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Pseudohyperkalemia related to blood sampling at the University Hospital Center Professor Zafisaona Gabriel Mahajanga

Francine Isabelle Rakotonindrina [1,*], Rivo Solotiana Rakotomalala [2], Miora Koloina Ranaivosoa [3], Rissa Dahlia Njariaina [4], Tahirimalala Rabenandrianina [2], Olivat Rakoto Alson [5] and Andry Rasamindrakotroka [6]

[1] *Laboratory of Mahavoky Atsimo University Hospital, Mahajanga, Madagascar.*
[2] *Laboratory of Professor Zafisaona Gabriel University Hospital, Mahajanga, Madagascar.*
[3] *Laboratory of Biochemistry of Joseph Ravoahangy Andrianavalona University Hospital Antananarivo, Madagascar.*
[4] *Faculty of Medicine, Mahajanga, Madagascar.*
[5] *Biological Haematology, Medical Biology Department, Faculty of Medicine, Antananarivo, Madagascar.*
[6] *Immunology. Laboratory of Training and Research in Medical Biology, University of Antananarivo, Madagascar.*

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Abstract

Pseudohyperkalemia is common in routine laboratory tests. The objective of the present study is to determine pseudohyperkalemia associated with blood sampling and to analyze other causes that may explain the occurrence of hyperkalemia.

A prospective descriptive and analytical study was carried out over a period of 3 months, from November 2020 to January 2021, at the University Hospital Center Professor Zafisaona Gabriel Mahajanga. Samples intended for the determination of plasma potassium, of which the pre-analytical phase could be followed from the blood sampling to their analysis were included.

One hundred and twenty nine samples were tracked. Hyperkalemia was observed in 51 cases, or 39.5%. The frequency of pseudohyperkalemia was 27.5% (n = 14). Pseudohyperkalemia predominated on samples from hospitalized patients, where the pediatric department was first (50%, n = 7), followed by the Emergency and Intensive Care Department (42.9%, n = 6). It was more frequent on samples taken by paramedical trainees (78.6%, n = 11). Pseudohyperkalemia associated with tourniquet placement for more than one minute was 42.9% (n = 6). The age of 0 to 15 years and over 60 years, the presence of edema, renal and / or cardiac signs, the use of hyperkalemic drugs, and hospitalization were significantly linked to the occurrence of hyperkalemia ($p<0.05$).

Pseudohyperkalemia must be differentiated from true hyperkalemia. Hyperkalemia should always be confirmed before aggressive treatment.

Keywords: Hyperkalemia; Pseudohyperkalemia; Pre-analytical phase; Blood sampling

1. Introduction

Hyperkalemia, defined as a serum or plasma potassium level above the upper limits of normal, generally greater than 5.0 mmol/L [1] [2], is an ionic disorder frequently encountered in clinical practice. Sometimes a sub-classification is introduced, namely mild (> 5.0 - <5.5 mmol / L), moderate (≥ 5.5 - <6.0 mmol / L) and severe (≥ 6.0 mmol / L)

* Corresponding author: Francine Isabelle Rakotonindrina
Laboratory of Mahavoky Atsimo University Hospital, Mahajanga, Madagascar.

hyperkalemia [3]. Pseudohyperkalemia represents a false rise in measured potassium, ie normal blood potassium *in vivo* and high potassium level measured in plasma and serum; due to collection, handling, or other causes. It is common in routine laboratory tests and should be distinguished from true hyperkalemia which can be caused by increased potassium uptake, transcellular movement of intracellular potassium to the extracellular space, and decreased renal excretion. Improper treatment of hyperkalemia can lead to life-threatening cardiac arrhythmias due to induced hypokalemia [2][4]. During a laboratory test, all tests combined, 32 to 75% of errors were found during the pre-analytical phase [5]. The objective of the present study is to determine pseudohyperkalemia associated with blood sampling and to analyze other causes that may explain the occurrence of hyperkalemia.

2. Material and methods

This is a descriptive, prospective observational study over a 3-month period from November 2020 to January 2021, at the University Hospital Center Professor Zafisaona Gabriel (UHC PZaGa) Mahajanga. The study was based on ionogram requests to the UHC PZaGa laboratory.

Samples intended for the determination of plasma potassium, of which the pre-analytical phase could be followed from the blood sampling to their analysis were included. These samples came from patients consenting to participate in this study and complete a questionnaire. Data collection was carried out to determine the modes and stages of blood sampling as well as the mode and delivery times until centrifugation and then analysis of the sample. The plasma potassium assay was performed with the URIT-C 910 Plus automated system, using the ion-selective electrode (ISE) analysis method. The validity of the measurements was guaranteed by the passage of control before each series of analysis.

