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Hypocalcemia was associated with increased perioperative blood loss and blood transfusion in elderly patients with hip fracture: a retrospective study



Yunqing Zhang¹, Kun Lu¹, Qi Liu¹, Chun Liu¹, Shilong Su^{2*} and Chunhua Yang¹

Abstract

Background Serum calcium is the critical coagulation factor in physiological coagulation, and hypocalcemia has been found to be associated with more blood loss in many diseases. The purpose of this study was to explore the effect of hypocalcemia on total blood loss (TBL) and blood transfusion in elderly patients with hip fracture.

Patients and methods Elderly patients with hip fracture undergoing surgery in our hospital were included in this study from January 2020 to May 2023. The demographic data, perioperative parameters, hemoglobin, hematocrit, and transfusion requirement were recorded and analyzed. Hypocalcemia was defined as an albumin-corrected calcium level of less than 2.15 mmol/L. TBL of each patient was calculated using the formulas of Nadler and Gross. Blood loss on the 1st and 5th postoperative days was calculated.

Results 682 elderly patients with hip fracture were included in the study. On admission, the prevalence of hypocalcemia was 40.47%. Both the TBL on the first day (714.91 \pm 396.05 ml vs. 640.31 \pm 398.83 ml, *P*=0.016) and the fifth day (1035.87 \pm 528.77 ml vs. 859.92 \pm 434.99 ml, *P*<0.001) after operation in the hypocalcemia group were higher than those in the normocalcemia group. The preoperative, postoperative and perioperative blood transfusion rates of hypocalcemia patients were higher than those of the normocalcemia group.

Conclusion Hypocalcemia was associated with increased TBL and blood transfusion in elderly patients with hip fracture during the perioperative period.

Keywords Hypocalcemia, Elderly, Hip fracture, Blood loss, Blood transfusion

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Introduction

Hip fracture, including femoral neck fracture and femoral intertrochanteric fracture, is a common fracture in elderly patients [1]. Due to the aging of the global population, it is estimated that there will be 4.5 million hip fractures worldwide by 2050 [2]. Hip fracture has become a major public health problem [1, 3, 4]. At present, there is a consensus that elderly patients with hip fracture need early surgery [5-7]. However, patients with hip fracture are at risk of massive blood loss during the perioperative period [8, 9]. According to literature reports, the total blood loss (TBL) in patients with femoral neck fractures and intertrochanteric fractures can reach 1148~1208ml [10, 11] and 1081~1301ml [9, 12] respectively. Perioperative anemia caused by massive blood loss is a risk factor for short-term and long-term mortality in elderly patients with hip fracture [13, 14]. Studies have shown that anemia is associated with increased mortality [13, 14], poor physical function and health-related quality of life [15], and prolonged hospital stays [16]. Currently, blood transfusion is the most commonly used treatment to correct anemia. However, high blood transfusion rates pose greater risks to patients and increase medical costs [17]. Blood transfusion may increase bacterial infections [18], transfusion reactions like transfusion associated lung injury and transfusion incompatibility, and mortality [19], as well as prolong hospitalizations [20]. The collection, preparation, transportation and management of blood also involve many expenses, which in turn increases medical costs. Perioperative anemia in patients with hip fracture has attracted attention, and several studies have analyzed the risk factors of blood loss [21-25].

Calcium is considered to be one of the most abundant electrolytes in the body. Almost 99% of the calcium is deposited in bones and teeth, and the remaining calcium circulates in the blood [26]. Serum calcium is an important cofactor in coagulation cascade, also known as coagulation factor IV, which plays an important role in platelet function and mediates coagulation through endogenous and exogenous pathways [27, 28]. Hypocalcemia can lead to more blood loss, which has been observed in a variety of diseases, such as total knee arthroplasty [29], cerebral hemorrhage [30], postpartum hemorrhage [31], and shock trauma [32]. The incidence of hypocalcemia in elderly patients with hip fracture is also as high as 39.5% [33]. So, does hypocalcemia increase blood loss and blood transfusion rate in elderly patients with hip fracture? At present, there are few reports on this issue in the literature [34]. Therefore, the purpose of this study was to investigate whether hypocalcemia affects TBL and blood transfusion in elderly patients with hip fracture. It provides a clinical basis for improving perioperative blood management in elderly patients with hip fracture.

