Efficacy and safety of two protocols of intravenous insulin therapy in the management of diabetic ketoacidosis

Efficacité et sécurité de deux protocoles d'insulinothérapie intraveineuse dans l'acidocétose diabétique

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Abstract

Introduction: The correction of insulin deficiency in ketoacidosis DKA is recommended by intravenous (IV) route. Despite abundant literature, the place of the initial bolus of insulin has remained controversial.

Aims: This study was designed to compare the safety and the efficacy of two protocols of intravenous (IV) insulin therapy in the management of DKA admitted in the emergency department.

Protocol (A): IV bolus of regular insulin 0.10 UI/Kg followed by a continuous IV infusion of insulin 0.10 UI/kg/H.

Protocol (B): No bolus, a continuous IV infusion of regular insulin 0.14 UI/kg/H.

Methods: This was a prospective, not blinded, randomized study including patients aged more than 16 years with moderate to severe DKA. Fluid therapy and potassium replacement were standardized. Patients were randomized into two groups: Bolus-maintenance 0.10 group received protocol (A) and Maintenance 0.14 group received protocol (B). The Primary outcome data was the time to recovery defined by the time to acidosis resolution. The safety was tested by the occurrence of complications: hypoglycemia and hypokalemia.

Results: We enrolled 129 consecutive DKA patients. There were no differences between the two groups in clinical and biochemical data on admission, Bolus-maintenance 0.10 group versus Maintenance 0.14 group: mean age (37±18 vs. 38±17 years; p=0.810), Type 1 diabetes n (%): 34(55.7) vs. 34(50); p=0.911, pH (7.14±0.13 vs. 7.15±0.12; p=0.43). There were no differences between the two groups in the outcomes data: Bolus-maintenance 0.10 group versus Maintenance 0.14 group: Time to recovery (17 vs. 16 hours; p=0.76), complication n (%): Hypoglycemia (7(11.5) vs. 10(15.9); p=0.57) and hypokalemia (32(56.1) vs. 30(46.9); p=0.30).

Conclusion: In the treatment of diabetic ketoacidosis, the two protocols of IV insulin were safe and had a comparable efficiency.

Keywords: Diabetic ketoacidosis, insulin, intravenous bolus, emergency department.

Résumé

Introduction: La correction du déficit en insuline dans la cétoacidose diabétique (ACD) est recommandée par voie intraveineuse (IV). Malgré de multiples études de recherche, la place du bolus initial d'insuline ordinaire reste controversée.

Objectifs : Cette étude visait à comparer la sécurité et l'efficacité de deux protocoles d'insulinothérapie intraveineuse dans la prise en charge de l'ACD aux urgences. Protocole (A): bolus IV d'insuline ordinaire 0,10UI/Kg suivi d'une perfusion IV continue d'insuline 0,10UI/Kg/H. Protocole (B) : Pas de bolus, une perfusion IV continue d'insuline régulière 0,14UI/Kg/H.

Méthode : Il s'agissait d'une étude monocentrique prospective, non en aveugle, randomisée incluant les patients âgés de plus de 16 ans admis aux urgences pour ACD modérée à sévère. La réhydratation et la supplémentation potassique ont été standardisées. Les patients ont été randomisés en deux groupes : le groupe Bolus-entretien 0,10 a reçu le protocole (A) et le groupe Entretien 0,14 a reçu le protocole (B). Le principal critère de jugement était le temps de résolution de l'ACD. La sécurité a été testée par la survenue de complications : hypoglycémie et hypokaliémie.

Résultats : Nous avons colligé 129 patients consécutifs atteints d'ACD. Il n'y a pas eu de différence entre les deux groupes sur les données cliniques et biochimiques à l'admission, groupe Bolus-entretien 0,10 versus groupe entretien 0,14 : âge moyen (37±18 vs 38±17 ans ; p=0,810), diabète de type 1 n (%) : 34 (55,7) contre 34 (50) ; p=0,911, pH (7,14±0,13 contre 7,15±0,12 ; p=0,43). Il n'y avait pas de différences entre les deux groupes concernant les données thérapeutiques : groupe Bolus-entretien 0,10 versus groupe entretien 0,14 : temps de résolution de l'ACD (17 vs 16 heures ; p=0,76), complications n (%) : Hypoglycémie (7(11,5) vs 10(15,9) ; p=0,57) et hypokaliémie (32(56,1) vs 30(46,9) ; p=0,30).