The studied variables were the age of the patients, the gender, the clinical signs, hyperkalemic treatment, the departments in which the blood samples were taken, the status of the phlebotomist, the type of disinfectant used, the tourniquet application time, the order of the collection tubes, the mode of transport, the time between collection and analysis, and the plasma potassium result.

Hyperkalemia associated with renal, cardiac or neuromuscular signs, diabetes and hyperkalemic treatments such as ACE inhibitors, potassium-sparing diuretics, ARB II, NSAIDs, heparin, digitalis, beta-blockers, potassium supplements, vitamins C, penicillins and imidazole derivatives were considered true hyperkalemia. Hyperkalemia which has no obvious explanation for true hyperkalemia was considered to be pseudohyperkalemia.

The data were entered in Microsoft Office Excel® 2013 then processed by R software version 3.5.2. Fisher's non-parametric test was used for the analytical study.

3. Results

The number of ionogram requests received during the study period was 384. The number of samples for which the pre-analytical phase could be followed was 129. The age of the patients varied between 1 month and 96 years old, with an average of 30.6 years (± 21 years). The sex-ratio was 1.5.

All phlebotomist used 70% alcohol as a disinfectant. All blood samples were taken on lithium heparin tube (with green cap). No pumping maneuver was observed during the blood sampling. All samples met the turnaround time in less than 2 hours.

The serum potassium value varied between 3.5 and 7.4 mmol / L, with an average of 5.0 (± 0.8) mmol / L. Hyperkalemia was observed in 51 cases, or 39.5% among the followed samples. Hyperkalemia was mild (> 5.0 - <5.5 mmol / l) in 39.2% (n = 20), moderate (≥ 5.5 - <6.0 mmol / l) in 35.3% (n = 18) and severe (≥ 6.0 mmol / L) in 25.5% (n = 13) of cases.

Tourniquet application time varied between 40 and 110 seconds, with an average of 57.7 (± 14.4) seconds, for samples with hyperkalemia.

For non-hospitalized patients, whose blood sample was taken in the laboratory by laboratory technicians, an NSAID intake was recorded in one patient and vitamin C intake in 7 patients (13.7%). The latter had mild hyperkalemia (≤ 5.5 mmol / L) but showed no clinical signs.

Table 1 Characteristics of the study population and distribution of results according to the value of plasma potassium

Variables	Effective	Value of plasma potassium (mmol/L)		OR	IC	p
	Total	**≤ 5.0**	**> 5.0**		**95%**	
	N=129 (100%)	n=78 (60.5%)	n=51(39.5%)			
Genre						
Male	77 (59.7)	48 (61.5)	29 (56.9)	0.82	0.37 – 1.80	0.71
Female	52 (40.3)	30 (38.5)	22 (43.1)			
Age group (years)						
[0 – 15]	24 (18.6)	9 (11.5)	15 (29.4)	3.16	1.16 – 9.07	0.01*
[16 – 30]	63 (48.8)	49 (62.8)	14 (27.5)	0.22	0.09 – 0.51	< 0.001*
[31 – 45]	14 (10.9)	8 (10.3)	6 (11.8)	1.16	0.31 – 4.12	0.78
[46 – 60]	13 (10.1)	7 (9)	6 (11.8)	1.34	0.35 – 5.02	0.76
> 60	15 (11.6)	5 (6.4)	10 (19.6)	3.52	1.01 – 14.08	0.02*
Origin of samples						
Hospitalised patients	90 (69.8)	48 (61.5)	42 (82.4)	0.89	1.17 – 7.75	0.01*
Non-hospitalised patients	39 (30.2)	30 (38.5)	9 (17.6)			
Department						
Emergency and intensive care	47 (36.4)	25 (32.1)	22 (43.1)	1.6	0.72 – 3.55	0.26
Laboratory	39 (30.2)	30 (38.5)	9 (17.6)	0.34	0.12 – 0.85	0.01*
Pédiatric	23 (17.8)	8 (10.3)	15 (29.4)	3.6	1.29 -10.81	< 0.01*
Surgery	14 (10.9)	11 (14.1)	3 (5.9)	0.38	0.06 – 1.55	0.16
Medicine	6 (4.7)	4 (5.1)	2 (3.9)	0.75	0.06 – 5.51	1
Status of the phlebotomist						
Paramedical trainees	66 (51.1)	34 (43.6)	32 (62.8)	2.16	0.99 – 4.80	0.04*
Laboratory technician	33 (25.6)	25 (32.1)	8 (15.7)	0.39	0.14 – 1.02	0.04*
Nurse	18 (14)	11 (14.1)	7 (13.7)	0.96	0.29 – 2.98	1
Medical intern	12 (9.3)	8 (10.3)	4 (7.8)	0.74	0.15 – 2.98	0.76
Tourniquet application time						
< 60 seconds	100 (77.5)	59 (75.6)	41 (80.4)	0.75	0.28 – 1.92	0.66
≥ 60 seconds	29 (22.5)	19 (24.4)	10 (19.6)			
Clinical signs						
- Edema						
Présence	13 (10.1)	2 (2.6)	11 (21.6)	10.26	2.09 – 99.79	< 0.001*
Absence	116 (89.9)	76 (97.4)	40 (78.4)			
- Kidney signs						
Présence	10 (7.8)	2 (2.6)	8 (15.7)	5.96	1.07 – 61.31	0.02*
Absence	119 (92.2)	76 (97.4)	43 (84.3)			
- Cardiac signs						

