Evaluation of a simple management protocol for hyperglycaemic crises using intramuscular insulin in a resource-limited setting

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Received 23 December 2008; received in revised form 6 April 2009; accepted 8 April 2009
Available online 17 September 2009

Abstract

Background. – Management of hyperglycaemic crises requires expensive and labour-intensive procedures that are not achievable in all clinical settings. Intramuscular (IM) insulin therapy is a more feasible alternative, but remains insufficiently evaluated. We report here on an audit of clinical outcomes of a simple management protocol that involves IM insulin therapy, careful rehydration and inexpensive monitoring in a resource-limited setting.

Methods. – In June 2006, we began the routine use of a protocol based on IM insulin administration, careful rehydration and affordable monitoring for the management of hyperglycaemic crises in Yaoundé Central Hospital. Clinical records of patients admitted for hyperglycaemic crises 6 months before and 6 months after introduction of the protocol were independently coded and compared for clinical outcomes, including the 48-hour death rate as a primary endpoint. Secondary endpoints were blood glucose (BG) normalization and duration of hospital stay.

Results. – A total of 112 patients’ files fulfilled the inclusion criteria, including 57 before and 55 after the introduction of the IM protocol (intervention). Patients of the pre-intervention group were aged 56.4 ± 2.1 years versus 53.9 ± 2.3 years in the intervention group (p = 0.41), with 23% versus 40%, respectively, with newly diagnosed diabetes (p = 0.05), and 45% versus 41%, respectively, with significant ketosis on admission (p = 0.84). As for the primary endpoint, 15.8% of the pre-intervention group died within 48 hours of admission versus 3.6% in the intervention group (p = 0.03). BG was normalized within 24 hours of admission in 28.1% patients of the pre-intervention group versus 3.6% in the intervention group (p = 0.03). BG was normalized within 24 hours of admission in 28.1% patients of the pre-intervention group versus 90.9% of the intervention group (p < 0.001). However, the overall duration of hospitalization was similar in both groups. Septic shock, ketosis and high serum creatinine on admission were associated with poor outcomes in both groups.

Conclusion. – The proposed protocol using IM insulin can be safely used to treat hyperglycaemic crises, with mortality rates comparable to those in specialized centres in developed countries.

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Keywords: Intramuscular; Insulin; Hyperglycaemia; DKA; HHS; Coma; Mortality; Audit

Résumé

Évaluation d’un protocole simplifié fondé sur l’insulinothérapie par voie intramusculaire pour la prise en charge des hyperglycémies aiguës dans un contexte de ressources médicales limitées.

La prise en charge des urgences hyperglycémiques est limitée par l’accessibilité de l’insulinothérapie intraveineuse et des moyens de surveillance biochimique adéquats dans de nombreux centres hospitaliers. Nous présentons les résultats d’une évaluation a posteriori d’un protocole peu coûteux fondé sur l’insulinothérapie intramusculaire.

Méthodes. – En juin 2006, nous avons mis en place un protocole de soins des urgences hyperglycémiques fondé sur l’insulinothérapie intramusculaire pour la prise en charge des hyperglycémies aiguës dans un contexte de ressources médicales limitées.

1. Introduction

Diabetic ketoacidosis (DKA) and hyperglycaemic hyperosmolar states (HHS) are the main acute metabolic complications of diabetes [1]. Despite progress in diabetes treatment, these complications are still seen in 0.3 to 6.6% of patients with diabetes [2,3]. Recurrent DKA rates are estimated to be between 4.6 and eight episodes per 1000 patient-years in developed countries [2], whereas admission rates due to hyperglycaemic crisis reached 18% in Jamaica [4]. In settings with low awareness and low rates of diagnosed cases, recurrent DKA is the main diagnostic feature of diabetes. Even in developed countries, newly diagnosed diabetes accounts for 10 to 22% of cases of hyperglycaemic crisis [5]. However, mortality due to DKA and HHS has been reduced in most developed settings, being smaller than 5% for DKA in specialized centres and around 11% for HHS [6–8], yet remains high in non-specialized centres, deprived areas and in unusual circumstances such as humanitarian disasters.

