Comparison of Two Intravenous Insulin Titration Methods in Hyperglycemic Crisis

Journal of Pharmacy Technology
2017, Vol. 33(2) 72–77
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122517690749
journals.sagepub.com/home/pmt

Eileen F. Rohrbach, PharmD¹, Kellianne Webb, PharmD, BCPS¹,
and Tracy Costello, PharmD, BCPS^{1,2}

Abstract

Background: Glycemic control using intravenous insulin infusions is an important component of hyperglycemic crisis treatment. Literature supports the use of standardized titration protocols; however, comparisons of specific methods are limited. **Objective:** Compare the safety and efficacy of 2 insulin infusion titration methods used in hyperglycemic crisis. **Methods:** A retrospective chart review was conducted including adults admitted to an inpatient facility from August 1, 2013, to August 1, 2015, who were treated for at least 4 hours with an intravenous insulin infusion. Primary efficacy outcomes of time to anion gap closure and time to goal blood glucose was studied in patients meeting criteria for diabetic ketoacidosis ($n = 79$), while the primary safety outcome of rates of hypoglycemia were compared among all study patients ($n = 200$). **Results:** The fixed-rate titration method had statistically shorter time to blood glucose <200 mg/dL compared to the multiplier titration group (6.1 [4.0] vs 8.8 [4.4], respectively; $P = .018$; mean time in hours [standard deviation]); however, no statistically significant difference was seen in the other primary efficacy and safety outcomes. Statistical improvements were found in secondary outcomes of intensive/progressive care units, length of stay, and infusion duration in the fixed-rate titration method, while less deviation from titration recommendations was found in the multiplier titration group. **Conclusions:** Significant differences seen in time to a goal blood glucose, deviation prevalence, and holds of the infusion for low blood glucose have identified areas for optimization, additional study, and staff education.

Keywords

insulin, critical care, clinical pharmacy, diabetes, pharmaceutical care, antihyperglycemics

Background

Hyperglycemic crises require rapid intervention to reduce the risk of mortality, which can be as high as 1 in 5 cases.¹ Early prevention and evidence-based treatment of hyperglycemic crisis has improved outcomes. Between 1980 and 2009, mortality in one specific hyperglycemic crisis, diabetic ketoacidosis (DKA), decreased by 64%.^{2,3} In spite of this improvement, mortality in patients with multiple comorbidities as well as health care dollars spent on treatment of this condition remain high.^{2,4,5}

The metabolic derangements seen in hyperglycemic crisis are driven by an absolute or relative insulin deficiency and an increase in counterregulatory hormones, such as cortisol and catecholamines. Insulin therapy, along with hydration and electrolyte correction, is able to reverse the pathologies and allow for glucose to move intracellularly.^{4,7} A continuous intravenous (IV) infusion of regular insulin has a favorable kinetic profile for titration making it an ideal treatment for these conditions.⁵

For safety and convenience, standardized protocols are often used for monitoring and adjusting IV insulin therapy, giving the health care team objective recommendations for

adjusting treatment in response to a patient's clinical status and laboratory values.^{4,5,8,9} Despite the benefits seen in these studies, no single standardized process is at this time supported in the literature, and comparisons of method effectiveness are limited making development of an individual protocol more challenging. Staff education on the proper use of the protocols also provides a barrier to successful implementation. Previous studies of insulin protocols have utilized a variety of methods of titration and initiation of infusions, differing in the initial rate, rate change parameters, and the use of an initial bolus.^{6,10-14} The American Diabetes Association (ADA) consensus statement in 2009 outlined a titration method utilizing a weight-based initial infusion with or without a bolus dose followed by titration based on the percent decrease in blood glucose

¹Community Health Network, Indianapolis, IN, USA

²Butler University, Indianapolis, IN, USA

Corresponding Author:

Eileen Rohrbach, Pharmacy Department, Community Health Network,
1500 North Ritter Avenue, Indianapolis, IN 46219, USA.
Email: ecarroll2@ecomunity.com

