Scientific Research Publishing

Open Journal of Endocrine and Metabolic Diseases, 2022, 12, 103-111
https://www.scirp.org/journal/ojemd
ISSN Online: 2165-7432
ISSN Print: 2165-7424

Hypercalcemia: Is Dialysis Still an Option?

Basmat Amal Chouhani[1,2*], Yassine Allata[1,2], Wafae Chouhani[1,2], Ghita Elberdai[1,2], Nadia Kabbali[1,2], Tarik Sqalli Houssaini[1,2]

[1]Department of Nephrology Dialysis and Transplantation, Hassan II University Hospital, Fez, Morocco
[2]Laboratory of Epidemiology and Health Science Research (ERESS), Faculty of Medicine-Fez, University Sidi Mohammed Ben Abdelalh, Fez, Morocco
Email: *basmatamal_ch@hotmail.com

How to cite this paper: Chouhani, B.A., Allata, Y., Chouhani, W., Elberdai, G., Kabbali, N. and Houssaini, T.S. (2022) Hypercalcemia: Is Dialysis Still an Option? *Open Journal of Endocrine and Metabolic Diseases*, **12**, 103-111.
https://doi.org/10.4236/ojemd.2022.124008

Received: March 4, 2022
Accepted: April 24, 2022
Published: April 27, 2022

Abstract

Hypercalcemia is a common disorder that can cause acute kidney failure, neurological damage up to coma, arrhythmia and cardiac arrest. The management of hypercalcemia is based on intravenous hydration with normal saline, when insufficient, bisphosphonate treatment is used. More recently, denosumab has shown significant benefit. Hemodialysis is an additional option in the treatment of severe refractory hypercalcemia when medical treatment is deemed ineffective or unavailable. It allows rapid correction of calcium levels, especially in patients with renal failure or cardiac co-morbidities, where hydration cannot be performed safely. The aim of our study was to compare hemodialysis as a therapeutic tool, to more conservative treatments. Our study is retrospective, descriptive, analytical and comparative, sprawling from January 2015 to June 2019 at the university hospital Hassan II in Fez. 78 patients with hypercalcemia were studied. The mean age was 55 ± 15 years and sex ratio M/F of 1.1. The mean corrected serum calcium at admission was 144 mg/l ± 23 mg/l. Malignancies represented 72.7% of all etiologies. Kidney injury was observed in 50 of our patients (64%). Mortality was noted in 16.6% of all cases. When comparing the 2 groups (patient on dialysis versus patient under other treatments), electrocardiogram abnormalities, patient who had high levels of calcium and those who had hyperparathyroidism were more likely to be on dialysis rate. In our study, even though we used relatively high calcium dialysate, we were able to achieve a decrease of 39% in patient's calcemia in the hemodialysis group versus 27% decrease when using a combination of forced saline dieresis and bisphosphonate without a difference in term of mortality.

Keywords

Hypercalcemia, Dialysis, Bisphosphonate, Mortality

1. Introduction

Calcium is a bivalent cation, essential for many physiological functions, in particular in neuromuscular activation, endocrine and exocrine secretion, coagulation, immunity and in bone metabolism [1]. Hypercalcemia is a life-threatening disorder that can cause muscle flaccidity, acute kidney failure, neurological disorders, arhythmia and cardiac arrest.

Limited data are available on the epidemiology of hypercalcemia in hospitalized patients in a study evaluating the frequency of hypercalcemia, the disorder was accounted for 4.74% (n = 585) of the 12,334 inpatients. The 2 main causes representing approximately 90%, of diagnoses are hyperparathyroidism and neoplasic causes [2].

Nowadays, the therapeutic tools to treat hypercalcemia are numerous; even if biphosphonates remains the treatment of choice especially in severe or symptomatic hypercalcemia secondary to tumor pathologies, its use can be limited in case of kidney failure in the case of use of zoledronic acid and side effects related to the use of other molecules such as pamedronic acid [3] whereas dialysis only has a place in cases where the hypercalcemia is associated with kidney or heart failure which does not allow significant hydration.

Our primary end point was to compare 2 groups: patients under dialysis (D) versus patients who received conservative therapies (ND) in term of clinical and biological characteristics, indication of the renal replacement therapy (RRT), mortality.

