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Effect of different hydration doses on renal function in patients with primary osteoporosis treated with zoledronic acid
A hospital-based retrospective cohort study

Xin Dai, MD[a], Yongtao Deng, MD[a], Yetao Luo, MD[b], Jianghong Xie, MD[a], Houxun Ma, MD[a] ID

Abstract

The objective was to investigate the association of different hydration doses and its effect on renal function in patients with primary osteoporosis treated with zoledronic acid.

The subjects with primary osteoporosis treated with zoledronic acid at the First Affiliated Hospital of Chongqing Medical University, China, from January 2015 to December 2018 were included in this study. The subjects were classified according to different hydration doses. Renal function indexes before and after treatment were collected and adverse reactions recorded to analyze the changes in renal function associated with different hydration doses.

1. A total of 170 subjects were included in the study. The hydration dose of group A (n = 50), group B (n = 44), group C (n = 36), group D (n = 40) is 250, 500, 750, and 1000 mL.

2. The difference (the level of renal function parameters after treatment minus that before treatment) and ratio (difference divided by before treatment) of Scr and eGFR of participants were statistically significant between group A and the other three groups (*P* < .001). Pairwise comparisons between group B, C, D showed no significant difference (*P* > .05).

3. There were 2 cases of Acute Kidney Injury in group A and no in other three groups.

4. There was no significant difference in the incidence of adverse reactions in four groups (*P* > .05).

The choice of the hydration dose treated with zoledronic acid deserves attention. The lower hydration dose is, the greater impact on renal function can be caused.

Abbreviations: BUN = blood urea nitrogen, CysC = CystatinC, eGFR = glomerular filtration rate, Scr = blood serum creatinine, UA = serum uric acid.

Keywords: adverse reaction, hydration dose, primary osteoporosis, renal function, zoledronic acid

[a] Department of Geriatrics, The First Affiliated Hospital of Chongqing Medical University, [b] Clinical Epidemiology and Biostatistics Department, Department of Pediatric Research Institute, Children's Hospital Affiliated with Chongqing Medical University, Chongqing, China.

Correspondence: Houxun Ma, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi St, Chongqing, China (e-mail: dd13399825465@163.com).

1. Introduction

Osteoporosis (OP) is a systemic osteopathy characterized with low bone mass, destruction of bone microstructure and easy fracture,[1] which has become a common disease that seriously endangers the health and longevity of elderly people. Fracture complications caused by OP (such as hip fracture, vertebral fracture, etc) often lead to the deterioration of the life quality of the elderly which brings heavy economic and psychological burden to patients and families. Therefore, it is important to choose appropriate intervention programs to reduce or avoid fracture complications.

Bisphosphonates, an anti-bone resorption inhibitor, is the most commonly used drug for OP. Studies have proved that zoledronic acid can comprehensively improve bone density, inhibit bone resorption of osteoclasts, reduce fracture risk and bone pain,[2] and improve the living standard of patients.[3] The early application of zoledronic acid (5 mg/year) has improvement and tolerance to bone mass in patients with OP.[4] However, as zoledronic acid is widely used in clinical practice.[5] Its adverse drug reactions gradually appear, among which renal function injury, gastrointestinal reaction, acute inflammatory reaction, and muscle pain are relatively common. There are some studies suggesting that zoledronic acid treatment may affect renal function in patients, especially in cases whose renal function has already been impaired.[6]

At the same time, studies have shown that intravenous hydration therapy can improve the damage of renal function when zoledronic acid is used.[7]Therefore, hydration therapy strategy has been widely used as an intervention method to reduce adverse drug reactions caused by zoledronic acid in patients with OP, but there are few reports on the selection of hydration method and hydration dose.

The purpose of this study was to explore the optimal hydration dose for elderly patients with OP by retrospectively analyzing the changes in renal function and related adverse reactions before and after treatment with zoledronic acid in different hydration dose groups.