Patients and methods Patients

All aspects of the study were reviewed and approved by the ethical committee of The First Hospital of Changsha. We performed a retrospective study to enroll patients with hip fracture who underwent surgery in our hospital between January 2020 and May 2023 from our electronic medical records. The inclusion criteria were: [1] closed hip fracture [2], age \geq 60 years [3], caused by low-energy fall [4], fracture less than 2 weeks [5], surgical treatment. Exclusion criteria were: [1] multiple fractures or confirmed pathological fracture [2], without completed medical data [3], neoplastic diseases or severe hematologic disorders [4], using antiplatelet drugs, anticoagulant drugs, or non-steroidal anti-inflammatory drugs within 1 month before surgery.

Data collection

Demographic characteristics included age, sex, height, weight, body mass index (BMI), surgical side. The perioperative parameters included fracture type, type of surgery, time from injury to hospital, time from hospital to surgery, medical history (hypertension, diabetes), duration of surgery, and intraoperative blood loss. Hip fracture type was classified as femoral neck fracture or intertrochanteric fracture. The type of surgery included proximal femoral nail anti-rotation (PFNA), cannulated compression screws (CCS), hemiarthroplasty (HA), and total hip arthroplasty (THA). Time from injury to hospital was calculated as the time interval between the date of injury and the date of admission. Time from hospital to surgery was calculated as the time interval between the date of admission and the date of surgery.

Hemoglobin (Hb) and hematocrit (HCT) were also measured on admission day, postoperative day 1, and postoperative day 5 in all patients. World Health Organization (WHO) defined anaemia as Hb levels < 120 g/l in women and <130 g/l in men. The degree of anemia was divided into four degrees: mild, moderate, severe and extremely severe, corresponding to Hb levels of >90 g/l, 60-90 g/l, 30-60 g/l and <30 g/l respectively. Due to the influence of albumin concentration, the correction formula for serum calcium was as follows: corrected calcium = measured serum calcium $(mmol/L) + 0.02 \times$ [40.0- albumin (g/L)]. Hypocalcemia was defined as a corrected calcium level of less than 2.15 mmol/L, according to the normal reference range (2.15-2.50 mmol/L)in our hospital, and all included patients were further divided into the normocalcemia group and hypocalcemia group. We did not focus on hypocalcemia and did not correct calcium levels before surgery. Moreover, the blood transfusion volume was collected in the medical records from admission to 5 days after the operation. According to the time when blood transfusion started, the blood transfusion situation was divided into three groups: preoperative, postoperative and perioperative blood transfusion. Among them, blood transfusion started before surgery but continued during the operation belonged to the preoperative category. Transfusions at our hospital were performed only when Hb level was < 80 or 100 g/L for symptomatic patients (extreme weakness, chest pain, extreme paleness, or major bleeding) with destabilizing vital signs (heart rate > 100 beats/min or systolic blood pressure < 90 mmHg).

Calculation of total blood loss

Total blood volume (TBV) of the patients was calculated according to the Nadler's formula [35]:

TBV (L) = $k1 \times height(m)^3 + k2 \times weight(kg) + k3$.

(k1 = 0.3669, k2 = 0.03219, and k3 = 0.6041 for men, and k1 = 0.3561, k2 = 0.03308, and k3 = 0.1833 for women).

TBL was calculated according to the Gross formula [36]:

TBL (ml) = TBV(L) × (Hct_{adm} - Hct_{post})/Hct_{ave} × 1000.

 Hct_{adm} is the initial admission Hct, Hct_{post} is Hct on the postoperative day 1 or postoperative day 5, and Hct_{ave} is the average of Hct_{adm} and Hct_{post} .

When blood transfusion was performed from admission to 5 days after the operation, the formula was calculated as follows:

TBL (ml) = TBV(L) × (Hct_{adm} -Hct_{post})/Hct_{ave}× 1000 + blood infusion (ml).

And 1 unit of red blood cells was recorded as 200 ml.

Statistical analysis

All statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, USA). Continuous variables were expressed as means with standard deviations and categorical variables were expressed as number of cases and percentages. Continuous data were analyzed with Student's t-test, while categorical variables were compared with the chi-squared test. If the data were not normally distributed, nonparametric tests were used. In order to verify the stability of the results, we carried out the subgroup analysis, mainly in types of surgery to verify the stability of the main results including TBL and transfusion requirements. A P value of less than 0.05 was considered to be significant.

Results

Finally, a total of 682 patients diagnosed with hip fracture were included in the analysis (Fig. 1). On admission, 276 of these patients had hypocalcemia, and the incidence of hypocalcemia was 40.47%. We did not find any patients with hypercalcemia. All included patients used regional anesthesia. The demographic characteristics and perioperative parameters of the patients were shown in Tables 1 and 2, respectively. The demographic characteristics and

perioperative parameters of the patients were similar between the two groups.