2. Patients and Methods

Our study is retrospective, descriptive, analytical and comparative, sprawling from January 2015 to June 2019 at the university hospital Hassan II in Fez.

We included all adult patients, over 18 with diagnosis of hypercalcemia > 2.7 mmol/l, admitted in the different departments of the Hassan II University Hospital Fez whose records were usable.

We collected several parameters, including the clinical and biological data of the patients, specifying the associated morbidities (hypertension, diabetes, the presence or not of a previous renal failure, hypercalcemic drug intake, the presence of neoplasia or known dysthroidism), the mode of revelation, risk factors including presence of reported dehydration and acute renal failure defined by creatinine greater than 12 mg/l (106 µmol/L). The cause of hypercalcemia if found, the treatments administered. For hemodialysis sessions, we collected the number of sessions, their duration, the fluid used and the area of the membranes. The short-term evolution of the calcemia, and kidney function (3 months), the survival at 3 months were collected on digital patient medical records.

We report for each patient the therapeutic modalities established in particular the indication of an extra-renal replacement therapy (ERR). We compared the 2 groups (patient who received hemodialysis versus patient who didn't).

The quantitative values were recorded in the form of numerical values and binomial way for qualitative values. The statistical analysis was carried out with

the collaboration of the Laboratory of Epidemiology, Clinical Research and Community Health of the Faculty of Medicine in Fez. The data was entered and coded in Excel 2016. After validation, we processed the data using the SPSS v26 statistical software. We used the chi2 and Fisher tests to compare the quantitative variables and the Student test to compare 2 means. ANOVA (variant analysis) was used to compare several means.

For the multivariate analysis, logistic regression was used, taking as the variable to explain dialysis and as the explanatory variable: the rate of corrected calcemia, the electrical signs, the evolution of calcemia, the evolution of renal function at 3 months the cause of hypercalcemia and death. We also took as a variable to explain death and as an explanatory variable: age, sex, dehydration, tumor causes, the level of corrected calcemia, natremia, hypokalemia, natremia, hypo albuminemia, QT shortens dialysis, taking Bisphosphonates.

All tests were bilateral and was considered significant if p was less than 0.05.

Ethics Committee approval and the written informed consent were not needed because the study was observational and retrospective. We conducted our study with absolute respect for international ethical rules, anonymity, and data protection.

3. Results

Out of 114 patients with hypercalcemia we were able to use 78 files, treated in different departments of a university hospital over a period of four and a half years, whose clinical-biological spectrum is as follows: the average age of our patients was 55 ± 15 years [22 - 85 years]. With a sex ratio male/female of 1.1.

The majority of our patients had a history of malignant tumor (46.2%), 9% were diabetic, 9% hypertensive, 5% were followed for dysthyroidism and 12.8% had chronic renal failure including 4 hemodialysis patients. While 5% had already a history of hypercalcemia and only one patient was on hypercalcemic medication (vitamin D supplement) (Figure 1).

The hypercalcemia in our population was secondary in the majority of cases to a malignant tumor with a predominance of solid tumors which was responsible of hypercalcemia in 39% of all, multiple myeloma in 24% and other hemopathies in 9%) Primary hyperparathyroidism was responsible of hypercalcemia in 10% of cases.

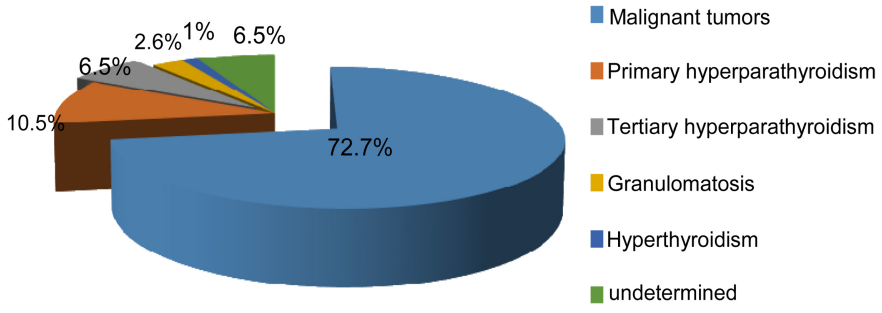

Figure 1. Distribution of hypercalcemia according to the cause.