2. Materials and methods

2.1. Study population and design

This study a hospital-based retrospective cohort study from 2015 to 2018. Subjects were patients with primary OP treated with zoledronic acid in the First Hospital Affiliated to Chongqing Medical University. A total of 471 subjects were enrolled.

The exclusion criteria were:

1. Osteoporosis caused by diseases that affect bone metabolism and/or drugs and other causes
2. eGFR < 35 mL/min/1.73 m^2
3. with cardiac failure and/or oedema
4. with Concomitant nephrotoxic drugs and/or diuretics
5. non-first dose of zoledronic acid

Some of the cases were excluded according to the exclusion criteria (Fig. 1). This study was approved by the local ethics committee of the First Hospital Affiliated to Chongqing Medical University (IRB2019-090). All patients' information was anonymized and de-identified prior to analysis. Approval to perform retrospective research using secondary data was granted by the Institutional Review Board (IRB2019-090). Our study was performed in accordance with the relevant guidelines and regulations.

2.2. Research methods

In this retrospective study, all the subjects were admitted to our hospital treated with zoledronic acid for primary OP. Subjects must be properly rehydrated before being treated with zoledronic acid. The hydration dose of each patient was decided by the doctor who was responsible for treatment according to the patients' conditions. Thus, the hydration dose received by each patient was different. Subjects were divided into 4 groups according to hydration dose. All hydration solutions were 0.9% sodium chloride solution. Zoledronic acid (5 mg/100 mL) was injected intravenously longer than 15 min. Hydration infusion rate controlled at 40 to 60 drops/min. Each group paused hydration at the half of the hydration treatment volume and changed to infusion of zoledronic acid. After the end of zoledronic acid, the remaining hydration amount was continued. All subjects needed to complete renal indices examination before treatment. Renal indices were re-examined 24 h after treatment and related adverse reactions were observed and recorded.

2.3. Drug information

Zoledronic acid (zoledronate) 5 mg/100 mL (Aclasta, Novartia Pharma Schweiz AG, Novartis Pharma stein AG).
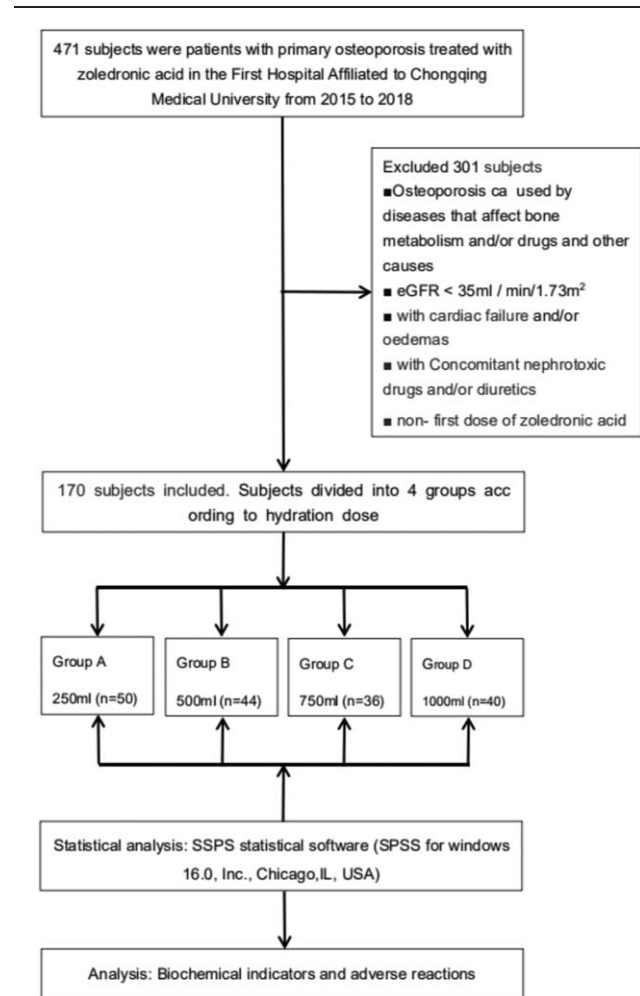

Figure 1. Flowchart of subjects selection.