Conclusion : Dans le traitement de l'ACD, les deux protocoles d'insuline IV étaient sûrs et avaient une efficacité comparable.

Mot clés : Acidocétose diabétique, insuline, Bolus intraveineux, urgences

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INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute and severe metabolic emergency. Its' elevated prevalence in the emergency department was associated with the increased of diabetes mellitus frequency worldwide [1-4].

Its management is based on insulin and fluid therapy in addition to the correction of electrolyte disorder [5, 6]. The benefits of insulin administration are showed in the correction of the relative or the absolute insulin deficiency, the decrease of insulin resistance and against the increase of counter to the regulation hormones [5, 7].

The correction of insulin deficiency in DKA is recommended by intravenous (IV) route [5]. Despite abundant literature, the place of the initial bolus of insulin has remained controversial. Did this bolus, which initially helped to reduce insulin resistance, increase the risk of complications such as hypoglycemia, hypokalemia and cerebral edema?

These controversies led to an American Diabetes Association (ADA) protocol change, which proposed to abstain from the bolus at the cost of increasing continuous insulin infusion doses.

Many studies showed that the adjunction of initial bolus of rapid insulin during treatment of DKA was safe however, it did not shorten the resolution of metabolic acidosis or the duration of hospitalization [8].

Some questions are still relevant :

- What is the most effective and safest route and dose of insulin in the treatment of DKA?

- What about the increasing of insulin doses in continuous infusion: efficacy and safety?

This study was designed to compare the efficacy and safety of two intravenous insulin therapy regimens in the management of DKA in emergency department :

- Protocol (A): IV bolus of regular insulin 0.10 UI/Kg followed by a continuous IV infusion of regular insulin 0.10 UI/Kg/H.

- Protocol (B): No bolus, continuous IV infusion of regular insulin 0.14 UI/Kg/H.

METHODS

Patients

This study enrolled patients over 16 years old presenting to the emergency department (ED) for a glycemic imbalance related to a moderate or severe DKA. Moderate to severe DKA was defined according to the American Diabetes Association (ADA) criteria associating: plasma glucose > 2.5 g/L, HCO3- <15 mEq/L and/or pH≤ 7.24, and ketones in the urine. Patients with initial serum potassium <3.5 mmol/L or transferred from another health facility after initiation of DKA treatment were not included. Patients with organic renal failure (creatinine clearance <30 ml/min) or those with hyperosmolar hyperglycemic state (osmolarity more than 320 mosm/l) associated to DKA were excluded.

Study design

Prospective, open, not blinded randomized study. Eligible patients were randomized by a permuted-blocks randomization scheme into one of two group's medication:

Protocol (A): IV bolus of regular insulin 0.10UI/Kg followed by a continuous IV infusion at the dose of 0.10 UI/Kg/H.

Protocol (B): No bolus, a continuous IV infusion of regular insulin at the dose of 0.14 UI/Kg/H.

Course of the study

All eligible patients received 1 liter of normal saline in the first hour; then they were randomized into one of the two treatment groups:

- Bolus-maintenance 0.10 group receiving protocol (A);

- Maintenance 0.14 group receiving protocol (B).

Fluid therapy and potassium replacement were standardized in the two groups: hydrating solution using 0.9% NaCl if glucose level > 200 mg/dL and 5% dextrose if glucose level ≤ 200 mg/dL; potassium replacement according to the potassium level. In case of insulin resistance defined by a decrease of glucose level less than 10% in the first hour or less than 50 mg /dL/H, patients received an IV bolus of insulin at the dose of 0.10UI/Kg regardless of their initial protocol. Figure 1 shows the study progress.