Table 1. Univariate analysis of 2 groups (receiving dialysis versus no dialysis).

Different parameters	Dialysis group (n = 38)	Non dialysis group (n = 40)	P
Age	52 [22, 85]	58 [27, 80]	0.058
Male gender	20 (52%)	22 (55%)	0.83
Diabetes mellitus	3 (7.8%)	3 (7.5%)	0.94
Arterial hypertension	2 (5.2%)	6 (15%)	0.16
End stage renal disease under dialysis	5 (13%)	0	0.008
Neoplasia	28 (74%)	33 (82%)	0.35
Hyperparathyroidism (primitive or secondary)	10 (26%)	3 (7.5%)	0.025
Presence of clinical manifestations	3 (7.8%)	11 (27%)	0.024
Electrocardiogram abnormalities	30 (79%)	2 (5%)	0 .0000
Renal failure	22 (71%)	23 (57.5%)	0.78
Mean calcium levels	3.56 ± 0.54	3.28 ± 0.52	0.049
Mean corrected calcium level	2.17 ± 0.59	2.37 ± 0.49	0.119
Mean serum potassium	4.25 [2.8, 8]	3.8 [2.7, 5.7]	0.085
Mean serum sodium	134.4 [104, 155]	135.4 [122, 147]	0.54
Rehydration	27 (71%)	38 (95%)	0.017
Biphosphonates	24 (63%)	26 (65%)	0.86
Loop diuretics	13 (34%)	15 (37%)	0.95
Steroids	11 (29%)	6 (15%)	0.13
Calcitonin	1 (2.6%)	1 (2.5%)	0.97
Deceased patients	8 (21%)	5 (12.5)	0.31

Hypercalcemia was responsible of symptoms in 12.5% of our patients, gastro intestinal symptoms in 8 patients (10%), while neurological signs were only present in 2 patients (2.5%), tetany were reported in a single case. The hydration status of our patients was evaluated clinically and noted dehydration in 67% of the cases.

The mean corrected serum calcium at admission was 3.59 mmol/L (2.7, 5.18) mmol/l ± 0.5. QT space shortening (QTc less than 360 ms) was noted in 38% of patients, while other electrical signs of hypercalcemia were not mentioned.

Management consisted of intravenous rehydration with saline fluids in 87% of the cases according to their volume and heart condition versus 13% of patients who did not receive intravenous rehydration. We used as Bisphosphonates, the zoledronic acid which was administered in 63% of our patients taking into consideration the degree of the acute kidney failure, while Conventional hemodialy-

sis sessions were indicated in 46% of patients, lasting a maximum of 4 h 30 minute per session, 48% of our patients received a single hemodialysis session with a maximum of 12 sessions in a single patient admitted with primary hyperparathyroidism without drop in serum calcium even after administration of bisphosphonates. The dialysis membranes surface was ranging from 1.6 m^2 to 1.8 m^2. The dialysis fluids contained 1.5 calcium.

Complications reported secondary to dialysis were bleeding after catheter removal in one patient and catheter infection in another patient.

By comparing the 2 hemodialysis and non-hemodialysis groups:

In univariate there was a significant difference in term of presence of and end stage renal disease, presence of symptoms, calcium levels and presence of electrocardiogram abnormalities. On a multivariate analysis, there was a significant difference only in the presence of electrical signs ($p = 0.001$, $\beta = 7.08$); however, there was no difference in term of mortality or rate of decline of calcemia (**Table 1**).

Out of the 78 patients and during 3 months of follow-up, 13 died (16.6%), all carriers of a malignant disease.

4. Discussion

Hypercalcemia is a relatively common disorder, primary hyperparathyroidism being the first cause accounting for more than 90% of cases [4]. In our study the causes were dominated by malignancies, this is probably due to the acute and severe character of hypercalcemia in our series, in fact hypercalcemia can affect up to 49% of all patients with neoplasia [5].