2.4. Baseline data

Age, gender, body mass index (BMI), smoking, drinking, coronary-heart-disease, hypertension, diabetes, blood-phosphorus,β-C-terminal-telopeptide-of-type-I-collagen (β-CTX), procollagen-type-1-amino-terminal-propeptide (PINP), alkaline-phosphatase (ALP), osteocalcin (OC), 25-hydroxy-vitamin D (25-OH-VD), parathyroid hormone (PTH), urinary protein (+).

Bone-mineral-density (T-score) measured at the femoral neck with dual-energy X-ray absorptiometry (DXA).

2.5. Renal function parameters

CystatinC (Cysc), serum uric acid (UA), blood urea nitrogen (BUN), serum creatinine (Scr), glomerular filtration rate (eGFR),

The calculation formula of eGFR is as follows: in males, eGFR = [(140-age) × body weight (kg)]/[0.818 × Scr (umol/L)]. In females, eGFR was obtained by multiplying the above calculation results by the 0.85 correction.

2.6. Adverse reactions

Gastrointestinal reaction (vomiting, nausea, dry mouth, and diarrhea), acute inflammation (chills, fever, fatigue, muscle pain,

and joint pain), nervous system reaction (delirium, myelitis, and conjunctivitis), respiratory response (pharyngeal pain and dyspnea), circulation system, reaction (arrhythmia, chest tightness, and chest pain), immune response (skin rashes, itching, sweat, and flush).

2.7. Statistical methods

The continuous variables were reported as means and standard deviations (SD) if the variables meet normal distribution, and one-way ANOVA was used to test the significance of difference between the four groups. Continuous variables that do not satisfied the normal distribution were expressed as median and interquartile range (IRQ), and the Kruskal–Wallis test was used for comparison between the four groups, post hoc analyses were conducted using the Dunn–Bonferroni method. The categorical variables were reported as numbers (n) and percentages of the total (%), and x^2 test and Fisher exact test were used to test the difference between four groups. Sign-paired rank sum test was used before and after treatment. Significant difference was determined at the α level of 0.05. Statistical analysis was done by SSPS statistical software (SPSS for windows 16.0, Inc, Chicago, IL).

3. Results

3.1. Baseline characteristics

A total of 170 subjects were included in the study, including 15 males (8.8%) aged 79.07 ± 6.64 years old and 155 females (91.2%) aged 70.57 ± 9.42 years old. BMI was $22.81 \pm 3.29 \, kg/m^2$ for males and $21.54 \pm 3.40 \, kg/m^2$ for females. The hydration dose of group A (n=50), group B (n=44), group C (n=36), group D (n=40) is 250, 500, 750, and 1000 mL.

Procollagen-type-1-amino-terminal-propeptide (PINP), 25-hydroxy-vitamin D (25-OH-VD) and alkaline-phosphatase (ALP) were significant differences in pairwise comparison between the four groups. Blood urea nitrogen in group A were significantly lower than other three groups. There were no groups differences in the rest of baseline characteristics (Table 1).

3.2. The difference and ratio of renal function parameters in four groups

The differences (the level of renal function parameters after treatment minus that before treatment) and ratios (difference divided by before treatment) were compared between groups to explore the degree of renal function after infusion of zoledronic acid. By comparing the differences and ratios of Scr and eGFR, there was statistically significant difference between group A and other three groups ($P < .001$). Pairwise comparisons between groups B, C, and D showed no significant difference ($P > .05$). The difference and ratio of UA showed no significant difference between group A and group B, and group C and group D showed no difference ($P > .05$). Other pairwise comparisons about the difference and ratio of UA showed statistical differences ($P < .001$). Compared with the same group before and after treatment, the values of Scr, UA, and eGFR were significantly different ($P < .001$). The values of CysC in group C after treatment was significantly different from that before treatment ($P < .05$), while that in other three groups showed no difference ($P > .05$). The values of BUN in the group B and C after treatment were significantly different from that before treatment ($P < .001$) while there were no difference in group A and D ($P > .05$) (Table 2) (see table, Supplemental Content 1, http://links.lww.com/MD/E445, which demonstrates difference in detail).