Présence	13 (10.1)	2 (2.6)	11 (21.6)	10.26	2.09 – 99.79	< 0.001*
Absence	116 (89.9)	76 (97.4)	40 (78.4)			
- Neuromuscular signs						
Présence	5 (3.9)	1 (1.3)	4 (7.8)	6.46	0.61 – 326.2	0.07
Absence	124 (96.1)	77 (98.7)	47 (92.2)			
Diabetes						
Présence	11 (8.5)	4 (5.1)	7 (13.7)	2.91	0.69 – 14.4	0.11
Absence	118 (91.5)	74 (94.9)	44 (86.3)			
Hyperkalemic medication						
Présence	22 (17.1)	4 (5.1)	18 (35.3)	6.56	0.37 – 1.88	< 0.001*
Absence	107 (82.9)	74 (94.9)	33 (64.7)			

Table 2 Characteristics of hyperkalemia associated with clinical signs and / or hyperkalemic treatments

Variables	**Effective**	**Value of plasma potassium (mmol/L)**		
	N=51 (100%)	[5.1 – 5.5] n=20 (39.2%)	[5.5 – 6.0] n=18 (35.3%)	≥ 6.0 n=13 (25.5%)
Edema	11 (21.6)	0 (0)	6 (33.3)	5 (38.4)
Kidney signs	8 (15.7)	0 (0)	4 (22.2)	4 (30.8)
Cardiac signs	11 (21.6)	0 (0)	3 (16.7)	8 (61.5)
Neuromuscular signs	4 (7.8)	0 (0)	3 (16.7)	1 (7.7)
Diabetes	10 (19.6)	3 (15)	4 (22.2)	3 (23.1)
Hyperkalemic medication	24 (47.1)	9 (45)	7 (38.9)	8 (61.5)

Pseudohyperkalemia and parameters of the pre-analytical phase

Pseudohyperkalemia cases represented 27.5% (n = 14), after excluding cases with an obvious cause of true hyperkalemia.

The order of the tubes was not respected in only one case (7.1%) where the Ethylene Diamine Tetra Acetate (EDTA) tube was taken before the heparinized tube by a paramedical trainee in the pediatric department, the value of the plasma potassium was 5.6 mmol/L.

Only one phlebotomist (7.1%), a paramedical trainee in a pediatric ward, made a brutal maneuver during the homogenization of the tube, and the plasma potassium was 5.4 mmol/L.

Two cases (14.3%) of proven difficult blood sampling were noted, including one case taken by a nurse in the pediatric ward, and the other case also taken by a nurse from an agitated patient in the Psychiatry ward. The plasma potassium values were respectively 5.8 and 5.6 mmol/L.

Table 3 Characteristics of pseudohyperkalemia according to the parameters of the pre-analytical phase

Parameters	Effective	Value of plasma potassium (mmol/L)		
	N=14 (100%)	[5.1 – 5.5] n=8 (57.1%)	[5.5 – 6.0] n=6 (42.9%)	≥ 6.0 n=0 (0%)
Tourniquet application time ≥ 60 seconds	6 (42.9)	4 (50)	2 (33.3)	0 (0)
Status of the phlebotomist				
Paramedical trainees	11 (78.6)	7 (87.5)	4 (66.7)	0 (0)
Nurse	3 (21.4)	1 (12.5)	2 (33.3)	0 (0)
Department				
Pediatric	7 (50)	4 (50)	3 (50)	0 (0)
Emergency and intensive care	6 (42.9)	4 (50)	2 (33.3)	0 (0)
Medicine (Psychiatry)	1 (7.1)	0 (0)	1 (16.7)	0 (0)

4. Discussions

Hyperkalemia was more common in patients who presented clinical signs in favor of renal failure and / or heart failure, neuromuscular signs, in diabetics and in those who took hyperkalemic drugs. These factors are already known as causes or signs of true hyperkalemia [6] [7]. These hyperkalemias were mainly moderate to severe hyperkalemia in our case (≥5.5 mmol / L) (Table 2).