Perioperative blood parameters of patients were shown in Table 3. The incidence of anemia in patients with hypocalcemia was significantly higher than that in the normocalcemia group (86.23% vs. 55.42%, P<0.001). Moreover, there were significant differences in the degree of anemia between the two groups. Both TBL on the first day $(714.91 \pm 396.05 \text{ ml vs. } 640.31 \pm 398.83 \text{ ml}, P = 0.016)$ and the fifth day (1035.87 ± 528.77 ml vs. 859.92 ± 434.99 ml, P < 0.001) after operation in the hypocalcemia group were higher than those in the normocalcemia group, and there were significant differences in TBL between the two groups from the first day to the fifth day after the operation (P < 0.001). In addition, the preoperative, postoperative and perioperative blood transfusion rates of hypocalcemia patients were higher than those of the normocalcemia group (32.61% vs. 21.67%, P=0.002; 10.87% vs. 5.42%, *P*=0.013; 36.23% vs. 22.41, *P*<0.001). Although the average blood transfusion volume before operation, after operation and perioperative period in the hypocalcemia group was higher than that in the normocalcemia group, only the postoperative blood transfusion volume had statistical difference (P = 0.028). There were statistical differences in HB and Hct levels on admission, the first day after operation, and the fifth day after operation between the two groups (P < 0.001). Moreover, there was a significant difference in the decrease of HB and Hct between the two groups on the first day after operation (P < 0.001).

The results of subgroup analyses showed that the main results were basically stable in different types of surgery (Table 4). Regardless of the type of surgery, the hypocalcemia group had higher TBL. In the PFNA and THA subgroups, the preoperative, postoperative and perioperative blood transfusion rates in the hypocalcemia group were significantly higher than those in the normocalcemia group. As for blood transfusion volume, although the blood transfusion volume in the hypocalcemia group was higher than that in the normocalcemia group in each period, statistical differences were only observed in the PFNA subgroup.

Discussion

In an aging society, hip fracture associated with osteoporosis and low-energy trauma is one of the most common fractures in elderly patients [1]. Due to the characteristics of elderly patients, they will lose more blood than young people, and they are more prone to perioperative anemia, thus more prone to a variety of postoperative complications and higher mortality [23]. In this study, our results showed that total blood loss on the first and fifth day after operation, and blood transfusion requirements were higher in patients with hypocalcemia on admission.



Fig. 1 Flow chart of patient inclusion

Table 1	Demograph	ic characteristics	of the patients

Characteristics	Normocalce-	Hypocalcemia	Ρ
	mia (<i>n</i> = 406)	(<i>n</i> = 276)	value
Age (years)	76.77 ± 8.45	77.93 ± 9.42	0.093
Sex (male/female)	139/267	104/172	0.357
Height (cm)	158.42 ± 6.14	159.25 ± 6.92	0.101
Weight (kg)	55.07 ± 9.20	56.14 ± 9.97	0.147
BMI (kg/m²)	21.95 ± 3.11	22.08 ± 3.26	0.621
Surgical side (left/right)	244/162	152/124	0.192

BMI, body mass index

These results were consistent with several studies [29–32, 34].

The incidence of hypocalcemia in this study was 40.47%, which was similar to the incidence in other studies [29, 33, 34]. However, puzzlingly, clinical symptoms associated with hypocalcemia are rare. There are two possible reasons for this problem: [1] Most patients with hypocalcemia do not have serum calcium levels that reach the threshold that triggers symptoms. Quiros et al. reported that the minimum threshold of serum calcium required to cause symptoms was 1.65 mmol/L [37] [2]. Another possible reason is that during clinical treatment, once severe hypocalcemia is discovered, we often take measures to correct the serum calcium concentration. However, we need to note that although serum calcium

Table 2 Perioperative parameters of the patients

	Normocalce-	Hypocalcemia	Ρ
	mia (<i>n</i> = 406)	(<i>n</i> =276)	value
Fracture type, n (%)			0.534
Femoral neck fracture	255 (62.81)	166 (60.14)	
Intertrochanteric	151 (37.19)	110 (39.86)	
fracture			
Type of surgery, n (%)			0.361
PFNA	109 (26.85)	88 (33.88)	
CCS	12 (2.96)	6 (2.17)	
HA	156 (38.42)	108 (39.13)	
THA	129 (31.77)	74 (26.81)	
Time from injury to hos- pital (h)	44.66±105.63	37.30±71.51	0.278
Time from hospital to surgery (h)	75.44±45.51	81.74±40.79	0.065
Hypertension, n (%)	215 (52.96)	162 (58.70)	0.161
Diabetes, n (%)	48 (11.82)	30 (10.87)	0.794
Duration of surgery (min)	86.16±28.19	83.61±27.68	0.243
Intraoperative blood loss (ml)	214.01±173.95	218.25±153.59	0.738