Table 1

Baseline characteristics of subjects.

	Group A	Group B	Group C	Group D	P
Age (years)	72.86 ± 9.74	68.86 ± 8.55	72.02 ± 8.84	71.47 ± 10.54	.102
BMI (kg/m^2)	22.09 ± 3.60	21.56 ± 3.84	20.52 ± 2.68	22.2 ± 3.06	.095
Female (%)	43 (86.00%)	43 (97.73%)	33 (91.67%)	36 (90.00%)	.221
bone mineral density (T-score) (g/cm^3)	−3.6 (−4.50,−3.40)	−3.6 (−4.45,−3.40)	−3.5 (−4,−3.25)	−3.45 (−4.35,−3.20)	.249
Urinary protein (+)	7 (14.00%)	11 (25.00%)	7 (19.44%)	7 (17.50%)	.59
PTH (Pg/mL)	38.85 (29,67)	36.85 (27.70,56.05)	38.25 (25.65,50.35)	36.6 (29.8,54.40)	.89
25 (OH)VD (ng/mL)	25.13 (18.83,32.83)	22.46 (15.23,32.00)	29.75 (21.99,34.25)	28.58 (20.54,34.27)	.045*
OC (ng/mL)	1.92 (0.50,4.32)	1.33 (0.50,4.26)	0.85 (0.50,3.94)	1 (0.50,4.32)	.706
ALP (ug/L)	6.49 (3.58,8.23)	8.17 (3.13,11.79)	8.9 (7.49,11.54)	3.7 (2.30,7.26)	<.001*
PINP (ng/mL)	60.27 (34.29,85.39)	39.55 (23.87,75.41)	47.02 (37.77,73.71)	33.31 (24.57,61.23)	.026*
β-CTX (ng/mL)	0.4 (0.26,0.64)	0.31 (0.18,0.49)	0.29 (0.18,0.45)	0.26 (0.18,0.42)	.056
Blood phosphorus (mmol/L)	1.2 (1.01,1.29)	1.2 (1.09,1.28)	1.2 (1.10,1.28)	1.23 (1.12,1.42)	.496
UA (mmol/L)	241 (221,277)	252 (228,331)	241.5 (217,301)	243 (209.5,329.5)	.573
CysC (mg/L)	0.81 (0.71,0.98)	0.83 (0.68,1.00)	0.94 (0.67,1.14)	0.85 (0.71,1.15)	.67
BUN (mmol/L)	2.9 (2.1,4.6)	5.2 (4.25,6.05)	6.05 (4.80,6.85)	3.4 (2.65,4.80)	<.001*
Scr (umol/L)	54.5 (49,67)	60.5 (51,69.5)	60.5 (56.5,69)	65 (53.5,73)	.066
eGFR (mL/min/1.73 m^2)	61.91 (48.27,90.08)	61.77 (46.84,78.91)	57.57 (43.61,68.84)	59.76 (47.96,72.71)	.303
Diabetes n (%)	7 (14.00%)	9 (20.45%)	4 (11.11%)	2 (5.00%)	.204
Hypertension n (%)	19 (38.00%)	17 (38.64)	14 (38.88%)	18 (45.00%)	.907
Coronary heart disease n (%)	8 (16.00%)	7 (15.91%)	4 (11.11%)	7 (17.50%)	.881
Smoking n (%)	5 (10.00%)	0 (0.00%)	2 (5.56%)	2 (5.00%)	.172
Drinking n (%)	2 (4.00%)	1 (2.27%)	2 (5.56%)	3 (7.50%)	.752

β-CTX = β-C-terminal-telopeptide-of-type-I-collagen, 25-OH-VD = 25-hydroxy-vitamin D, ALP = alkaline-phosphatase, BMI = body mass index, BUN = blood urea nitrogen, CysC = CystatinC, eGFR = Glomerular filtration rate, OC = osteocalcin, PINP = procollagen-type-1-amino-terminal-propeptide, PTH = parathyroid hormone, Scr = blood serum creatinine, UA = Serum uric acid.
* $P < .05$.