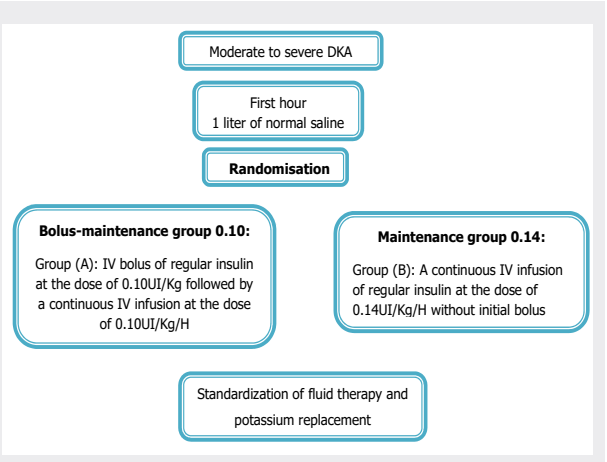

Figure 1. Randomization scheme

Outcomes measurements

The primary outcome was the time to recovery or acidosis resolution defined by the delay to achieve a glucose level less than 2 g/L, a pH >7.30 and a bicarbonate level>15 mEq/L; this delay correspond to the IV insulin therapy duration expressed in hours.

The secondary outcomes were:

i) Time to reach capillary blood glucose <2 g/L.

ii) IV insulin dose to recovery (UI).

iii) Safety was tested by the occurrence of adverse events: Hypoglycemia defined by capillary blood glucose< 0.5 g/L or hypokalemia defined by: K +< 3.5 mmol/L.

iv) Duration of hospital stay and recurrent DKA or capillary blood glucose ≥2 g/L during hospitalization.

Statistical analysis

SPSS was used for different statistical analysis. Statistical significance was declared at $p < 0.05$.

RESULTS

Clinical characteristics

During the study period (May 2015- December 2016), 156 patients with moderate to severe DKA were admitted, and only 129 patients were eligible. Figure 2 shows the patients flow diagram through this work. DKA predominated in patients with type 1 diabetes mellitus and in young people under 45 years (68.21%) and under 25 years (34.11%). Among the 129 patients included; 101 have been diagnosed with severe DKA and 28 patients with a moderate DKA. Sixty-one patients were randomized to the Bolus-maintenance 0.10 group; sixty height patients were randomized to the Maintenance 0.14 group. There were no differences between the two groups in demographic and initial clinical and biological data as shown in table 1 and 2.

