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RESEARCH ARTICLE

INTEREST OF ULTA-SLOW INSULINS IN MANAGEMENT OF KETO- ACID DECOMPENSATIONS IN EMERGENCY

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Abstract

Introduction:-

Ketoacid decompensation is a serious acute complication of diabetes. Its incidence, constantly decreasing in educated and independent patients, it is estimated at 5 cases/patient-years and the mortality observed in developed countries is now significantly less than 1% [1 , 2]. This is due, alongside to good education for diabetic patients, to better care which continues to evolve.

In fact, and because of its pharmacokinetic properties, a 2nd generation ultra-slow insulin administered subcutaneously has been proposed in combination with intravenous insulin therapy in order to accelerate the transition from intravenous to subcutaneous insulin treatment, and to avoid the appearance of a rebound of hyperglycemia upon stopping intravenous insulin therapy. This study aims to evaluate this protocol as well as the feasibility of subcutaneous insulin therapy and its safety.

Materials and Methods:-

Study type and site:

This is a prospective, randomized, single-blind study, which was carried out during the period from November 2021 to October 2022 at the Mohammed V Military Instruction Hospital in Rabat.

Population :

Patients were recruited in the medico-surgical emergency department and the endocrinology department of the Mohammed V military training hospital, using the following inclusion criteria: any patient presenting with ketoacidotic decompensation with: Blood sugar greater than 2, 5g/l, RA less than 18 and an anion gap greater than 16.

We excluded from our study: patients with simple diabetic ketosis without acidemia and diabetic patients with slow insulin in their antidiabetic treatment.

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Course of the study :
After diagnosis of KAD, patients are admitted, depending on the severity of their condition, to the observation room or to the intensive care unit of medical and surgical emergency. The patients included in the study were selected according to the mentioned inclusion criteria. Initial treatment was based on intravenous rehydration with isotonic or glucose solutions (if blood sugar drops below 2.5g/l) to which potassium supplementation was added; patients in both groups received IV insulin. at a dose of 0.1 units / kg / h. Additionally, patients in the experimental group received 2nd generation ultra-slow insulin (Glargine U300, Degludec U100) subcutaneously, at a rate of 0.3 units/kg, upon admission (after performing a serum potassium test). Continuous assessment consisted of hourly monitoring of capillary blood glucose and ketonuria, and measurement of alkaline reserves and calculation of the anion gap every 4 hours. After negativation of ketonuria and normalization of the anion gap, the patients in the control group received long-acting subcutaneous insulin, the experimental group, for its part, only received the 2nd dose of ultra-slow insulin. only after 24 hours.

The endpoints in this study are: the duration of treatment for disappearance of ketonuria, the duration of treatment for a return to normal of the anion gap, the incidence of recurrence of KAD, hypoglycemia (defined as blood glucose less than 0.7g/l), the need for hospitalization in intensive care and the duration of hospitalization in the emergency room and in the endocrinology department. Our sample included 104 patients, 52 for each arm of the study.

Data entry and statistical analysis:
Data entry for the entire study was carried out using Excel software, statistical analysis was carried out using SPSS 25.0 software.

The qualitative or categorical variables were expressed as a percentage, and compared using the Chi square test, and the Fisher test when the validity conditions of the Chi square were not met.

The quantitative or continuous variables were expressed as means +/- standard deviation, for their comparison we used the Student T test.

A difference is only considered statistically significant when $p < 0.05$.

Results and Analysis:-
All demographic characteristics and admission assessment data were comparable in the two groups.

Table I:- Demographic characteristics:

	With ultra-slow insulin injection	Without ultra-slow insulin injection	p-Value
Age	30,9+/- 13,3	34,4+/-15 ,4	0,426
Sexe : Male	26(50%)	40(77%)	0,06
Female	26(50%)	12(23%)	
Associeted comorbidities	8(15%)	6(12%)	0,429
Diabetes Type:			0,775
Type 1 :	34(65,38%)	32(61,53%)	
Type 2 :	18(34,61%)	20(38,46%)	
Length of diabetes:			0,071
Inaugural:	36(69,23%)	28(53,84%)	
known	16(30,7%)	24(46,15%)	

The average age of the sample was 32.66 +/- 14.37 years [15-68], that of the experimental group was 30.91 +/- 13.38 years with extremes ranging from 15 to 68 years, the control group had an average age of 34.41 +/-15.41 years, with extremes ranging from 17 to 67 years, no statistically significant difference was revealed (p=0.426).