The clinical signs are not specific, misleading and depend on three factors: the speed of onset of hypercalcemia, its rate and its cause [6]. It is interesting to observe that only 4 of our patients had neurological signs with calcium levels from 3.19 to 4.31 mmol/L. While 35 of 42 patients (83%) with hypercalcemia greater than 3.49 mmol/L did not present any symptoms. In the study led by Guimard in order to assess the correlation between severe hypercalcemia and clinical signs of severity, notably cardiac and neurological, only one patient presented a coma which could be explained by other metabolic disorders and no case of serious cardiac complications [1].

Treatment for hypercalcemia should aim to reduce the concentration of serum calcium and, if possible, treat the underlying disease. Effective treatments reduce serum calcium levels by inhibiting bone resorption, by increasing calcium excretion in the urine or by decreasing calcium absorption in the intestine. The optimal choice varies depending on the cause and severity of the hypercalcemia.

The degree of hypercalcemia, as well as the rate of increase in serum calcium concentration, often determines the symptoms and whether it is an emergency for treatment or not. The therapeutic approach must reflect these differences [6] [7].

Patients with asymptomatic hypercalcemia or (calcemia less than 3 mmol/L) do not require immediate treatment. Similarly, a serum calcium level of 3 to 3.5 mmol/L can be well tolerated chronically and do not require immediate treatment. However, an acute increase in these concentrations can lead to marked changes in the sensorium, which requires more aggressive measures. In addition, patients with a serum calcium concentration greater than 3.5 mmol/L should be treated regardless of symptoms [8].

In our study, all patients with a calcium level greater than 2.9 mmol/l received at least a hyper hydration except for patients with hypervolemia or those on chronic hemodialysis. This volume expansion is generally administered first at the same time as the administration of calcitonin or bisphosphonates, to avoid or correct volume depletion secondary to a urinary salt loss or vomiting. The goal should be establishing an adequate urine output (>75 ml per hour) and that imply a high-volume saline infusion (200 - 500 ml/hour).

Large volumes should be administered with caution due to the likelihood of congestive heart failure and third spacing, especially in the case of hypercalcemia associated with a malignant tumor, where patients often tend to have a hypo albuminemia [9].

Hemodialysis can be a good alternative especially in the treatment of patients with severe hypercalcemia associated with malignancy and renal or heart failure, in whom hydration cannot be administered safely [10]. The diffusion of Ca in HD depends on the Ca gradient between the serum concentration and the dialysate concentration. A negative balance is obtained with a dialysate Ca of 1.25 mmol/L [11]. Dialysate free of Ca has been shown in one early human study to produce symptomatic hypocalcemia within the first 60 min of dialysis for chronic HD patients and hypotension can also result from inadvertent use of a Ca-free dialysate [12]. however the use of a normal calcium dialysate of 1.5 mmol/L seem to be as effective, in our study we used a calcium dialysate of 1.5 mmol/L, as a result no patient had a hypotension or major incident (heart rhythm disturbances, cardiac arrest, un consciousness) during the dialysis session.

Loop diuretics, such as furosemide, used to enhance calcium excretion, may worsen electrolyte perturbation and volume depletion when administered at high doses. They should be used with caution. A recent review shows limited or no evidence to support the use of loop diuretics in people with hypercalcemia [13].

Since usually severe hypercalcemia is due to an increased bone resorption, bisphosphonates are the treatment of choice as they inhibit the osteoclast's activity. Pamidronate and zoledronic acid both having shown effectiveness in clinical trials, [14] [15] the later being superior in both efficacy and duration of response [16]. A single 15-minute intravenous infusion of 4 mg of zoledronic acid in 100 mL of isotonic saline, with adequate hydration is enough for a normalization of serum calcium levels in less than three days in most patients. Another dose can be read ministered if necessary to control hypercalcemia. The dose is usally reduced in the case of low creatinine clearance (less than 30 ml/min/1.73m^2). Zo-

ledronic acid is used routinely in our study with a dose of 3 to 4 mg and we didn't encounter any serious or life-threatening complications even in advanced kidney failure cases. Unless the cause of the hypercalcemia is dealt with we often needed a second dose 2 to 3 weeks later in order to maintain a controlled calcium level.