Hyperkalemia was significantly more common in subjects over 60 years of age and children 0 to 15 years of age in this study. The elderly are often prone to comorbidities, such as renal failure, diabetes, high blood pressure and heart disease, known to cause true hyperkalemia by a mechanism directly related to the pathology itself, or induced by their treatment [8]. On the other hand, these risk factors are quite rare in children where the mechanism of hyperkalemia could be linked either to pseudohyperkalemia, or to the side effects of certain drugs such as anti-infectives, or to other causes [9]. Pseudohyperkalemia, or artefactual elevation of potassium, occurs during the pre-analytical phase. Several factors during this phase have been identified as being able to affect the serum or plasma potassium dosage. They are related to the conditions of collection and storage of the sample [10].

In this study, cases of pseudohyperkalemia represented 27.5% (n = 14). They were characterized by mild to moderate hyperkalemia (<6.0 mmol / L) (Table 3). Half (50%) of the cases were found on samples from the pediatric department, the majority of which were taken by paramedical trainees (6/7 cases). This could be explained by the fact that taking samples from children are quite difficult, and all the more so if the collector is not sufficiently trained to perform these more delicate sampling compared to samples from adults. A large part (42.5%) was found on samples from the Emargency and intensive care department, where the majority (5/6 cases) were also taken by paramedical trainees.

Pseudohyperkalemia may be secondary to the locoregional release of potassium by muscle cells during sampling following the application of a tourniquet that is too tight or for more than one minute, to the clenching of the fist or pumping maneuver, and to tapping on the puncture site especially when the collection is difficult [11] [12] [13] [14]. In our case, the pseudohyperkalemia linked to the tourniquet fitting for more than one minute was 42.9% (n = 6) and that linked to the difficult harvesting was 14.3% (n = 2).

Contamination of the tube with an anticoagulant containing potassium such as Ethylene Diamine Tetra-Acetate (EDTA) can also induce pseudohyperkalemia [15]. One case (7.1%) related to non-observance of the order of the tubes during blood collection was noted, where the EDTA tube preceded the heparinized tube. In fact, the inside of the wall of EDTA tubes, widely used in hematology, is coated with K2-EDTA or K3-EDTA, so they contain a high concentration of potassium. This potassium contained in the ETDA tubes could contaminate the tubes which follow them. If the tube intended for the dosage of potassium is taken after the EDTA tube, then the serum or plasma potassium result could be

falsely high. Care should therefore be taken to respect the order of the tubes when sampling in order to avoid errors due to this effect [16].

Pseudohyperkalemia may also be linked to the cellular release of potassium in the collection tube during hemolysis, major leukocytosis or thrombocytosis, or late centrifugation [14] [17] [18]. In vitro hemolysis due to poor collection / handling technique and delayed separation of plasma / serum from the whole blood sample are among the most common causes of pseudohyperkalemia [19]. In this study, there was a case related to a sudden homogenization of the collection tube. Abrupt maneuvers during tube homogenization promote hemolysis during which there will be release of intraerythrocytic potassium, thus overestimating the plasma potassium concentration [20].

Both false maneuvers were performed by paramedical trainees. We found that pseudohyperkalemia was much more frequent on samples taken by paramedical trainees (78.6%), while it was not observed on samples taken by laboratory technicians (0%). This could be explained by the fact that the laboratory technicians are more accustomed to blood sampling and they know better the techniques as well as the recommendations for the good performance of blood samples.

As for the paramedical trainees, they are still learners who could make mistakes in the manners and gestures to be done during blood sampling by being less used to these techniques. The qualification of the sampler therefore has a major role to play, hence the importance of authorizing the personnel concerned. Adherence to phlebotomy technique recommendations is essential to the integrity of patient test results [21]. The World Health Organization (WHO) has issued best practice recommendations for performing phlebotomy [22] as well as for transport and storage of tubes to obtain representative samples [23].

5. Conclusion

Pseudohyperkalemia is very common in hospitals. It mainly concerned the samples taken by the paramedical trainees. It can be the source of misinterpretation and poor management and should be differentiated from true hyperkalemia. Hyperkalemia should always be confirmed before aggressive treatment in cases where serum or plasma potassium is elevated without an obvious cause. It is essential to seek out and identify risky situations as well as to respect the preanalytical conditions described in the literature. Continuous training of medical and paramedical personnel on the standards of the preanalytical phase and the recommendations of good practices for carrying out the blood collection is the rule to avoid and / or reduce errors related to non-compliance with this crucial step for any biological examination, because the validity and reliability of the medical analysis results depend on the preanalytical phase.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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