Hidden Blood Loss and Its Influencing Factors Post Cement Augmentation of Vertebral Metastasis

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Research Article

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Abstract

Introduction

Cement augmentation is an effective approach and can provide a temporary local control and pain relief for pathologic vertebral compression fractures (PVCFs). However, few reasearch focused on the risk factors of HBL post cement augmentation surgery in PVCFs. Hence, this retrospective research was founded to calculate the HBL amount during perioperative period, given a measured visible blood loss.

Method

From January 2014 to December 2020, a total of 169 PVCFs patients with 283 levels who underwent cement augmentation were retrospectively analyzed. Clinical information was extracted from medical records, including sex, age, BMI, hypertension, diabetes, duration of pain, bone metastases type, vertebral location, bone lesion quality, number of PVCF(s), VAS, Tomita, Tokuhashi, preoperative radiotherapy, surgery type, surgical duration, the amount of bone cement, bone cement leakage, postoperative pathology, percentage of VHL, percentage of VHR. HBL was calculated according a linear formula of Gross using the patient's average Hct during the perioperative course and PBV. Multivariate linear regression analysis was performed to evaluate the independent factors associated with HBL.

Results

The mean HBL was 448.2 ± 267.2 ml, with a percentage of 10.8% ± 6.2% in PBV. The mean preoperative Hct and Hb were 38.1 ± 5.4 and 127.6 ± 19.1g/l. The mean postoperative Hct and Hb were 34.2 ± 4.9 and 114.8 ± 17.6g/l. There were significant differences between pre- and postoperative Hct ($P<0.001$) and Hb ($P<0.001$), and 132 patients developed anemia postoperative compared with 79 patients suffered from preoperative anemia ($P < 0.001$). Multivariate linear regression showed that bone lesion quality ($p=0.028$), number of PVCF(s) ($p=0.002$), the amount of bone cement ($p=0.027$), bone cement leakage ($p=0.001$), percentage of VHL ($p=0.011$) were independent risk factors for HBL.

Conclusion

In conclusion, the present study indicates that the HBL in patients with PVCFs is much greater than generally considered in OVCFs. Orthopedic surgeons should be on guard against those patients with lytic vertebral destruction, the greater amount of bone cement, bone cement leakage, more numbers of PVCF(s), higher percentage of VHL.

Introduction

Currently, though cancer incidence is rising, life expectancy is improving due to systemic and local therapies for malignant tumors patients.[1] Metastatic bone disease (MBD) especially for spinal metastases is becoming the most common problem to be affected by metastatic cancer, and serious skeletal-related events (SREs) including pain, hypercalcemia, pathologic fracture, and spinal cord or nerve

root compression seriously reduce quality of life.[2; 3] As the most common site of involvement in patients with bone metastases, spine metastasis may cause serious pain and lead to permanent neurological disability if pathologic vertebral compression fractures (PVCFs) occurs and involves the spinal cord and/or nerve root occurs.[1; 4] Cement augmentation including percutaneous vertebroplasty (PVP) and percutaneous kyphoplasty (PKP) is an effective approach and can provide a temporary local control and pain relief for PVCFs. Radiofrequency ablation (RFA) is an effective cytoreductive surgery associated with an improved therapeutic ratio.[5; 6]

Hidden blood loss (HBL) presents the decrease of blood volume and hemoglobin caused by blood penetrating tissues or retained in a dead space and blood hemolysis, which is always disregarded by orthopedic surgeons. The concept of HBL was firstly proposed by Sehat et al.[7] in 2000, and has been attracted more and more attention in the blood loss of PKP/PVP for OVCFs.[8–10] However, these analysis of HBL were mainly about the OVCFs, few study focused on the risk factors of HBL post cement augmentation surgery in PVCFs. For the patients of PVCFs, due to the invasion and destruction of bone, the problem of rich blood supply for metastatic tumor and poor physical fitness, HBL plays a more significant influence on the postoperative of cement augmentation, especially with the adjuvant RFA therapy. As we known, there is still no published analysis dedicated to the research of HBL during cement augmentation with or without RFA.

Hence, this retrospective research was founded to calculate the HBL amount during perioperative period, given a measured visible blood loss. The risk variables that may interrupt and predicate HBL amount were analyzed.