American Diabetes Association, 2009 ¹	
1) Initiate regular insulin infusion with either method listed below: a. 0.1 unit/kg IV bolus followed by 0.1 unit/kg/hour IV b. 0.14 unit/kg/hour IV	
2) Does BG decrease by $\geq 10\%$ in first hour? If yes: Continue infusion rate If no: Give 0.14 units/kg IV bolus and continue previous rate	
3) When BG ≤ 200 mg/dL: a. Decrease insulin infusion to 0.02 – 0.05 units/kg/hour IV b. Maintain BG of 150 – 200 mg/dL until DKA resolution c. Overlap subcutaneous insulin by 1 – 2 hours	
Fixed Rate Titration (FRT)	
1) Initiate infusion at 0.1 units/kg/hour +/- 0.15 unit/kg IV bolus	
2) While BG > 250 mg/dL, at what rate did the BG in one hour decrease?	
< 50 mg/dL: Double the rate 50 – 75 mg/dL: Maintain current rate > 75 mg/dL: Decrease rate by 1 unit/hour	
3) Once BG < 250 mg/dL, adjust rate according to below instructions:	
BG (mg/dL)	Action
> 280	Increase by 1 unit/hour and give bolus of 8 units
221 – 280	Increase rate by 1 unit/hour
161 – 220	Continue current rate
100 – 160	Decrease rate by 1 unit/hour
71 – 99	Stop infusion and monitor glucose every 30 minutes until > 100 mg/dL; Restart infusion at half the previous rate
Multiplier Titration (MT)	
Calculate each rate adjustment using the following equation: Drip rate (units/hour) = (Blood Glucose – 60) x multiplier*	
*Multiplier:	
- Initial multiplier: 0.02	
- Subsequent multipliers: Adjusted based on current BG	
o > 140 : Increase multiplier by 0.01	
o 90 – 140: No change in multiplier	
o 70 – 89: Decrease the multiplier by 0.01	
o < 70 : Hold drip and follow hypoglycemia procedures	

Figure 1. Discussed insulin titration methods.

1. Kitabchi AE, Miles JM, Umpierrez GE, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32(7):1335-1343.

Abbreviations: IV, intravenous; BG, blood glucose; DKA, diabetic ketoacidosis.

(BG) within the first hour. Further titrations in DKA patients specifically were based on maintaining the BG within a goal range until anion gap closure, a marker of crisis resolution.⁶ Recent publications reinforce the IV insulin recommendations originally included in the 2009 consensus statement.⁴ More details regarding this titration method are included in Figure 1. By evaluating the outcomes of 2 protocols used for hyperglycemic crisis treatment at the each study facility, the study aims to contribute to what is known about which components make up an ideal titration regimen.

Objectives

The primary objective of the project was to compare the efficacy and safety of 2 insulin titration methods used in hyperglycemic crisis management within each study facility. Efficacy endpoints included the primary outcomes of time to goal BG <200 mg/dL and time to anion gap closure of <13 mg/dL, and secondary outcomes of intensive care unit (ICU)/progressive care unit (PCU) and hospital length of stay (LOS). The safety endpoints were the primary outcomes of prevalence of hypoglycemia defined as a BG <70

mg/dL with secondary safety outcomes of percent compliance with titration recommendations and number of holds required based on titration instructions.

Methods

Current State

The 2 titration methods utilized at each study facility are available in the hospital electronic medical record. Each is a nursing-driven process whereby titrations are made based on hourly BG levels. Similar to the ADA consensus statement, the fixed-rate titration (FRT) method initiates insulin at a weight-based rate and adjustments are made based on the rate of BG decrease after the first hour. In contrast to the ADA recommendations, there are differences in the goal BG and titration recommendations when not within the goal BG range. Additionally, the instructions have a provision in place to help prevent hypoglycemia, which recommends a hold to the infusion when BG falls below 100 mg/dL and decrease the rate by 50% prior to restarting.