Of the 52 people in the experimental group, 26 were male, i.e. 50%, while 77% of the control group was male, i.e. a total of 40 patients; the difference was not statistically significant (p=0.06).) 8 people in the group who received an ultra-slow insulin injection had comorbidities associated with diabetes, i.e. a percentage of 15%, for the control group, 6 patients had at least one comorbidity associated with diabetes, i.e. a percentage of 12%.

Regarding the type of diabetes; type 1 diabetes was represented by 34 patients in the experimental group (65.38%) and by 32 patients in the control group (61.53%).

Diabetes was initial, revealed by KAD in 36 patients in the experimental group (69.23%) and in 28 people in the control group (53.84%).

Table II:- Admission and evolving parameters.

	With ultra-slow insulin injection	**Without ultra-slow insulin injection**	**p Value**
	Paramètres d'admission		
Average blood glucose	3.2 +/- 1.3	2.84 +/- 1.5	0.695
Alcaline Reserve (AR)	11.22 +/- 3.89	12.59 +/- 3.81	0.247
Anionic GAP (	27.68 +/- 5.4	26.4 +/- 7.6	0.529
	Paramètres évolutifs		
Average duration for ketonuria disappear	34.27+/-19.57h	69.81+/-71.19h	0.033
Average of anionic gap normalisation	25.54+/-19.57	64.4+/-78	0.029
Emergency hospitalisation (days)	2,24 +/- 1,3	3,45+/- 2,1	0.230
Endocrinology hospitalisation (days)	6,36+/-2,1	8,54 +/- 2,52	0,013
Recurrences KAD	11% (6)	19,23% (10)	0.10
hyperglycemia Rebound	11% (6)	23% (12)	0,04
Hypoglycemia	7,6% (4)	3,8% (2)	0.11

The average blood glucose at admission was 3.2+/- 1.3 g/l for the experimental group, and 2.84+/-1.5 for the control group, the average AR value was 11 .22+/- 3.89 in the experimental group and 12.59+/-3.81 in the control group.

The mean value of the anion gap on admission was comparable in the two groups (27.68 +/-5.4 in the experimental group versus 26.4 +/- 7.6 in the control group)

Regarding the cause of decompensation, it was a urinary infection in 7 patients in the experimental group and in 9 patients in the control group. In the others cases, the KAD was revealing without a triggering factor or secondary to treatment cessation.

The estimated average duration necessary for ketonuria to disappear was 34.27 hours (+/-25.27 hours) in the experimental group, and 69.81 (+/-71.19) in the control group, the difference was statistically significant (p=0.033).

The anion gap returns to its normal value in an average duration of 25.54 hours (+/-19.57 hours) for the experimental group, and in an average duration of 64.4 hours (+/-78 hours) for the control group, the difference was statistically significant (p=0.029)

For the duration of hospitalization in the emergency room, it was comparable in the 2 groups (2.24± 1.3 days versus 3.45±2.1 days successively in the experimental group and in the control group), however, the average length of

hospitalization in the department was reduced by 2 days for the experimental group (6.36 ± 2.4 days in the experimental group versus 8.54 ± 2.52 in the control group) with a statistically significant difference (p=0.019).

Recurrences of KAD after stopping the intravenous infusion as well as the occurrence of rebound hyperglycemia were more frequent in the control group (19% and 23% respectively) than in the experimental group (11% and 11% respectively) , this difference is statistically significant for hyperglycemic rebound and not significant for CAD recurrences (p=0.04 and 0.11 respectively).

Among the 52 patients in the control group, 4 patients (7.6%) required a stay in intensive care following a worsening of their condition, while in the experimental group, 2 people (3.8%) needed treatment in an intensive care unit, the difference between the two groups was not statistically significant.

Hypoglycemia was more frequent in the experimental group (4 people (7.6%) versus 2 people (3.8%) in the control group), no statistically significant difference was revealed.