Patients And Methods

Patients

Retrospective analysis the clinical data of 169 PVCFs patients who underwent cement augmentation from January 2014 to December 2020. This study protocol was reviewed and approved by the National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College. All the involved patients diagnosed as PVCFs were confirmed through previous cancer history, clinical manifestations and the most important imaging examinations include X-ray, CT and MRI.

The inclusion criteria were complete medical record materials, specifically diagnosis of PVCFs, clearly surgical indications and cement augmentation performed, complete informed consent for patients. The exclusion criteria were specifically diagnosis of OVCFs, cement augmentation combined with pedicle screw fixation, and coagulation disorders patients. Clinical information was extracted from medical records, including sex, age, BMI, hypertension, diabetes, duration of pain, bone metastases type, vertebral location, bone lesion quality, number of PVCF(s), VAS, Tomita, Tokuhashi, preoperative radiotherapy,

surgery type, surgical duration, the amount of bone cement, bone cement leakage, postoperative pathology, percentage of VHL, percentage of VHR.

Surgical technique and postoperative therapy

All of the operations were primary procedures and performed by the same surgical team using local anesthesia under the guidance of the conventional C-arm fluoroscopy. PKP, PVP and RFA surgery was all carried out in accordance with a standard published technique, namely, bilateral pedicle approach[11–13]. All the vertebral specimens underwent histopathological examination to confirm clinical diagnosis. All patients received denosumab or zoledronic acid to inhibit the progression of bone metastasis.

Calculation of patient's blood volume (PBV) and HBL

No haemostatic material and drainage tube were used, and no blood transfusion. In this study, visible blood loss with low blood loss could not assessed clearly, and was always overlooked. HBL can be calculated by deducting the amount of visible loss from the calculated TBL. Therefore, HBL was approximated to TBL in this artical. All the patients were tested with a full blood count preoperation and 2–3 days postoperation, in order to compare the change of Hct and Hb. The patients' haemodynamics were stable and fluid shifts have been mostly completed by this time in Sehat and Newman's[14] article.

According to the weight and height of the patients, the patient's blood volume (PBV) can be calculated using the formula of Nadler[15]:

$PBV\ (L) = K_1 \times height\ (m)^3 + K2 \times weight\ (kg) + K3$
(Male: K1 = 0.3669, K2 = 0.03219 and K3 = 0.6041; Female: K1 = 0.3561, K2 = 0.03308 and K3 = 0.1833)

Total blood loss (TBL) was calculated according a linear formula of Gross[16] using the patient's average Hct during the perioperative course and PBV.

$TBL\ (L) = PBV \times (Hctpre - Hctpost)/Hctave \approx HBL\ (L)$
(Hctpre is the initial preoperative Hct, Hctpost is the Hct on postoperative two or three days, and Hctave, is the average of the Hctpre and Hctpost)

Calculation of the percentages of vertebral height loss and restoration

Vertebral height (VBH) was determined according to the average of the first, middle and last three parts of vertebral body by the plain radiographs. The percentages of vertebral height loss (VHL, %) and vertebral height restoration (VHR, %) were computed according to the following formula:

$VBH_{ave} = (VBH_{upper} + VBH_{lower})/2$

$VHL\ (\%) = (VBH_{ave} - VBH_{pre})/VBH_{ave} \times 100\%$

$VHR (\%) = (VBH_{post} - VBH_{pre})/VBH_{ave} \times 100\%$

(VBHupper and VBHlower represent the upper and lower adjacent vertebrae height of malignant vertebral fractures, respectively. VBHave is the average height of VBHupper and VBHlower and represents the predicted height of the fractured vertebral. VHL% and VHR% represent the percentage of vertebral height loss and restoration, respectively. VBHpre and VBH_{post} represent the fracture vertebral height of preoperation and postoperation, respectively)

Additional measurements

Hb concentration was used to define the anemia. According to the World Health Organization/National Cancer Institute, anemia is characterized by Hb levels of < 120g/L for women and < 140 g/L for men[17]. BMI was confirmed by the World Health Organization criteria.

Statistical analysis

Mean ± SD deviation for the descriptive statistics was used to present the data. Independent samples Student t test was used to test for significant differences of two quantitative variables. One-way ANOVA was performed to identify significant differences of three and more quantitative variables. Pearson product-moment correlation analysis was used to reflect the degree of linear correlation between two quantities. t, F and r is its special symbol for independent samples Student t test, One-way ANOVA, and Pearson product-moment correlation analysis, respectively. A positive coefficient indicated a positive influence, whereas a negative coefficient denoted a negative influence on the dependent variable (HBL). The closer the absolute value is to 1, the stronger the correlation (negative or positive correlation). Significant variables with $P < 0.05$ in above analysis were included the Multivariate linear regression analysis, which was performed to evaluate the independent factors associated with HBL. Data analyses were performed with SPSS version 19.0 and Graphpad prism 8. The significant level of statistical was set at $P < 0.05$.

