition of PN almost doubles the rate of hyperglycaemia[7]. Hyperglycaemia is associated with poor outcomes in the context of critical illness and PN use with higher infection rates, higher mortality and renal injury[4,8-10]. PN-associated hyperglycaemia also correlates with increased rates of cardiovascular complications and systemic sepsis[4,6]. Hyperglycaemia therefore results in greater lengths of stay in intensive care units (ICUs), and greater lengths of stay in hospital generally[10].

Outside of the critical care setting, prospective data in humans confirm that there is an increased risk of mortality associated with hyperglycaemia[11]. This risk is five-fold greater in PN recipients who develop hyperglycaemia at a serum glucose level of 10mmol/l or higher, when compared to those with a serum glucose level less than 7.8mmol/l[11]. However, there are few data on the effects of insulin treatment on reducing this risk. In particular there is a dearth of data to inform healthcare providers on which modality of insulin therapy can offer the best outcomes. Studies using rat models of sepsis have shown survival in PN-associated hyperglycaemia is improved when intravenous insulin is used to correct the hyperglycaemia[12]. There have been human studies in specific cohorts, such as patients post-gastrectomy for gastric cancer, which have reported improved outcomes with intensive glycaemic control[13].
However, this has not been well replicated in the non-critically ill patient.

Current guidelines recommend maintaining blood glucose concentrations between 7.8 and 10mmol/l when on PN[14]. Insulin therapy can be most effectively delivered when a specific protocol is utilised to guide health providers[15,16]. However, major guidelines do not offer clear recommendations on how to deliver insulin therapy with PN[17,18]. Intravenous insulin and regular subcutaneous insulin can be used to deliver glycaemic targets in PN-associated hyperglycaemia[19]. Further data are needed to determine best practice, and to indicate whether intravenous or subcutaneous insulin therapy is more effective in the management of PN-associated hyperglycaemia outside of the critical care setting.

Methods

We conducted a retrospective review of patients admitted to our centre who received PN. The data was collected over a two-year period up to January 2010. In April 2009, a protocol was introduced whereby it was recommended that patients who developed PN-associated hyperglycaemia, as defined by a recorded capillary blood glucose levels of greater than 10mmol/l on two or more consecutive occasions, commence intravenous insulin while on PN. An algorithm for dose adjustment according to the blood glucose level was devised (Table 1).

Prior to this, patients were treated with subcutaneous insulin on individually prescribed supplemental scales. In this regimen, the doses of insulin prescribed subcutaneously were not standardised and varied from patient to patient. We compared those who had received the subcutaneous insulin regimens with the intravenous insulin protocol. Patients were identified from a detailed hospital-based clinical register of those receiving PN over the two-year period. This register is maintained by the parenteral nutrition clinical nurse manager and the Department of Nutrition and Dietetics. From these records, medical and surgical patients who were commenced on insulin therapy for hyperglycaemia during PN outside of the critical care setting were identified. The ICU and critical care patients were excluded, as the focus of our study was the efficacy of the two insulin modalities in non-critically ill patients. This study was completed in accordance with Beaumont Hospital ethical guidelines. Those on the intravenous protocol had dose titrations under nurse supervision in accordance with the protocol (Table 1). Those on subcutaneous insulin had a mixture of rapid acting insulin analogues and basal insulin, which was prescribed by the primary medical or surgical team, often in consultation with the diabetes care team.

An anonymised study database was constructed. Clinical parameters including gender, age, body mass index (BMI), admission diagnosis, indication for PN, and steroid use were recorded. The length of time PN was used, patient length of stay and patient outcomes were also recorded in the study database. Patients who had a diagnosis of diabetes before admission to the hospital had additional measurements including HbA1c levels. Duration of diabetes and the individualâ s pre-admission glycaemic therapy were also recorded. Blood glucose levels were tested using point of care testing four times a day while on PN. All patients had glycaemic profiles recorded with reference to the rate of hypoglycaemia (defined as a blood glucose less than 4.0mmol/l), time spent in glycaemic target (defined as a capillary blood glucose reading between 4.0 and 10.0mmol/l inclusively), time spent in hyperglycaemia (defined as a blood glucose of greater than 10mmol/l), and mean daily capillary blood glucose levels. Descriptive statistics were used and we compared the subcutaneous insulin group with the intravenous insulin group using Studentâ s t-test and Mann-Whitney U tests for parametric and non-parametric data respectively. Regression analysis was used in the cohort as a whole to evaluate for associations between use of each insulin treatment paradigm and glycaemic and clinical outcomes. Statistical significance was assumed at $p<0.05$. All statistics were completed on the R software (Version 2.11.1).