The multiplier titration (MT) method, in contrast, utilizes an equation to calculate the insulin infusion rate that factors in the current BG and a multiplier that is adjusted and carried through the duration of infusion, taking into account overall BG trends. Calculations are completed manually by nursing staff using a paper monitoring sheet. The goal BG in the MT method is lower than that of the FRT and recommends the infusion be held only when BG is <70 mg/dL. This method was not originally developed for the treatment of hyperglycemic crises, but instead with the intent to treat inpatient hyperglycemia, in general. The method selected for use at each study facility is based on physician preference, and not every patient placed on these orders has a laboratory confirmed hyperglycemic crisis. The FRT and MT methods are described further in Figure 1.

Study Design

A retrospective, observational chart review was performed at 3 community-based hospitals within a health network ranging in size from 108 to 389 licensed patient beds. Studied patients were randomly selected from those admitted to one of the site hospitals between August 1, 2013, and August 1, 2015. Included patients had received an IV insulin infusion titrated by 1 of 2 insulin titration methods, FRT and MT. Patients were excluded if the infusion duration was less than 4 hours or if more than one titration method was used during admission. Orders on patients with protected status were excluded including pregnancy, imprisonment, or age less than 18 or greater than 89 years. In order to align outcomes with treatment goals, only patients with laboratory-confirmed DKA were included in evaluation of the

primary efficacy outcomes. Laboratory-confirmed DKA was defined as BG >250 mg/dL and an anion gap >13 mg/dL plus at least one of the following: ketosis or acidosis. All study participants were included in evaluation for safety outcomes. This study obtained institutional review board exempt approval.

Data Analysis

An initial electronic medical record report was generated and a manual review of the patients' electronic medical record provided information regarding patient demographics; insulin infusion rate, duration, and appropriateness of titration given protocol dosing instructions; and select laboratory values such as hourly BG level, hemoglobin A1c, electrolytes, and markers of acidosis.

Background demographics were analyzed using descriptive statistics. Nominal data were analyzed using χ^2 or Fisher's exact methods, as appropriate. Continuous data were analyzed using an independent 2-samples *t* test or a Mann-Whitney *U* test for nonparametric data. A *P* value of .05 was considered statistically significant. SPSS version 16.0 was used to perform statistical analysis.

Results

Using a population size similar to available literature, a goal sample size of 200 was set for the study.^{13,15} A total of 271 randomly selected patients from the study timeframe were screened to obtain the goal sample size following the exclusion of one patient based on age and seventy who received continuous insulin infusions for less than 4 hours. The entire study population was included for primary safety and all secondary outcomes, while only those with laboratory-confirmed DKA were studied for efficacy outcomes (*n* = 79). FRT patients were statistically more likely to have been previously diagnosed with type 1 diabetes mellitus and to have an initial bolus administered prior to the infusion. MT patients had statistically more orders for steroids and a diet than FRT patients. The groups were not statistically different with regard to age, admission hemoglobin A1C, or resolution of DKA at the infusion cessation. Complete analysis of patient demographics and background information for the efficacy subgroup is provided in Table 1.

In the efficacy subgroup, there was a statistical difference between time to initial BG <200 mg/dL with the FRT more quickly achieving this primary outcome; however, no difference was seen between the group with regard to time to anion gap closure (mean time to BG < 200 mg/dL [standard deviation] for FRT vs MT: 6.1 [4.0] vs 8.8 [4.4], respectively; *P* = .018). The primary safety outcome of total hypoglycemic events for each method was numerically identical between the 2 methods with 40 events out of the

Table 1. Efficacy Subgroup Baseline Characteristics.