Results

A total of 169 patients, 79 males and 90 females, mean age 58.5 ± 9.9 years, mean BMI 24.1 ± 3.9, were included in this study. The demographic information and clinical results are summarized in Table 1 and Table 2. 27.2% (46/169) and 7.1% (12/169) patients suffered from hypertension and diabetes, respectively. 25.4% (43/169) and 74.6% (126/169) patients are with single and multiple bone metastases, respectively. Bone metastases in this study are predominantly osteolytic, osteoblastic and mixed osteolytic/osteoblastic metastasis, which accounted for 66.3% (112/169), 9.5% (16/169), and 24.3% (41/169), respectively. In conclusion, a total of 169 patients with 283 levels were reviewed retrospectively. 14.8% (25/169), 71% (120/169) and 14.2% (24/169) patients underwent PVP, PKP and PKP plus RFA for PVCFs, respectively.

Table 1
Patients'demographics

Parameters	Statistics
Total patients	169
Sex	
Male	79
Female	90
Hypertension	46
Diabetes	12
Bone metastases type	
Single	43
Multiple	126
Bone lesion quality	
Lytic	112
Blastic	16
Mixed lytic/blastic	41
Preoperative radiotherapy	26
Postoperative pathology	
Lung cancer	73
Breast cancer	32
Digestive system tumor	29
Urinary system tumor	19
Other tumors	16
Age, years	58.5 ± 9.9
BMI, kg/m^2	24.1 ± 3.9
Duration of pain, day(s)	117.5 ± 112.7
VAS	5.8 ± 1.7
Tomita	5.9 ± 1.9

BMI, body mass index; VAS, visual analog scale.

Parameters	Statistics
Tokuhashi	8.6 ± 2.9
BMI, body mass index; VAS, visual analog scale.	

Table 2
Clinical results related to operation in the patients

Parameters	Statistics
Number of PVCF(s)	
One level	102
Two levels	36
Three or more levels	31
Vertebral location	
Thoracic vertebra	41
Lumbar vertebra	90
Thoracic and lumbar vertebra	38
Surgery type	
PVP	25
PKP	120
PKP + RFA	24
Bone cement leakage	41
The amount of bone cement, ml	5.7 ± 3.2
Surgical duration, min	100.6 ± 50.8
Percentage of VHL, %	17.7 ± 12.4
Percentage of VHR, %	15.3 ± 11.5
PBV, l	4.17 ± 0.69
HBL, ml	448.2 ± 267.2
HBL/PBV, %	10.8 ± 6.2
PVCF, pathologic vertebral compression fraction; PVP, percutaneous vertebroplasty; PKP, percutaneous kyphoplasty; RFA, radiofrequency ablation; VHL, vertebral height loss; VHR, vertebral height restoration; HBL, hidden blood loss; PBV, patient's blood volume.	

The mean preoperative Hct and Hb were 38.1 ± 5.4 and 127.6 ± 19.1g/l. The mean postoperative Hct and Hb were 34.2 ± 4.9 and 114.8 ± 17.6g/l. There were significant differences between pre- and postoperative Hct ($P < 0.001$) and Hb ($P < 0.001$), and 132 patients developed anemia postoperative compared with 79 patients suffered from preoperative anemia ($P < 0.001$, Table 3). The mean PBV was 4.17 ± 0.69 L, and the mean HBL was 448.2 ± 267.2 ml, with a percentage of 10.8% ± 6.2% in PBV.

Table 3
Perioperative blood changed in the patients and results of the Pearson or Spearman correlation analysis for hidden blood loss

Parameters	Preoperative (n = 169)	Postoperative (n = 169)	Statistical significance
Hct, %	38.1 ± 5.4	34.2 ± 4.9	**P < 0.001**
Hb, g/l	127.6 ± 19.1	114.8 ± 17.6	**P < 0.001**
Anemia	79	132	**P < 0.001**
Hct, Hematocrit; Hb, Hemoglobin.			