Table 2

The difference and ratio of renal function parameters in four groups.

	Group A		Group B		Group C		Group D	
	Difference	Ratio (%)	Difference	Ratio (%)	Difference	Ratio (%)	Difference	Ratio (%)
UA (umol/L)	−22.5 (−34,−10)[**,a,b]	−10 (−14,−4)[a,b]	−33 (−82.5,−11.5)[**,a,b]	−14 (−30,−5)[a,b]	−93.5 (−145.5,−35)[**,c,d]	−33 (−54,−16)[c,d]	−69 (−149.5,−35)[**,c,d]	−35 (−47,−17)[c,d]
CysC (mg/L)	−0.04 (−0.13,0.17)	−6 (−21,17)	0.04 (−0.1,0.2)	4 (−14,23)	0.07 (−0.07,0.15)[*,b]	8 (−9,16)[b]	−0.11 (−0.17,0.09)[a]	−11 (−20,11)[a]
BUN (mmol/L)	−0.2 (−0.4,0.3)[a]	−6 (−14,10)	−0.55 (−1.8,0.1)[**,a]	−11 (−33,20)	−7 (−1.7,−0.2)[**,c,d]	−13 (−38,−3)	−−0.4 (−0.65,0.15)[a]	−11 (−20,4)
Scr (umol/L)	5 (4,8)[**,a,b,d]	9 (6,14)[a,b,d]	3.5 (0.5,6)[**,c]	6 (1,10)[c]	3.5 (3,5)[**,c]	6 (4,7)[c]	3 (−1,4)[**,c]	4 (−2,7)[c]
eGFR (ml/min/1.73m²)	−6 (−8.73,−3.48)[**,a,b,d]	−8 (−12,−6)[a,b,d]	−2.51 (−6.89,−0.44)[**,c]	−6 (−9,−1)[c]	−3.13 (−4.31,−2.04)[**,c]	−6 (−7,−4)[c]	2.09 (−3.83,0.76)[*,c]	−4 (−7,2)[c]

Difference means the level of renal function parameters after treatment minus that before treatment.

Ratio means difference divided by the level of renal function parameters before treatment.

BUN = Blood urea nitrogen, CysC = CystatinC, eGFR = Glomerular filtration rate, Scr = Blood serum creatinine, UA = Serum uric acid.

[a] Means significant compare to group C.

[b] Means significant compare to group D, for example: after group A, there are [a,b] means that the significant differences between groups A and C and between groups A and D (P<.001).

[c] Means significant compare to group A.

[d] Means significant compare to group B.

[*] P<.05.

[**] P<.001. Compared with the same group before and after treatment was significant.

3.3. Adverse reactions

The overall incidence of adverse reactions which occurred in this study and the number of cases of adverse reactions in the four groups (Fig. 2) vomiting (3.53%), nausea (6.47%), sweat (8.82%), flush (8.82%), pharyngeal-pain (1.18%), dry-mouth (1.76%), diarrhea (1.18%), chills (5.88%), fever (5.29%), fatigue (11.18%), joint-pain (1.18%), muscle-pain (5.88%).

The incidence of adverse reactions after infusion of zoledronic acid in four groups was no statistical difference (P > .05) (see table, Supplemental Content 2, http://links.lww.com/MD/E446, which demonstrates in detail).

4. Discussion

Since the FDA approved the use of zoledronic acid to treat primary OP, zoledronic acid has been widely used in clinical practice.[8,9] Studies have shown that zoledronic acid is excreted through the kidneys. Previous studies have suggested that zoledronic acid may cause renal insufficiency.[10] Studies have shown that bisphosphonates directly inhibit farnesyl diphosphate (FPP) synthase activity, which also occurs in renal cells and may lead directly to renal toxicity.[11] Based on the above situation, All the specification and literature of zoledronic acid recommend hydration plan to increase renal blood flow, promote drug excretion and reduce the duration of drug retention in the kidney,[12,13] but no specific hydration dose has been proposed. Therefore, it is of great clinical value to explore "appropriate hydration dose" to reduce the adverse effects of zoledronic acid on renal function of patients.