Results

We identified 555 patients who received PN in the study period. Of these 122 received PN outside of the critical care setting and had recorded capillary blood glucose readings of greater than 10mmol/l on two or more readings. Many of those treated with subcutaneous insulin did not have a complete glycaemic record with clear insulin doses given the ad hoc nature of this regimen. Therefore, these data could not be included in our analysis. This resulted in a final group of 53 patients who had complete records. Of this analysed group of 53 patients, 32 (60%) were treated with intravenous insulin as per protocol.

On comparing the intravenous insulin group to the subcutaneous insulin group, there were no statistically significant differences in age or BMI (Table 2). However, there were differences in glycaemic outcomes (Table 3). The group treated with intravenous insulin had a significantly lower daily mean capillary blood glucose level (9.6 – 2.1mmol/l Vs 11.2 – 2.6mmol/l, p=0.009), and spent a greater proportion of time in glycaemic target (62% Vs 43%, p=0.008). There was no significant difference in hypoglycaemia rates (1% Vs 2%, p=0.14). On regression analysis, intravenous insulin was associated with a greater time spent in glycaemic target (p=0.02) and a lower mean blood glucose level (p=0.03). There was no association with other glycaemic variables. The use of intravenous insulin was not associated with hypoglycaemia.

Length of hospital stay (61 – 49 days Vs 43 – 35 days, p=0.08) and survival to discharge (77% Vs 67%, p=0.2) were comparable between groups. Of the total cohort, 73% survived to discharge. Male gender was positively associated with survival to discharge (p=0.003). Men comprised 73% of survivors, and only 20% of those who died in hospital. Length of stay was significantly associated with duration of PN (p<0.001). Intravenous insulin use was not associated with length of stay. Pre-admission diabetes requiring insulin therapy was significantly associated with a longer length of stay on logistic regression analysis (p=0.04). Pre-existing diabetes was not associated with mortality.

Discussion

This study demonstrates that use of a standardised intravenous insulin infusion protocol in the treatment of PN-associated hyperglycaemia results in improved glycaemic outcomes outside of the critical care setting. The mean capillary blood glucose levels were lower, and users of intravenous insulin therapy spent more time in glycaemic target as compared to those prescribed subcutaneous insulin on an individual basis without an increased rate of hypoglycaemia. These data are in agreement with previous studies that report improved outcomes with prescribed protocols as compared to an ad hoc insulin prescription strategy[15,19]. Our data shows that an intravenous insulin protocol is superior to subcutaneous insulin delivered on an individual basis, and outside of a prescribed protocol, in PN-associated hyperglycaemia outside of the critical care setting. Our data is retrospective and has limitations, including the lack of randomization. This may have introduced selection bias. The absence of a control group or a parallel design also weakens the conclusion, as it cannot take into account extraneous factors such as infectious outbreaks that could have affected outcomes, including length of stay. However, given the current evidence, testing ad hoc subcutaneous insulin administration and a prescribed intravenous insulin protocol in PN-associated hyperglycaemia in a prospective study may not be ethically acceptable.

Complete prescription records were not always available in the subcutaneous insulin group, resulting in over half of the initial group being excluded from the data. Unfortunately, the ad hoc insulin prescribing in that group, and the absence of formal prescription protocols to facilitate complete prescription recording and insulin delivery, mean that reliable data were not available for comparison. This is a weakness of our study. However, this illustrates another strength of the prescribed intravenous insulin protocol, as it offers a clear record of the insulin prescribed and given, and is likely to reduce drug prescribing and administering error.

Our data in the subcutaneous group are comparable to several clinical scenarios still employing ad hoc subcutaneous insulin prescribing[15,19]. Frequent glycaemic assessment and insulin dose adjustment are vital in any inpatient insulin protocol as patients are often experiencing acute physiological stresses which can lead to rapid fluctuations in glycaemia. Intravenous insulin offers the flexibility to address this problem given the rapid onset of action and clearance. Our findings support the use of intravenous insulin protocols in the management of PN associated-hyperglycaemia. This can deliver significant improvements in glycaemic control in the non-critical inpatient setting.

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References

1. Lee H, Koh SO, Park MS. Higher dextrose delivery via TPN related to the development of hyperglycemia in non-diabetic critically ill patients. Nutr Res Pract. 2011 Oct;5:450-4.