Discussion:-

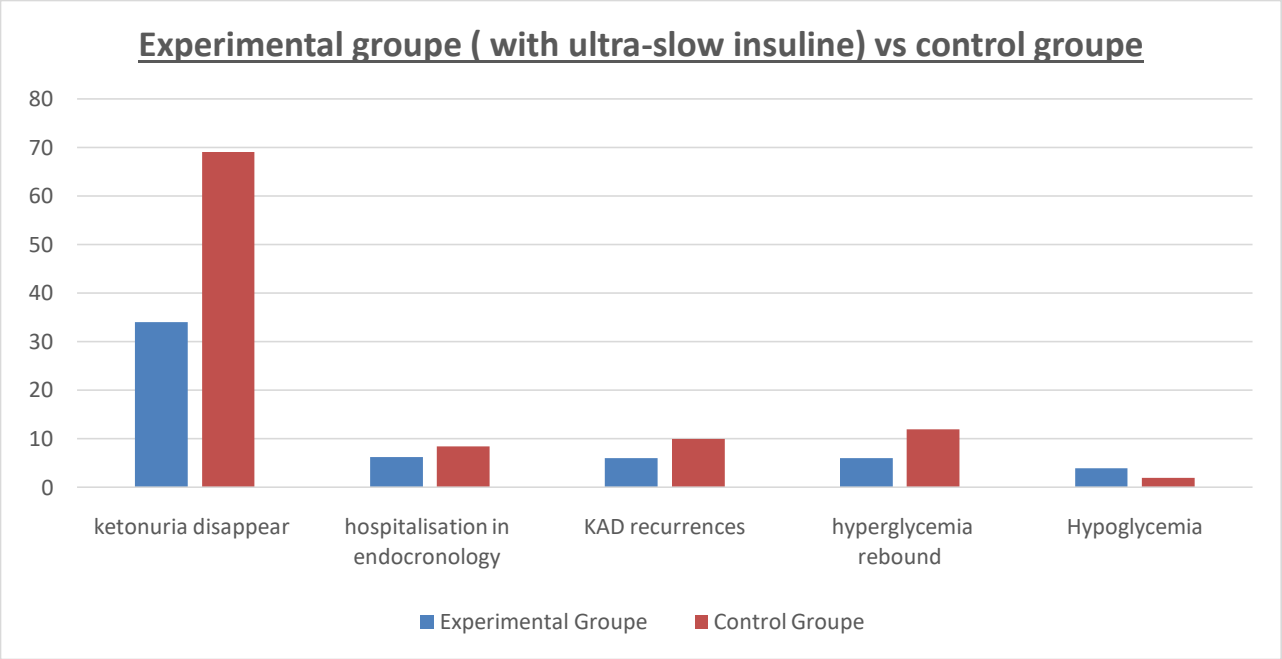
Ketoacid decompensation is a serious and frequent complication of diabetes, it represents a diagnostic and therapeutic emergency whose treatment is classically based on: the restoration of blood volume by an appropriate infusion of solutes, intravenous insulin therapy allowing correction of the hyperglycemia and acidemia, correction of electrolyte disturbances, mainly hypokalemia, and treatment of the triggering factor.

Due to its pharmacokinetic properties, long-acting subcutaneous insulin therapy has been proposed in combination with intravenous insulin therapy either from the diagnosis of KAD[3] or at the time of transition when intravenous insulin therapy must be stopped[4], in order to accelerate the transition from intravenous to subcutaneous insulin treatment, and to avoid the appearance of a rebound of hyperglycemia upon stopping intravenous insulin therapy, this was confirmed by our study which found a significantly faster correction of ketonemia with a return to normal of the anion gap in the group with ultra-slow insulin injection with a statistically significant difference. The study carried out by Shankar V et al [5] which included 71 diabetic children, found similar results: Co-administration of 2nd generation insulin with a regular insulin infusion was associated with faster resolution of the KAD as well as a shorter total hospital stay. Another study by Hsia E et al. [6] Was also in favor of a significant reduction in the time to resolution of KAD as well as the incidence of occurrence of a hyperglycemic rebound, However, the time to resolution of KAD, as well as the duration of hospitalization were similar in the two groups studied in the study by Doshi P et al [7].

In our study, the early injection of an ultra-slow insulin allowed a reduction in the duration of hospitalization, rapid negativation of ketonuria and less hyperglycemic rebound.

Despite these results reported in several studies, the use of long-acting subcutaneous insulin therapy in the treatment of CAD has long been controversial. In fact, and due to the state of dehydration that accompanies CAD, subcutaneous insulin absorption is often considered unreliable; the pharmacokinetic properties of ultra-slow insulins in cases of dehydration have never been studied, however, our results suggest that this protocol deserves to be expanded and refined, given its advantages in terms of reducing the length of hospitalization and rapid negativation of ketonuria.

Regarding the risk of hypoglycemia, 4 cases were reported in our study in the experimental group versus 21 cases in the control group; this difference was not statistically significant. In the study by Harrison VS et al. [8], the use of slow insulin was not associated with an increased risk of hypoglycemia. Other larger studies are needed to confirm these data.



Conclusion:-

This is a prospective randomized study which studied the contribution of co-administration of an ultra-slow insulin in the management of ketoacidotic decompensation in comparison with the classic protocol, our results suggest that this protocol allows a rapid resolution of CAD, as well as a significant reduction in overall hospital time and therefore a reduction in the cost of care. Other larger studies are necessary to evaluate the safety of this therapeutic protocol.

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