Our study sought to find the optimal hydration dose by the changes in renal function and related adverse reactions before and after treatment with zoledronic acid in different hydration dose groups. Most of the participants were elderly patients with deficiencies in 25(OH)VD. Although the values of ALP and PINP were significantly different between the four groups before infusion, the values of ALP and PINP were within the normal range. There were no groups differences in the rest of baseline characteristics. While, the values of BUN before treatment were significantly different among the four groups. Therefore, we do not take this indicator as a research indicator. At the same time, there was no significant change in CysC in some participants before and after treatment, and it could not be used as an accurate
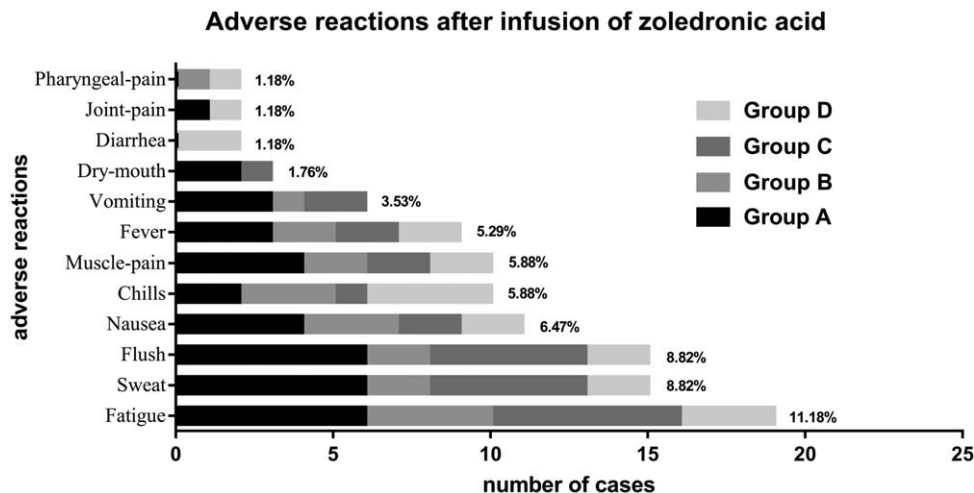

Figure 2. Adverse reactions after infusion zoledronic acid.

indicator. The levels of UA in the four groups were all reduced to varying degrees. The reason may be related to increased renal excretion due to increased hydration dose. In this retrospective study, Scr and eGFR were used as the main analysis indicators.[14,15] Compared with the same group before and after treatment, the levels of Scr and eGFR were significantly different which indicate that the use of zoledronic acid in the treatment of primary OP has varying degrees of adverse effects on renal function. By pairwise comparison of the differences and ratios of Scr and eGFR in the four groups, the change in group A was the most obvious compared with the other three groups. Compared with the hydration dose group of 250 mL, the other three groups were more conducive to relieving an increase in Scr and a decrease in eGFR, which means the lower hydration dose is, the greater impact on renal function can be caused. Increasing hydration dose will increase urine flow rate that would mitigate the exposure of renal tubule cells to direct toxic effects of drugs.[16] Intuitively, toxicity can be reduced by giving as many hydration doses as possible. However, an over hydration dose of intravenous infusion can lead to renal dysfunction and impaired excretion because of excess water and salt load.[17] What's more, excessive hydration dose affects renal recovery.[18] Those may explain why there is no significant difference in Scr and eGFR when hydration dose exceeds 500 mL. For the ratios of eGFR the change in group A is 8%, which is significantly different from 6% change in group B and C and 4% change in group D after hydration intervention treatment. In order to further investigate the relationship between hydration dose and renal function, the difference of Scr (the level of after treatment minus before treatment) was conducted as an another important index to evaluate the degree of renal function between group A and the other three groups. There were significant statistical differences between group A and the other three groups in pairwise comparison which also indicated that the lower hydration dose would have a greater influence on renal function. However, the changes in these indicators can only indicate that hydration affects renal function to some extent. The degree of change in these indicators and their clinical relevance need further follow-up. All the subjects included are treated with zoledronic acid for the first time, and we plan to treat them with annual infusions of zoledronic acid for 3 years totally. We will further follow up the changes of renal index and the relevant renal impairment.