Calcitonin inhibits bone resorption and decreases renal tubular reabsorption of calcium. Its onset of action is within two hours of administeration. It's used as an early treatment for severe hypercalcaemia until the onset of the hypocalcaemic effects of other drugs like biphophonate.

Corticosteroids can reduce calcemia by inhibiting 1α-hydroxylase conversion of 25-hydroxyvitamin D to calcitriol in cases where it's hyper produced like in some Hodgkin or non-Hodgkin lymphoma. A propsed regime of 200 - 300 mg/d of hydrocortisone for 3 to 5 days may be used [17].

Denosumab is a human monoclonal antibody that binds to RANKL and inhibits osteoclast maturation, activation, and function. It can be used in treating forms of malignancy-associated hypercalcemia.

The use of these new therapeutics in the late years overshadowed the use of hemodialysis. They are easy to manipulate and has a quick effect on calcium levels. However, hemodialysis can be an alternative in the case of unavailability of these medications or in case of contraindication.

Hemodialysis can clear up to 682 mg of calcium per hour as compared to 124 mg per hour for peritoneal dialysis and 82 mg per hour with an 8 fold higher rate than forced saline dieresis [8]. In our study, even though we used relatively high calcium dialysate we were able to achieve a decrease of 39% in patient's calcemia in the hemodialysis group versus 27% decrease when using a combination of forced saline dieresis and bisphosphonate. A high potassium dialysate was used whenever the kidney function was normal to avoid a sudden drop of potassium levels. The duration of treatment ranged from 4 to 12 hours and dialysis was interrupted as soon as we could achieve a calcemia under 120 mg/l and no EKG signs of hyper calcemia namely a shortened corrected QT space (less than 360 ms). A decline in calcium level induced by a calcium-free dialysate could result in a fall in blood pressure leading to intradialytic hypotension [18] [19]. No complications directly linked to dialysis were noted in our study thanks to the high calcium dialysate reducing the hemodynamic instabilities.

In a multivariate analysis, only the presence of electrical signs (Qtc < 360 ms) was associated with mortality ($p < 0.0001$) which was one of the major indications of RRT in our series.

In a univariate analysis between the dialysis and no-dialysis groups there was no difference between the two groups in term of mortality or long-term calcium levels.

5. Conclusion

Our study showed no difference in term of mortality between the D and ND group. Dialysis had a fast impact on calcium reduction. In our opinion, it re-

mains a viable option in emergency settings particularly in the absence of other options. Adjuvant therapies and treatment of the underlying cause should be considered to limit calcium rebound. However, our study has some limits, the indications of dialysis session was based mostly on the presence of electrocardiogram abnormalities.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Guimard, C. and Trewick, D. (2014) L'hypercalcémiesévèreestellevraiment à l'origine de coma et/ou de complications Cardiaquesengageant le pronostic du patient?

[2] Catalano, A., Chilà, D., Bellone, F., *et al.* (2018) Incidence of Hypocalcemia and Hypercalcemia in Hospitalized Patients: Is It Changing? *Journal of Clinical & Translational Endocrinology*, **13**, 9-13. https://doi.org/10.1016/j.jcte.2018.05.004

[3] Drake, M.T., Clarke, B.L. and Khosla, S. (2008) Bisphosphonates: Mechanism of Action and Role in Clinical Practice. *Mayo Clinic Proceedings*, **83**, 1032-1045. https://doi.org/10.4065/83.9.1032

[4] Minisola, S., Pepe, J., Piemonte, S., *et al.* (2015) The Diagnosis and Management of Hypercalcaemia. *British Medical Journal*, **350**, h2723. https://doi.org/10.1136/bmj.h2723

[5] Banu, S., *et al.* (2021) Malignant and Non-Malignant Causes of Hypercalcemia: A Retrospective Study at a Tertiary Care Hospital in Pakistan. *Cureus*, **13**, e15845. https://doi.org/10.7759/cureus.15845

[6] Maier, J.D. and Levine, S.N. (2015) Hypercalcemia in the Intensive Care Unit: A Review of Pathophysiology, Diagnosis, and Modern Therapy. *Journal of Intensive Care Medicine*, **30**, 235-252. https://doi.org/10.1177/0885066613507530