The current consensus for the management of hyperglycaemic crises relies upon intravenous (IV) insulin administered by syringe pumps, rehydration, correction of electrolyte imbalances and treatment of associated conditions, with regular 2- to 4-hour monitoring of serum electrolytes, creatinine, glucose and pH until stable [9]. Unfortunately, such treatment and monitoring are seldom available in the majority of resource-limited settings, humanitarian disasters and where there is a failure of power supply. Also, hyperglycaemic crises are more likely to occur in underserved populations. Alternative guidelines are therefore mandatory to address the needs of all populations with diabetes.

As far back as 1973, Alberti et al. [10] used a protocol involving small intramuscular (IM) doses of insulin in 14 cases of DKA, with successful clinical and metabolic outcomes. Based on the reported experience of major teams dealing with hyperglycaemic crises and on the unpublished experience of other teams, we adapted and implemented a treatment protocol for hyperglycaemic crises involving IM insulin administration, careful rehydration, affordable monitoring and treatment of associated conditions. We report here on an audit of the clinical outcomes with the protocol.

2. Methods

2.1. Study setting

This report addresses the retrospective audit of patients’ files from the Internal Medicine Unit (IMU) of Yaoundé Central Hospital. The endocrinology department is a 16-bed specialized service within the IMU where all patients from the casualty department with hyperglycaemic crisis are first admitted whether they are comatose or not. Nurses work on a rota basis across services within the IMU and are, therefore, not exclusively dedicated to the management of diabetes or other endocrine disorders.

2.2. Study population

We retrospectively reviewed the files of patients admitted to the diabetes and endocrine diseases unit of the Central Hospital Yaoundé 6 months before, and 6 months after the introduction of an intensive IM insulin protocol for the management of hyperglycaemic crises. Patients with blood glucose (BG) levels greater than 400 mg/dL, with or without coma on admission and initially managed with insulin, were eligible irrespective of age, presumed type of diabetes, evidence of DKA and associated conditions.

2.3. Treatment protocols

In June 2006, an IM insulin protocol for the management of hyperglycaemic crises was introduced in the entire IMU. Patients admitted to the unit in the 6 months prior to the start of the IM insulin protocol are referred to as the “reference” group, and those treated with the protocol are referred to as the “intervention” group. Treatment in the reference group was not a routine protocol; it was based on the administration of an IV starting dose in the emergency room followed by 4- to 6-hour doses of subcutaneous regular insulin, according to capillary BG levels. In the intervention group, IM insulin was administered to patients every 1 to 2 hours, according to the level of capillary BG. The dose was 10 IU of regular insulin if BG was greater than 400 mg/dL and 5 IU if BG was 250 to 399 mg/dL, with a switch to subcutaneous intensive insulin therapy if BG fell to
Fig. 1. The management protocol used in the intramuscular insulin intervention group.

<table>
<thead>
<tr>
<th>IM insulin</th>
<th>Careful rehydration</th>
<th>Continued medicine</th>
<th>Affordable monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>If BG &gt; 400 mg/dL</td>
<td>As normal saline 0.9% or glucose 5% if persistence of ketonuria and BG &lt; 250 mg/dL; Daily maintenance fluids + 0.5 of the estimated deficit in 24 hours (1st litre given in 2 hours).</td>
<td>Diagnosis and management of associated infections is mandatory.</td>
<td>Clinical monitoring hourly (diabetes is mandatory).</td>
</tr>
<tr>
<td>IM insulin 10 UI / 2h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If BG: 250-399 mg/dL</td>
<td>1-2 g KCL /litre starting with the second litre of normal saline.</td>
<td>Routine management of associated conditions.</td>
<td>Blood glucose every 2 hours.</td>
</tr>
<tr>
<td>IM insulin 5UI / 2hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>If BG &lt; 250 mg/dL and no significant ketonuria.</td>
<td>Drinks (water) allowed on demand when the patient is conscious.</td>
<td>If unconscious and/or measured alkaline reserve (where available) &lt; 10, refer to a specialised unit.</td>
<td>Ketonuria at least every 4 hours if initial ketosis.</td>
</tr>
<tr>
<td>Switch to subcutaneous protocol.</td>
<td></td>
<td></td>
<td>Serum creatinine and electrolytes and pH where available.</td>
</tr>
</tbody>
</table>

less than 250 mg/dL without significant ketonuria (≥ 2+). In all cases, capillary BG was monitored using a One Touch Ultra® BG meter and its corresponding electrodes.