	FRT (n = 57)	MT (n = 22)	P ^a
Patient demographics			
Type 1 DM (%)	58.5	25.0	.019
Steroid use (%)	3.5	18.2	.048
Nothing by mouth (NPO) (%)	93.0	36.4	.003
New diagnosis (%)	10.5	31.8	.039
Insulin use prior to admission (%)	87.7	57.1	.009
Patient age (mean years [SD])	43.2 [14.8]	52.8 [13.6]	.570
Admission hemoglobin A1C (mean % [SD])	10.4 [2.5]	11.0 [2.6]	.896
Initial BG (mean mg/dL [SD])	582.9 [272.1]	493.1 [281.7]	.540
Female (%)	45.6	54.5	.476
Order characteristics			
Bolus use (mean % [SD])	73.7 [0.44]	36.4 [0.49]	.002
Maximum infusion rate (mean units/kg/h [SD])	23.6 [26.3]	19.3 [13.2]	.674
Anion gap closed at IC (%)	60.7	68.2	.539
Bicarbonate ≥ 15 mg/dL at IC (%)	80.4	90.0	.083
BG stable $\times 4$ hours at IC (%)	43.6	54.5	.145

Abbreviations: FRT, fixed-rate titration; MT, multiplier titration; DM, diabetes mellitus; SD, standard deviation; BG, blood glucose; IC, infusion cessation.

^aP < .05 represents statistical significance.

Table 2. Comparisons of Outcomes Between FRT and MT.

Efficacy Outcomes	FRT (n = 57)	MT (n = 22)	P ^a
Time to BG <200 mg/dL (mean hours [SD])	6.1 [4.0]	8.8 [4.4]	.018
Time to anion gap closure (mean hours [SD])	14.7 [12.0]	12.98 [11.0]	.664
ICU/PCU LOS (mean days [SD])	2.98 [2.8]	4.62 [3.8]	.03
Hospital LOS (mean days [SD])	4.46 [3.9]	6.33 [6.0]	.07
Safety Outcome	FRT (n = 100)	MT (n = 100)	P ^a
Hypoglycemic events (total)	40	40	1
Infusion holds (total)	96	48	<.0005
Orders with at least one protocol deviation (%)	72.7	53	.004
Breakdown of low versus high deviations (low % to high %)	53/47	71/29	—

Abbreviations: FRT, fixed-rate titration; MT, multiplier titration; BG, blood glucose; SD, standard deviation; ICU, intensive care unit; PCU, progressive care unit; LOS, length of stay.

^aP < .05 represents statistical significance.

100 orders studied. Complete results for primary and secondary outcomes are shown in Table 2.

Nursing deviation from titration method recommendations was statistically higher in the FRT group. A comparison of ICU and PCU LOS found a statistically shorter LOS for FRT patients but no statistical difference in hospital LOS between the 2 groups. Statistical significance was also seen in the secondary safety endpoint of total number of infusion holds required by protocol instructions, with the FRT method having a greater number of holds than the MT method. This difference is to be expected based on the titration method design and clinical significance of this difference was unable to be determined.

Discussion

Overall, the patient groups were relatively similar with no statistical differences in age, sex, or diabetes mellitus control at admission, as measured by the surrogate marker admission hemoglobin A1c. No difference was seen in protocol prescribing between each study facility. Similarly, the maximum infusion rate and DKA resolution markers at the time of the infusion cessation (ie, anion gap, stable BG < 200 mg/dL for 4 hours, and normalized serum bicarbonate) were not significantly different. There were differences in the use of an initial bolus though this is most likely secondary to this protocol's inclusion of a bolus option within the order. Also, significant differences were seen in the number

of patients receiving concomitant steroids and those with a diet ordered between the 2 subgroups. Steroid use and consumption of carbohydrates may both increase insulin requirements and lead to prolonged time to control, potentially confounding the results.