[7] Mousseaux, C., Dupont, A., Rafat, C., *et al.* (2019) Epidemiology, Clinical Features, and Management of Severe Hypercalcemia in Critically Ill Patients. *Annals of Intensive Care*, **9**, Article No. 133. https://doi.org/10.1186/s13613-019-0606-8

[8] Goltzman, D. (2000) Approach to Hypercalcemia. In: Feingold, K.R., Anawalt, B., Boyce, A., *et al.*, Eds., *Endotext*, MDText.com, Inc., South Dartmouth. https://www.ncbi.nlm.nih.gov/sites/books/NBK279129/

[9] Penel, N., Dewas, S., Doutrelant, P., *et al.* (2008) Cancer-Associated Hypercalcemia Treated with Intravenous Diphosphonates: A Survival and Prognostic Factor Analysis. *Supportive Care in Cancer*, **16**, 387-392. https://doi.org/10.1007/s00520-007-0322-z

[10] Koo, W.S., Jeon, D.S., Ahn, S.J., Kim, Y.S., Yoon, Y.S. and Bang, B.K. (1996) Calcium-Free Hemodialysis for the Management of Hypercalcemia. *Nephron*, **72**, 424-428. https://doi.org/10.1159/000188907

[11] Malberti, F. and Ravani, P. (2003) The Choice of the Dialysate Calcium Concentration in the Management of Patients on Haemodialysis and Haemodiafiltration. *Nephrology Dialysis Transplantation*, **18**, vii37-vii40. https://doi.org/10.1093/ndt/gfg1077

[12] Toussaint, N., Cooney, P. and Kerr, P.G. (2006) Review of Dialysate Calcium Concentration in Hemodialysis. *Hemodialysis International*, **10**, 326-337.

https://doi.org/10.1111/j.1542-4758.2006.00125.x

[13] LeGrand, S.B., Leskuski, D. and Zama, I. (2008) Narrative Review: Furosemide for Hypercalcemia: An Unproven yet Common Practice. *Annals of Internal Medicine*, **149**, 259-263. https://doi.org/10.7326/0003-4819-149-4-200808190-00007

[14] Kawada, K., Minami, H., Okabe, K., Watanabe, T., Inoue, K., Sawamura, M., Yagi, Y., Sasaki, T. and Takashima, S. (2005) A Multicenter and Open Label Clinical Trial of Zoledronic Acid 4 mg in Patients with Hypercalcemia of Malignancy. *Japanese Journal of Clinical Oncology*, **35**, 28-33. https://doi.org/10.1093/jjco/hyi005

[15] von Au, A., Milloth, E., Diel, I., *et al.* (2016) Intravenous Pamidronate versus Oral and Intravenous Clodronate in Bone Metastatic Breast Cancer: A Randomized, Open-Label, Non-Inferiority Phase III Trial. *OncoTargets and Therapy*, **9**, 4173-4180. https://doi.org/10.2147/OTT.S103130

[16] Yang, L.Q. and Du, S. (2015) Efficacy and Safety of Zoledronic Acid and Pamidronate Disodium in the Treatment of Malignant Skeletal Metastasis: A Meta-Analysis. *Medicine*, **94**, e1822. https://doi.org/10.1097/MD.0000000000001822

[17] Mathur, M., Sykes, J.A., Saxena, V.R., Rao, S.P. and Goldman, G.M. (2003) Treatment of Acute Lymphoblastic Leukemia-Induced Extreme Hypercalcemia with Pamidronate and Calcitonin. *Pediatric Critical Care Medicine*, **4**, 252-255. https://doi.org/10.1097/01.PCC.0000059423.62268.02

[18] Kim, H.W., Kim, S.H., Kim, Y.O., *et al.* (2015) Impact of Dialysate Calcium Concentration on Clinical Outcomes in Incident Hemodialysis Patients. *Medicine*, **94**, e1694. https://doi.org/10.1097/MD.0000000000001694

[19] Trabulus, S., Oruc, M., Ozgun, E., Altiparmak, M.R. and Seyahi, N. (2018) The Use of Low-Calcium Hemodialysis in the Treatment of Hypercalcemic Crisis. *Nephron*, **139**, 319-331. https://doi.org/10.1159/000488502