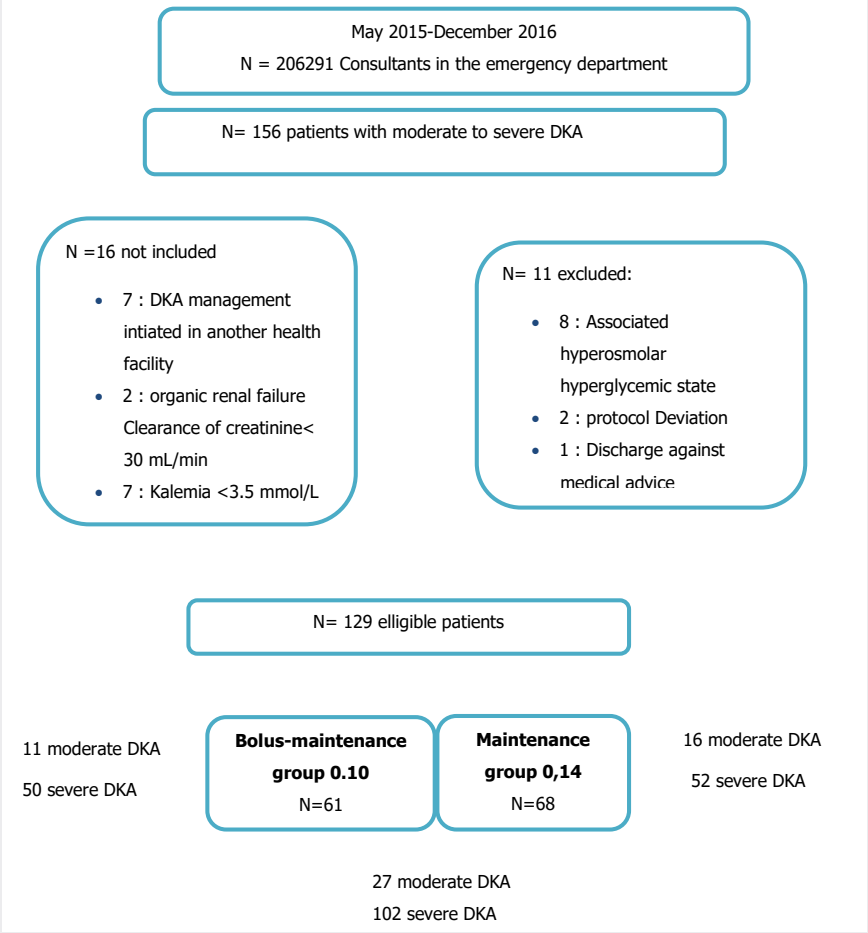

Figure 2. Patients flow through study

Table 1. Demographic and epidemiologic data.

	Patients with moderate to severe DKA (N=129)	Bolus-maintenance 0.10 Group (N=61)	Maintenance 0.14 Group (N=68)	P
Demographic data :				
Age (years)	38 ± 18	37± 18	38±17	0.810
Sex-ratio (M/F)	1.04	1.03	1.06	0.94
Weight (means ± SD) (Kg)	66.8± 9.5	68±8	65.5±10.71	0.187
Smokers n (%)	34 (26.4)	14 (23)	20 (29.4)	0.406
History of diabetes and comorbidities n (%):				
Diabetes mellitus	115 (89)	57 (93)	58 (85)	0.165
Type 1 diabetes	68 (52.7)	34 (55.7)	34 (50)	0.911
Type 2 diabetes	47 (36.4)	23 (37.7)	24 (35.3)	0.911
Inaugural DKA	14 (11)	4 (6.5)	10 (15.7)	0.165
Hypertension	20 (15.5)	10 (16.4)	10 (14.7)	0.791
Dyslipidemia	8 (6.2)	3 (4.9)	5 (7.4)	0.721
Background therapy: n (%)				
Insulin	110 (85.2)	55 (90.2)	55 (80.8)	0.138
Mean insulatard® dose (UI/Kg/day) ± SD	0.55±0.18	0.50±0.16	0.70±0.24	0.28
OAD	8 (6.2)	1 (1.6)	7 (10.3)	0.067
Precipitating factor: N (%)				
Treatment discontinuation	62 (48.4)	30 (49.2)	32 (47.8)	0.873
Infection	42 (32.8)	23 (37.7)	19 (28.4)	0.261

P: *p*-value for comparative study between groups 0.10 and 0.14, DKA: diabetic ketoacidosis; OAD: Oral anti diabetes

Table 2. Clinical and biological data on admission.

	Patients with moderate to severe DKA (N=129)	Bolus-maintenance 0.10 Group (N=61)	Maintenance 0.14 Group (N=68)	P
Clinical data				
Glasgow Coma Scale n (%)	124 (96)	58 (95)	66 (97)	0.667
[14-15]	5 (3.8)	3 (5)	2 (3)	0.667
[9-13]				
Respiratory rate (per min)	28 ± 6	27±6	28±6	0.220
Heart rate (per min)	103 ±17	104±18	102±17	0.551
Systolic blood pressure (mm Hg)	119 ±19	119±20	120± 18	0.675
Biological data				
Blood glucose level (mmol/l ou mg/dl)	31.6 ± 10.7	30.4±9.5	32.6±11.5	0.283
pH	7.14± 0.13	7.14±0.13	7.15±0.12	0.438
HCO3- (mmol/L)	7.03±3.47	6.7±3.18	7.33±3.71	0.305
Anion gap (mEq/L)	28.9± 6	28.8±5.4	28.9±6.6	0.891
Serum potassium (mmol/L)	4.6 ± 0.9	4.6±0.9	4.5±0.9	0.746
Osmolarity (mosm/L)	292 ± 16.4	291.9±12.7	292.1±19.1	0.925

P: *p*-value for comparative study between groups 0.10 and 0.14, DKA: diabetic ketoacidosis

Outcome measurement

The primary endpoint represented by metabolic acidosis resolution was comparable between the two groups. In the same way, the secondary endpoints represented by the time to obtain a blood glucose <2g /L, the initial insulin resistance, the recurrence of the DKA during hospitalization, the recurrence of blood glucose> 2g /L and the duration of hospital stay as well as the occurrence of insulin side effects were comparable between the two groups. Table 3 summarizes the outcome measurements.