What calls for special attention is that there were 2 cases of Acute Kidney Injury (AKI) in group A and no in other three groups. In addition, previous FDA sent out a newsletter to physicians reporting on 24 cases of acute renal failure reported postmarketing with intravenous zoledronic acid in the OP population (Reclast).[19] This individual case of AKI in the treatment of OP with zoledronic acid also deserves attention. The value of Scr increased by 30 (umol/L) and 44 (umol/L), respectively within 24 h after treatment in these two patients in group A. According to KDIGO Clinical Practice Guidelines for AKI,[20] the value of Scr increased by more than 26.5 (umol/L) within 48 h, which was clearly diagnosed as AKI. Neither of these patients had any clinical manifestations of decreased urine output and other renal impairment. The urine output was monitored at about 1500 mL/day. Considering that these two cases are both elderly female patients, the clinical manifestations of AKI may be atypical. During the treatment, hydration treatment and appropriate diuretic treatment were performed. While, urine volume, renal function indexes and electrolyte indicators were closely monitored. The value of Scr in these two patients was decreased by 15 (umol/L) and 20 (umol/L), respectively after re-examination before discharge. After discharge, the renal function indexes were followed up in the outpatient department, and the value of Scr returned to the original level after about 1 month and 2 months, respectively.

Additionally, the incidence of adverse reactions with different hydration doses shows no statistical difference. Study has shown that the adverse reactions of zoledronic acid are mostly transient, and resolved spontaneously.[21] In our study, most of the adverse reactions were alleviated or disappeared within 3 days after using.

Taken together, the choice of the hydration dose treated with zoledronic acid deserves attention. The lower hydration dose is, the greater impact on renal function can be caused. In addition, too much fluid can have a deleterious effect by provoking acute decompensated heart failure (ADHF).[22] While ensuring the safety of kidney function, it is also necessary to be alert to the onset of ADHF. Combined with the above findings, the treatment of zoledronic acid should pay attention to the choice of hydration dose and related adverse reactions in clinical application. According to the specific situation of the patient, individualized treatment should be selected clinically.

On account of the optimal hydration dose was not clearly recommended in the previous studies, the main strength of this work is that to explore the changes of renal function and adverse reactions caused by different hydration doses. Moreover, there are some limitations in our study. This was a single-center retrospective cohort study which might cause selection bias and uncorrected confounding. Due to the retrospective nature of the study, this limited some of the data collection. What's more, the sample size was relatively small which might reduce the statistical power. Meanwhile, the renal function indicators were re-examined within 24 h after injection, requiring further long-term follow-up. As it is an observational study, the results need be confirmed in a prospective clinical trial.

5. Conclusion

The choice of the hydration dose treated with zoledronic acid deserves attention. The lower hydration dose is, the greater impact on renal function can be caused. Our study emphasizes paying attention to the safety of the kidney and the adverse reactions treated with zoledronic acid, and simultaneously proposing that the selection of a suitable hydration dose is vital to reduce the harmful effects on renal function caused by zoledronic acid treatment.

Author contributions

Conceptualization: Houxun Ma, Xin Dai
Data curation: Jianghong Xie
Formal analysis: Xin Dai
Methodology: Yetao Luo
Project administration: Yongtao Deng
Writing – original draft: Xin Dai
Writing – review & editing: Houxun Ma

All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work and read and approved the final manuscript.

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