2. Rosmarin DK, Wardlaw GM, Mirtallo J. Hyperglycemia associated with high, continuous infusion rates of total parenteral nutrition dextrose. Nutr Clin Pract. 1996 Aug;11:151-6.

3. Wright J. Total parenteral nutrition and enteral nutrition in diabetes. Curr Opin Clin Nutr Metab Care. 2000 Jan;3:5-10.

4. Cheung NW, Napier B, Zaccaria C, Fletcher JP. Hyperglycemia is associated with adverse outcomes in patients receiving total parenteral nutrition. Diabetes Care. 2005 Oct;28:2367-71.

5. Schloerb PR. Glucose in parenteral nutrition: a survey of U.S. medical centers. JPEN J Parenter Enteral Nutr. 2004 Nov-Dec;28:447-52.

6. der Voort PH FR, Bakker AJ, Heide L, Boerma EC, der Horst IC. Intravenous glucose intake independently related to intensive care unit and hospital mortality: an argument for glucose toxicity in critically ill patients. Clin Endocrinol. 2006;64:141-4.

7. Petrov MS, Zagainov VE. Influence of enteral versus parenteral nutrition on blood glucose control in acute pancreatitis: a systematic review. Clin Nutr. 2007 Oct;26:514-23.

8. Pasquel FJ, Smiley D, Spiegelman R, Lin E, Peng L, Umpierrez GE. Hyperglycemia is associated with increased hospital complications and mortality during parenteral nutrition. Hosp Pract (Minneap). 2011 Apr;39:81-8.

9. Sarkisian S, Fenton TR, Shaheen AA, Raman M. Parenteral nutrition-associated hyperglycemia in noncritically ill inpatients is associated with higher mortality. Can J Gastroenterol. 2010 Jul;24:453-7.

10. Pasquel FJ, Spiegelman R, McCauley M, Smiley D, Umpierrez D, Johnson R, et al. Hyperglycemia during total parenteral nutrition: an important marker of poor outcome and mortality in hospitalized patients. Diabetes Care. 2010 Apr;33:739-41.

11. Olveira G, Tapia MJ, Ocon J, Cabrejas-Gomez C, Ballesteros-Pomar MD, Vidal-Casariego A, Olivarez J, Marquez E, Tous MC. Parenteral Nutrition-Associated Hyperglycaemia in Noncritically Ill Inpatients Increases the Risk of In-hospital Mortality (Multicenter Study): Study Group of Hyperglycaemia in Parenteral Nutrition: Nutrition Area of the Spanish Society of Endocrinology and Nutrition (SEEN). Diabetes Care. 2012 Dec 6 [Epub ahead of print].

12. Heuer JG, Sharma GR, Zhang T, Ding C, Bailey DL, Stephens EJ, Holmes KC, Grubbs RL, Fynboe KA, Chen YF, Jakubowski JA. Effects of hyperglycemia and insulin therapy on outcome in a hyperglycemic septic model of critical illness. J Trauma. 2006 Apr;60:865-72.

13. Cao S, Zhou Y, Chen D, Niu Z, Wang D, Lv L, Li Y. Intensive versus conventional insulin therapy in nondiabetic patients receiving parenteral nutrition after D2 gastrectomy for gastric cancer: a randomized controlled trial. J Gastrointest Surg. 2011 Nov;15:1961-8.

14. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, Inzucchi SE, Ismail-Beigi F, Kirkman MS, Umpierrez GE. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Endocr Pract. 2009 May-Jun;15:353-69.

15. Jakoby MG, Nannapaneni N. An insulin protocol for management of hyperglycemia in patients receiving parenteral nutrition is superior to ad hoc management. JPEN J Parenter Enteral Nutr. 2012 Mar;36:183-8.

16. Umpierrez GE, Hellman R, Korytkowski MT, Kosiborod M, Maynard GA, Montori VM, Seley JJ, Van den Berghe G. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2012 Jan;97:16-38.

17. Singer P, Berger MM, Van den Berghe G, Biolo G, Calder P, Forbes A, Griffiths R, Kreyman G, Leverve X, Pichard C. ESPEN Guidelines on Parenteral Nutrition: intensive care. Clin Nutr. 2009 Aug;28:387-400.

18. McClave SA, Martindale RG, Vanek VW, McCarthy M, Roberts P, Taylor B, Ochoa JB, Napolitano L, Cresci G. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). JPEN J Parenter Enteral Nutr. 2009 May-Jun;33 277-316.

19. Gosmanov AR, Umpierrez GE. Management of Hyperglycemia During Enteral and Parenteral Nutrition Therapy. Curr Diab Rep. 2012 Oct 12.