All patients, irrespective of the type of intervention, received fluid according to the degree of dehydration. In the intervention group, careful rehydration was mandatory, with correction of dehydration planned for at least 48 hours. None of these patients received more than 5.5 L of fluid IV over the first 24 hours (Fig. 1). Serum electrolytes and arterial pH were neither readily available nor affordable except for patients with renal failure; potassium was added after the first litre of fluid. Comorbidities were treated according to protocols developed in the service. The intervention protocol is detailed in Fig. 1.

### 2.4. Study variables

For each patient, the initial BG level, the BG level at 48 hours from the time of admission and the time spent to achieve a capillary BG level of less than 250 mg/dL were recorded. The presence of significant ketonuria, defined as greater or equal to 2+ on a urine dipstick, was determined using Ketodiastix® strips and visual reading in all cases. The Glasgow coma scale on admission was used to grade all patients. Dehydration on admission was evaluated according to the clinical signs noted by the attending physician, and was scored as less than 5%, 5 to 10% and greater than 10%. All other findings during the initial examination by the attending physician were also recorded, including initial creatinine levels.

### 2.5. Endpoints

The primary endpoint of the study was the 48-hour death rate. Secondary endpoints were the overall death rate, 24-hour BG control, time to achieve BG less than 250 mg/dL and ketonuria disappearance, and duration of the hospital stay.

### 2.6. Data management and statistical analysis

Using a precoded questionnaire, data were collected from the patients’ files by a physician who was not aware of the study and had nothing to do with management of the patients (A.L.). These data were then entered into a Microsoft Excel 2003 worksheet and analyzed by a pre-written syntax file using SPSS 15.0 software. The results are presented as frequencies and means ± standard deviation (SD). Comparison of variables was done using one-way analysis of variance (ANOVA) and Student’s t test. Associations between variables were determined using Fisher’s exact test.
3. Results

3.1. Characteristics of patients on admission

A total of 112 patients (57 in the reference group and 55 in the intervention group) were eligible for the defined study period. The male/female gender ratio was 59/53 and the mean age was 55.2 ± 1.5 years. Diabetes was newly diagnosed in 35 patients (31.3%) and, of the 77 patients (68.7%) previously known to be diabetic, 90.9% had type 2 diabetes (ketosis- and non-ketosis-prone) and 9.1% had type 1 diabetes. Mean BG (± SEM) on admission was 513.8 ± 6.9 mg/dL. Ketonuria was present in 42% of the 42 patients formally tested on admission. As serum bicarbonates and pH are not routinely measured in our unit for reasons of cost, the presence of DKA could not be ascertained. As shown in Table 1, except for a higher initial BG and a greater number of patients with altered consciousness in the intervention group, there were no baseline differences between the pre-intervention and intervention groups.

3.2. Clinical outcomes

3.2.1. Primary endpoint

As shown in Table 2, the 48-hour death rate was significantly lower in the intervention versus pre-intervention group (OR = 4.97, 95% CI 1.02–24.15). Overall, five patients (9.1%) died in the intervention group versus 12 patients (21.1%) in the pre-intervention group (P = 0.046), and 11 patients (64.7%) of all deaths (including nine during the intervention and two during the pre-intervention group) died within the first 48 hours, including nine in the pre-intervention group (15.8% of the entire group) and two in the intervention group (3.6% of the entire group; P = 0.025). The death rate after 48 hours was similar in both the pre-intervention and intervention groups.

3.2.2. Secondary endpoints

After 24 hours, BG levels dropped from 497 ± 9 to 305 ± 14 mg/dL in the pre-intervention group, and from 531 ± 10 to 168 ± 10 mg/dL in the intervention group (P < 0.001). The percentage of patients in whom BG was less than 250 mg/dL at 48 hours was higher in the intervention versus pre-intervention group (100% versus 54%, respectively; P < 0.001). The mean duration of hospitalization was similar in both groups (10.1 ± 0.9 days in the pre-intervention group versus 9.6 ± 0.8 days in the intervention group; P = 0.72).

3.3. Analysis of deceased patients

A total of 17 deaths (15.2%) were recorded during the 12 months of the study: 12 in the pre-intervention group and five in the intervention group – and 65% of all these deaths occurred within 24 hours of admission. Three of the deaths were directly attributable to other causes: in the pre-intervention group, death was due to end-stage renal disease with associated congestive heart failure and a case of encephalitis in an HIV-infected patient; in the intervention group, death was due to carcinoma of the pharynx. The absence of significant ketonuria on admission (in those tested), septic shock and high creatinine levels on admission were associated with higher mortality, irrespective of the patient group (Table 3).