Table 3. Outcomes measurements.

	Patients with moderate to severe DKA (N=129)	Bolus-maintenance 0.10 Group (N=61)	Maintenance 0.14 Group (N=68)	p
Primary outcome measurement: mean ± SD				
Time to acidosis resolution (H)	17±16 [4-144]	17±13 [6-58]	16±19 12* [4-144]	0.766
Secondary outcome measurements				
Initial insulin resistance n (%)	49 (38)	19 (31.15)	30 (44.12)	0.217
Time to blood glucose ≤ 2 g/L (mean ± SD)	6.5 ± 3.7	6 ± 3	7± 4	0.173
Total dose of IV insulin (UI)	77 ± 51	77 ± 54	78 ± 19	0.892
Hypoglycemia n (%)	17 (14.2)	7 (11.5)	10 (15.9)	0.573
Hypokalemia n (%)	62 (51.2)	32 (56.1)	30 (46.9)	0.309
Glycemia rebond ≥ 2 g/L n (%)	78 (66.7)	36 (59)	42 (67.7)	0.793
DKA recurrence during hospitalization n (%)	6 (4.56)	1(1.6)	5 (7.35)	0.211
Length of stay in emergency department (mean ± SD hours)	52 ± 32	55 ± 34	49.5 ± 31	0.353

P: *p*-value for comparative study between groups 0.10 and 0.14, DKA: Diabetic ketoacidosis; SD: standard deviation; ED: Emergency Department

Only one patient died after 36 hours of well-conducted insulin therapy and rehydration without known precipitating factor (from the maintenance 0.14 group).

The length of hospital stay of patients admitted for moderate to severe DKA was about 52 ± 32 hours. The majority of patients were fully managed in the emergency department; only 18 patients (14%) were secondarily transferred to another hospital ward.

DISCUSSION

In this open randomized prospective study including 129 patients with moderate to severe DKA; patients were randomized into two groups:

- Bolus-maintenance 0.10 group: IV bolus of regular insulin 0.10 IU/kg followed by continuous infusion 0.10 IU/kg/H.

- Maintenance 0.14 group: No bolus, continuous insulin infusion (0.14 IU/kg/H).

These two protocols were safe and had a comparable efficiency.

Since the discovery of insulin in 1921, mortality related to DKA was significantly decreased to become less than 5% currently with predominance for extreme ages mainly the elderly [4, 9-13].

These goals have been achieved thanks to multiple studies that have made it possible to better understand the pathophysiology of DKA and to codify its management, which is based on three main therapeutic components combining rehydration, insulin therapy and potassium supplementation in addition to treatment of the precipitating factor [3, 14, 15].

Insulin therapy, which is the corner stone of DKA treatment, has been the goals of many studies to identify and validate its most effective and safest type, route and dose [8,14,16].

Based on prospective studies, the efficacy of low dose insulin or physiological doses (0.10 UI/kg/H) has been proven over high doses therapy for years [14, 17].

Some studies suggest the use of initial bolus of insulin before continuous insulin infusion to counterbalance the insulin resistance observed in DKA by mimicking the physiological insulin peak in case of hyperglycemia [18, 19]. However its role remains controversial [8, 20, 21].

To ensure a balance between the efficacy and safety of therapeutic protocols, some studies have proposed continuous infusion of regular insulin at a higher dose of 0.14 UI/kg/H in order to decrease initial insulin resistance without IVD bolus [1, 16].