The results of the primary efficacy outcome had mixed significance. While a difference was seen in the time to goal BG, no difference was seen in the time to anion gap closure, an important marker of DKA resolution. Likewise, no statistical difference was seen in primary safety outcomes. While numerically identical, the prevalence of hypoglycemic events for each method occurred in 40% of patient orders. While in line with previously published rates of hypoglycemia between 31% and 50% of patients on an insulin infusion, the 40% event rate likely underrepresents the total number of events in this study as it does not include the hypoglycemic events caused by the infusion that occurred once the infusion order was discontinued.¹³ Given the potential complications of hypoglycemia, the total number of events has clinical significance. A confounding factor to the number of events was the presence of more stringent hold parameters in the FRT method compared to the MT. This difference may have reduced study-defined hypoglycemia and may be a protective component desirable in the design of a titration protocol. Goal BG ranges also differed between titration methods. Lower ranges may have unnecessarily increased the risk of hypoglycemia without changing efficacy outcomes and may be an area to focus on when optimizing protocols.

Significant differences were seen in the secondary outcome of frequency of titration deviation. A deviation was defined as a discrepancy between the recommended hourly titration and the titration that was documented as occurring. A low deviation was one wherein the actual rate was less than that which was recommended and a high deviation was the opposite. Presence of at least one deviation per order was seen more frequently in patients receiving the FRT method (72.7% of orders) than in MT (53% of orders), and total number of deviations was also higher with the FRT ($n = 169$) versus the MT ($n = 99$). The breakdown of low versus high deviations in the FRT (53%/47%) and MT (71%/29%) methods reveals that the MT method had a disproportionate number of low deviations compared to the FRT, which had roughly equivalent numbers of each. Further analysis was conducted using univariate logarithmic regression, which found that low deviations as a whole were associated with hypoglycemia. While surprising that a lower infusion rate would be associated with hypoglycemia, this could suggest nursing staff reaction to downward trending BGs with rate adjustment and potentially intentional deviation rather than one due to a lack of education. Further investigation is needed to compare the underlying causes of deviations.

The FRT orders were associated with statistically shorter ICU/PCU LOS and numerically shorter hospital LOS.

While not clinically significant, the almost 2-day shorter hospital LOS is significant from an overall cost and patient comfort perspective. In comparison to previously cited statistics for DKA hospital LOS of an average 4.9 days, patients in this study, regardless of method, had an average hospital LOS of 3.4 days.⁷ A difference in average LOS in study patients may be affected by illness severity or physician preferences for discharging patients.

This study was limited by the retrospective design, which did not allow for the collection of data points such as nursing rationale for deviation. The efficacy population did not reach the targeted sample size given the exclusion of either orders with a duration less than 4 hours or which had switched to or from an alternative titration method. Additionally, DKA prevalence was low in remaining selected orders. Differences in protocol deviation rates between the 2 order subgroups may have skewed overall results, but serve as a realistic snapshot into the prescribing and titration patterns of patients at the study facilities. The frequency of rate deviations cited in literature varies from 5.1% to 68.2% of adjustments.^{15,16} In our study, the rate of titration compliance was not measured compared with the total number of indicated rate changes, limiting the comparison of these rates to those available in literature. The definition of hypoglycemia was standardized in data analysis to less than 70 mg/dL, which matches the point at which each study facility indicates the need for treatment with dextrose. This definition, however, does not match the definition of severe hypoglycemia, a Center for Medicare and Medicaid Core Measure. Compliance with titration recommendations for fluids and electrolytes were not studied; however, the authors recognize these contribute to the overall efficacy of treatment. Finally, while an attempt was made to compare diabetes severity with initial hemoglobin A1c and admission BG, patients were not compared using other validated severity markers. Severity also contributes to overall treatment success. In future studies, a comparison of severity or control of demographic differences, percentage of rate deviations compared with all titrations, and measurement of percent time within goal BG or BG variability could be considered as data points.

Conclusion

While a shorter ICU/PCU LOS, shorter infusion duration, and faster time to BG are supported with the FRT method, the rate of deviation, under-documentation, and the number of infusion holds conducted suggest the need for further protocol optimization. The MT method had significantly fewer deviations and may represent a more simplified approach, particularly if a computerized calculator is developed and implemented into each study facility. The percentage of low deviations combined with no differences between rates of hypoglycemia and misalignment of the goal BG

range with published literature indicates the need for further optimization and staff education on IV insulin infusion titration methods.