4. Discussion

The present report shows that effective management of severe hyperglycaemic crises is feasible in all clinical settings. In fact, IM insulin administration, gentle rehydration and affordable monitoring achieved similar mortality rates as those...
of specialized centres in developed countries. Also, in spite of the absence of routine monitoring of serum electrolytes and pH, and even with comatose patients being managed in a general ward, a significant reduction in early death rates was possible.

The present study did not use ad-hoc methods to compare two clinical protocols, but was designed as an audit of clinical practice. For this reason, its conclusions have only limited implications. Nevertheless, we observed a significant reduction in early mortality with no excess late mortality observed, and all patients in the intervention group normalized their BG level within 48 hours. The rapid control of BG has a physiological basis in that insulin is better taken up by blood capillaries in muscles than in poorly hydrated subcutaneous tissue. Given the numbers of patients with severe dehydration in the pre-intervention and intervention groups, this parameter is an unlikely confounder. However, we cannot exclude the contribution of glucose toxicity as a confounder, given the high prevalence of newly diagnosed diabetes in the intervention group. Furthermore, the inability to confirm ketoacidosis in all cases may have generated a potential bias in the group comparison, as it is uncertain whether or not one group had more severe metabolic abnormalities.

The consensus statement of the American Diabetes Association recommends that, during therapy for DKA or HHS, blood should be drawn every 2 to 4 hours for determination of serum electrolytes, glucose, blood urea nitrogen, creatinine, osmolality and venous pH (for DKA) [9]. However, it may be difficult to apply such a recommendation in limited-resource settings and under conditions of humanitarian disasters. This suggests that the IM protocol may be an attractive alternative, especially as it has proved to be less harmful than an IV line for potassium homoeostasis and to induce fewer hypoglycaemic events [11].

More than 35 years ago, Alberti et al. [10] reported on the use of low-dose IM insulin for hyperglycaemic crises with high “metabolic safety”, as confirmed by potassium, lactate and ketone monitoring. The insulin dose was considered small compared with a much earlier report by Assan et al. [12] in 1969 comparing mortality in patients receiving less than 200 IU and those treated with 200 to 600 IU of insulin. Fisher et al. [13] in the US suggested that the more gradual absorption of IM insulin (taking 3–4 hours to peak levels versus a few minutes with the IV route) could account for the “metabolic safety” of such a treatment. The main difference between those earlier protocols and our present one is what we call “careful” or “gentle” rehydration. Indeed, in the paper by Alberti et al. [10], they infused an average of 7 L of fluid over the first 24 hours, with a mean positive fluid balance of just over 5 L, as an important part of the treatment.

In the present audit, the IM regimen had no effect on the length of stay in hospital, probably because the initial clinical and metabolic statuses were more severe in the intervention group (more patients had altered consciousness and higher BG). Indeed, the duration of hospitalization depends on a number of other parameters, including socioeconomic ones that could not be readily assessed by our audit. Nevertheless, our audit has shown that patients with hyperglycaemic crisis may be managed as well in a general ward as in an intensive care unit, thereby allowing substantial hospitalization cost-cutting. Furthermore, the IM regimen – through its rapid metabolic efficacy compared with the previous regimen used by our service – leads to a quicker shift from IV to oral rehydration and, thus, can further reduce hospital costs. However, it should be pointed out that the IM route is reported to be more painful than other routes of drug administration. Indeed, the need for additional and repeated painful treatments in critically ill patients is a drawback of the proposed protocol. More recently, Umpierrez et al. [14,15] carried out a thorough evaluation of the subcutaneous route for the administration of insulin in DKA, and found a satisfactory outcome that was comparable to the IV route. However, this was achieved using new short-acting insulin analogues that are often not available in resource-limited settings.

In conclusion, despite its limited sample size, our study shows that the use of an IM insulin regimen with careful rehydration for the management of hyperglycaemic crises in a context of limited availability of appropriate monitoring facilities and/or short-acting insulin analogues was associated with a reduction of early mortality. In addition to its efficacy, the protocol is inexpensive, simple and applicable not only in resource-limited settings, but also in the developed world in the event of electricity supply failure or humanitarian disasters. A randomized controlled trial with electrolyte monitoring is now required to clarify the safety of, and to highlight ways to improve, the proposed protocol.

5. Conflicts of interest

None.

References