Kitabchi and al. [16], have conducted a randomized study to evaluate the safety and efficacy of this insulin dose (0.14 IU/kg/H) compared to two other IV insulin protocols. In the study conducted by Kitabchi et al. comparing three protocols of insulin (Bolus group receiving IVD bolus of 0,07 UI/Kg before a continuous infusion of 0,07 UI/kg/H ; Maintenance group receiving a continuous infusion of 0,07 UI/kg/H without bolus; Dual dose maintenance group receiving a continuous dose of 0,14 UI/Kg without bolus); the time to acidosis recovery was comparable between the three groups. However, five of the twelve patients in the maintenance dose group required additional doses of insulin to achieve these goals, making this dose of 0.07 IU/kg inadequate for the resolution of metabolic acidosis. Based on these results, the authors concluded that the initial bolus was not useful if continuous insulin infusion of 0.14 IU/ kg/H was used.

In our study, the duration of intravenous insulin therapy or time to recovery, which is the primary endpoint, was comparable between the two groups with similar delays in the literature and with comparable doses of IV insulin between the two groups.

The use of low doses of insulin allows a progressive correction of hyperglycemia with targets for decreasing blood glucose levels of 0.5 to 0.75 g/L/H and 10% in the first hour [5].

The ADA recommends a bolus of 0.14 IU/kg in case of insulin resistance during the first hour as well as the addition of 5% dextrose when the blood glucose level drops to 2 g/L to reduce insulin complications such as hypoglycemia and hypokalemia.

In our study, the bolus delivered in case of insulin resistance was limited to 0.10 IU/kg for more safety. The blood glucose target in the other studies was 2.5 g/L contrary to the ADA recommendations' of 2 g/L. This threshold was respected in our study.

In this study, the rate of insulin resistance and the delay to achieve glucose concentration below 2 g/L was comparable in both groups.

In addition, the recurrence of blood glucose greater than 2 g/L after recovery was comparable in both groups and was observed in 78 patients.

This rebound effect was identified in the literature. Hsia E et al. showed in a prospective randomized study that the adjunction of a subcutaneous dose of semi lent insulin equal to 0,25 UI/Kg within the first 12 hours reduced the blood glucose level rebound after switching from IV to subcutaneous insulin without increasing the risk of hypoglycemia [22].

In the literature, hypoglycemia has been reported in 5-25% of cases [5, 23], which is similar to the results observed in our study. However, its occurrence at the top of the list of complications of DKA treatment in the literature was replaced in our study by the hypokalemia whose frequency was higher [15, 23].

DKA is associated with a potassium deficiency that can be masked or even initially replaced by hyperkalemia due to acidosis, proteolysis and insulinopenia [5, 24, 25]. The correction of these disorders by fluid and insulin therapy can unmask this deficit. To overcome this complication, potassium intake should be considered below a value of 5 - 5.3 mEq/L in patients with normal renal function at the dose of 20-30 mEq/L to maintain serum potassium between 4 and 5 mEq/L [5, 23, 24].

These recommendations were considered in our study but not strictly

followed, first because of the absence of serum pump flow meter that distributes adequately potassium replacement and second because the delay of the biological assessment (which causes a delay to appropriate modification of the potassium intakes).

Moreover, this high incidence of hypokalemia can be explained by the difference in sample size compared to previous studies. The recurrence of the DKA in the same hospitalization was comparable in both groups. This data has not been well studied in literature [8].

The length of hospital stay in ED was comparable between the two groups; but shorter than reported in literature [16, 20, 23]. This can be explained by the achievement of the study in an emergency department with a large number of patients so that the length of hospitalization covered only the duration of resolution of the DKA in the majority of cases. Patients were secondary transferred to specialized services for insulin adjustment.

In our study, the mortality was low consistent with the results observed in the literature testing the efficacy and safety of DKA protocols.

Some weak points have to be noted; mainly the absence of blood ketones measurement. However, the originality of our work rests on several strength points mainly the randomization scheme and the large number of patients included.

CONCLUSIONS

This study concluded that in the treatment of moderate to severe diabetic ketoacidosis, the two protocols of IV insulin were safe and had a comparable efficiency.

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