Authors' Note

Previous presentations: Poster—American Society of Health Systems Pharmacists Midyear Clinical Meeting; New Orleans, Louisiana; December 6, 2015. Verbal presentation—Great Lakes Regional Pharmacy Residency Conference; West Lafayette, Indiana; April 28, 2016.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Westerberg D. Diabetic ketoacidosis: evaluation and treatment. *Am Fam Physician*. 2013;87:337-346.
2. Centers for Disease Control and Prevention. Number of deaths for hyperglycemic crises as an underlying cause, United States, 1980-2009. <http://www.cdc.gov/diabetes/statistics/mortalitydka/fNumberOfDKA.htm>. Published May 10, 2012. Accessed August 12, 2015.
3. Kitabchi AE, Miles JM, Umpierrez GE, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 2009;32:1335-1343.
4. Nyenwe EA, Kitabchi AE. The evolution of diabetic ketoacidosis: an update of its etiology, pathogenesis, and management. *Metabolism*. 2016;65:507-521.
5. Bull SV, Douglas IS, Foster M, Albert RK. Mandatory protocol for treating adult patients with diabetic ketoacidosis decreases intensive care unit and hospital lengths of stay: results of a non-randomized trial. *Crit Care Med*. 2007;35:41-46.
6. Corwell B, Knight B, Olivieri L, Willis GC. Current diagnosis and treatment of hyperglycemic emergencies. *Emerg Med Clin North Am*. 2014;32:437-452.
7. Anzola I, Gomez PC, Umpierrez GE. Management of diabetic ketoacidosis and hyperglycemic hyperosmolar state in adults. *Expert Rev Endocrinol Metab*. 2016;11:177-185.
8. Hara JS, Rahbar AJ, Jeffres MN, Izuora KE. Impact of hyperglycemic crisis protocol. *Endocr Pract*. 2013;19:953-962.
9. Ilag LL, Kronick S, Ernst RD, et al. Impact of a critical pathway on inpatient management of diabetic ketoacidosis. *Diabetes Res Clin Pract*. 2003;62:23-32.
10. Goyal N, Miller JB, Sankey SS, Mossallam U. Utility of initial bolus insulin in the treatment of Diabetic Ketoacidosis. *J Emerg Med*. 2010;38:422-427.
11. DeSantis AJ, Schmeltz LR, Schmidt K, et al. Inpatient management of hyperglycemia: the northwestern experience. *Endocr Pract*. 2006;12:491-505.
12. Shetty S, Inzucchi SE, Goldberg PA, Cooper D, Siegel MD, Honiden S. Adapting to the new consensus guidelines for managing hyperglycemia during critical illness: the updated Yale Insulin Infusion Protocol. *Endocrin Pract*. 2012;18:363-370.
13. Faraon-Pogaceanu C, Banasiak KJ, Hirshberg EL, Faustino EVS. Comparison of the effectiveness and safety of two insulin infusion protocols in the management of hyperglycemia in critically ill children. *Pediatr Crit Care Med*. 2010;11:741-749.
14. Kitabchi AE, Murphy MB, Spencer J, Matteri R, Karas J. Is a priming dose of insulin necessary in a low-dose insulin protocol for the treatment of diabetic ketoacidosis? *Diabetes Care*. 2008;31:2081-2085.
15. Cyrus RM, Szumita PM, Greenwood BC, Pendergrass ML. Evaluation of compliance with a paper-based, multiplication-factor, intravenous insulin protocol. *Ann Pharmacother*. 2009;43:1413-1418.
16. Campion TR, May AK, Waitman LR, Ozdas A, Lorenzi NM, Gadd CS. Characteristics and effects of nurse dosing overrides on computer-based intensive insulin therapy protocol performance. *J Am Med Inform Assoc*. 2011;18:251-258.