PFNA, proximal femoral nail antirotation; CCS, cannulated compression screws; HA, hemiarthroplasty; THA, total hip arthroplasty

	Table 3	Perioperative blood	parameters of the	patients
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	Normocalce-	Hypocalcemia	Р
	mia (<i>n</i> =406)	(n=276)	value
Anemia on admission,	225 (55.42)	238 (86.23)	< 0.001
n (%)			
Mild	201 (49.51)	190 (68.84)	< 0.001
Moderate	24 (5.91)	40 (14.49)	< 0.001
Severe	0 (0.00)	8 (2.90)	0.002
TBV (L)	3.59 ± 0.52	3.67 ± 0.57	0.060
TBL values (ml)			
TBL _{post1}	640.31 ± 398.83	714.91 ± 396.05	0.016
TBL _{post5}	859.92 ± 434.99	1035.87±528.77	< 0.001
ΔTBL	219.61±356.65	324.99 ± 265.40	< 0.001
Transfusion rate, n (%)			
Preoperative	88 (21.67)	90 (32.61)	0.002
Postoperative	13 (3.20)	22 (7.97)	0.009
Perioperative	91 (22.41)	100 (36.23)	< 0.001
Transfusion volume (ml)			
Preoperative	486.36 ± 151.00	566.67±385.12	0.068
Postoperative	430.77±75.11	536.36±191.60	0.028
Perioperative	531.87±207.03	620.00 ± 396.96	0.053
Hb values (g/L)			
Admission day	120.42±19.63	106.27±18.46	< 0.001
Postoperative day 1	105.99±18.72	87.49±13.65	< 0.001
Postoperative day 5	99.33±16.58	83.00 ± 12.96	< 0.001
∆Hb1	14.43 ± 12.47	18.70 ± 16.20	< 0.001
ΔHb5	21.10±13.68	23.27±16.52	0.072
Hct values (%)			
Admission day	37.10 ± 5.79	32.83 ± 5.58	< 0.001
Postoperative day 1	32.56 ± 5.61	26.33 ± 4.07	< 0.001
Postoperative day 5	30.61 ± 4.83	25.06 ± 3.90	< 0.001
∆Hct1	4.54±3.72	6.50 ± 4.89	< 0.001
∆Hct5	6.49±4.20	7.70 ± 5.04	0.001

TBL_{post1} was total blood loss on the postoperative day 1; TBL_{post5} was total blood loss on the postoperative day 5; Δ TBL was difference from postoperative day 1 to postoperative day 5; Δ Hb1, Δ Hct1 was difference from admission to postoperative day 1; Δ Hb5, Δ Hct5 was difference from admission to postoperative day 5

TBV, total blood volume; TBL, total blood loss; Hb, hemoglobin; Hct, hematocrit

levels are corrected, the effects of severe hypocalcemia will not disappear immediately. Therefore, the possible effects of hypocalcemia on patients are often overlooked. Regarding the harms of hypocalcemia, a literature review showed that hypocalcemia on admission was associated with higher mortality in trauma patients [32] and that hypocalcemia may affect the function of the central nervous system or cardiovascular system [38]. At present, some scholars have observed that hypocalcemia would increase the total blood loss in several diseases such as total knee arthroplasty [29], cerebral hemorrhage [30], postpartum hemorrhage [31], shock trauma [32]. In this study, we found that hypocalcemia can increase TBL and blood transfusion requirements in elderly patients with hip fracture, suggesting that attention should be paid to hypocalcemia in elderly patients with hip fracture.

	Normocalcemia	Hypocalcemia	P value
Table 4	Results of subgroup analyses		

PFNA (<i>n</i> = 197)			
TBL values (ml)			
TBL _{post1}	749.03±383.27	871.20±444.29	0.040
TBL _{post5}	983.97±412.30	1164.82±550.14	0.009
Transfusion rate n (%)			
Preoperative	25 (22.94)	32 (36.36)	0.039
Postoperative	1 (0.92)	6 (6.82)	0.046
Perioperative	26 (23.85)	34 (38.64)	0.025
Transfusion volume (ml)			
Preoperative	400.00 ± 0.00	425.00 ± 89.69	0.185
Postoperative	366.67 ± 57.74	730.00 ± 200.28	0.012
Perioperative	517.86±176.50	775.00 ± 412.31	0.029
CCS(n = 18)			
TBL values (ml)			
TBL _{post1}	320.79 ± 150.45	640.94 ± 139.20	< 0.001
TBL _{post5}	435.03 ± 114.54	808.32 ± 113.94	< 0.001
Transfusion rate n (%)			
Preoperative	0 (0)	0 (0)	
Postoperative	0 (0)	0 (0)	
Perioperative	0 (0)	0 (0)	
Transfusion volume (ml)			
Preoperative	0	0	
Postoperative	0	0	
Perioperative	0	0	
HA (n=264)			
TBL values (ml)			
TBL _{post1}	489.58±320.81	669.38±367.31	< 0.001
TBL _{post5}	710.13 ± 408.01	1031.19±523.09	< 0.001
Transfusion rate n (%)			
Preoperative	38 (24.36)	32 (29.63)	0.340
Postoperative	10 (6.41)	10 (9.26)	0.390
Perioperative	40 (25.64)	40 (37.04)	0.048
Transfusion volume (ml)			
Preoperative	481.40 ± 146.80	633.33 ± 428.95	0.049
Postoperative	400.00 ± 0.00	414.29±134.52	0.788
Perioperative	518.18±188.35	566.67±353.15	0.433
THA (n=203)			
TBL values (ml)			
TBL _{post1}	509.06 ± 272.77	640.69±317.93	0.002
TBL _{post5}	783.52±314.12	982.41±472.33	0.002
Fransfusion rate n (%)			
Preoperative	25 (19.38)	26 (35.14)	0.013
Postoperative	2 (1.55)	6 (8.11)	0.023
Perioperative	25 (19.38)	26 (35.14)	0.013
Iranstusion volume (ml)			
Preoperative	534./8±194.49	592.59 ± 458.20	0.555
Postoperative	400.00 ± 0.00	480.00±109.54	0.1/8
Perioperative	5/0.59±246.89	692.11±427.68	0.281

Type of surgery

PFNA, proximal femoral nail antirotation; CCS, cannulated compression screws; HA, hemiarthroplasty; THA, total hip arthroplasty; TBL, total blood loss Although most transfusions occurred preoperatively, more transfusion volume occurred postoperatively. This suggested that the effects of hypocalcemia required our attention throughout the perioperative period.

On the pathophysiological mechanism that hypocalcemia increases blood loss, two potential mechanisms are the effect of calcium on blood pressure [39] and the effect on coagulation [30, 40]. First, calcium may play a role in vascular reactivity [41, 42]. Previous studies have found that hypocalcemia led to increase arterial vascular reactivity, which in turn increased blood pressure, which can lead to more bleeding [42]. However, in this study, we did not observe any significant association between calcium level and blood pressure on admission. Another possible mechanism is that serum calcium is a key component of the coagulation cascade, which is very important for the timely formation and stabilization of fibrin polymerization sites, and the decrease of calcium concentration leads to the decrease of platelet-related activities [43]. A study found that calcium supplements acutely increased the coagulation index in post-menopausal women [44]. Wang et al. conducted a similar study [34], and the results showed that hypocalcemia was associated with more total blood loss and blood transfusion. This was consistent with our findings. However, we have conducted a more detailed analysis of preoperative, postoperative and perioperative blood transfusion, which can lead to a better understanding of the effects of hypocalcemia.

Our study has several limitations. First of all, the study was a single-center, retrospective analysis, and the sample size was relatively small. Second, hypocalcemia was defined by albumin-corrected calcium levels instead of ionized calcium, which may underestimate the presence of hypocalcemia. Third, the use of antiplatelet drugs and anticoagulant drugs can increase bleeding, which might then affect TBL. Fourth, differences in anemia at admission may affect transfusion requirements. Finally, TBL was calculated based on several clinical parameters which could be a source of error, especially when the fluid volume administered perioperatively was not controlled, but it should not affect the difference because all the patients were treated with the same protocol.

Conclusion

Hypocalcemia was associated with increased TBL and blood transfusion in elderly patients with hip fracture during the perioperative period.

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Author contributions

S.S. and C.Y. conceived the original ideas of this manuscript. Y.Z., K.L., Q.L. and C.L. executed the follow-up examination and materials collection. Y.Z. and C.Y. read the examination results, participated in the surgical and medical

treatment. Y.Z. and S.S. prepared the manuscript and the figures. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study design was approved by the ethical committee of The First Hospital of Changsha. Permission to waive the informed consent was obtained from the ethical committee of The First Hospital of Changsha for this observational retrospective study. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

The study design was approved by the ethical committee of The First Hospital of Changsha. Permission to waive the informed consent for publication was obtained from the ethical committee of The First Hospital of Changsha for this observational retrospective study.

Competing interests

The authors declare no competing interests.

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