In order to analyze the correlation between HBL and 26 risk factors, the independent samples Student t test, one-way ANOVA and Pearson product-moment correlation analysis were used. We found the following parameters with a $P < 0.05$ (Table 4): bone metastases type ($t = -2.374$, $p=0.019$), RFA ($t = 2.305$, $p=0.022$), bone cement leakage ($t =-3.777$, p0.01), bone lesion quality ($F = 4.097$, $p=0.018$), number of PVCF(s) ($F = 3.407$, $p=0.035$), Tokuhashi ($r = -0.159$, $p=0.039$), the amount of bone cement ($r = 0.304$p0.01), percentage of VHL ($r = 0.321$, p0.01), percentage of VHR ($r = 0.337$, p0.01), preoperative Hct ($r = 0.246$, $p = 0.001$), preoperative Hb ($r = 0.228$, $p = 0.003$), PBV ($r = 0.176$, $p=0.022$). Multivariate linear regression showed that bone lesion quality ($p=0.028$), number of PVCF(s) ($p=0.002$), the amount of bone cement ($p=0.027$), bone cement leakage ($p=0.001$), percentage of VHL ($p=0.011$) were independent risk factors for HBL (Table 5).

Table 4
Results of the Pearson or Spearman correlation analysis for hidden blood loss

Parameters	▯▯▯	***P***
Sex	t = 1.870	0.063
Hypertension	t =-0.345	0.731
Diabetes	t = 1.217	0.225
Preoperative anemia	t = 1.407	0.161
Bone metastases type	t = -2.374	**0.019**
Preoperative radiotherapy	t = 1.740	0.084
RFA	t = 2.305	**0.022**
Bone cement leakage	t =-3.777	**< 0.01**
Bone lesion quality	F = 4.097	**0.018**
Number of PVCF(s)	F = 3.407	**0.035**
Vertebral location	F = 0.254	0.776
Surgery type	F = 2.736	0.068
Postoperative pathology	F = 1.034	0.391
Age	r = -0.018	0.817
BMI	r = 0.135	0.080
Duration of pain	r = 0.027	0.729
VAS	r = 0.134	0.082
Tomita	r = 0.075	0.330
Tokuhashi	r = -0.159	**0.039**
The amount of bone cement	r = 0.304	**< 0.01**
Surgical duration	r = 0.059	0.445
Percentage of VHL	r = 0.321	**< 0.01**
Percentage of VHR	r = 0.337	**< 0.01**
Preoperative Hct	r = 0.246	**0.001**
Preoperative Hb	r = 0.228	**0.003**

RFA, radiofrequency ablation; PVCF, pathologic vertebral compression fraction; BMI, body mass index; VAS, visual analog scale; VHL, vertebral height loss; VHR, vertebral height restoration; Hct, Hematocrit; Hb, Hemoglobin; PBV, patient's blood volume.

Parameters	▯▯▯	*P*
PBV	r = 0.176	**0.022**
RFA, radiofrequency ablation; PVCF, pathologic vertebral compression fraction; BMI, body mass index; VAS, visual analog scale; VHL, vertebral height loss; VHR, vertebral height restoration; Hct, Hematocrit; Hb, Hemoglobin; PBV, patient's blood volume.		

Table 5
Results of multivariate linear regression for hidden blood loss

Coefficients[a]	Unstandardized		Standardized		
	β	SE	β	t	P
Constant	-526.941	184.366		-2.858	**0.005**
Bone metastases type	81.249	46.405	0.134	1.751	0.082
RFA	-40.464	49.294	-0.055	-0.821	0.413
Bone cement leakage	146.860	41.515	0.235	3.538	**0.001**
Bone lesion quality	-43.891	19.784	-0.141	-2.218	**0.028**
Number of PVCF(s)	83.938	27.205	0.244	3.085	**0.002**
Tokuhashi	-1.348	6.572	-0.015	-0.205	0.838
The amount of bone cement	12.969	5.824	0.153	2.227	**0.027**
Percentage of VHL	5.216	2.033	0.244	2.565	**0.011**
Percentage of VHR	3.356	2.148	0.145	1.562	0.120
Preoperative Hct	2087.208	1320.678	0.422	1.580	0.116
Preoperative Hb	-2.266	3.720	-0.163	-0.609	0.543
PBV	16.798	25.842	0.044	0.650	0.517
aDependent variable: HBL (ml)					
RFA, radiofrequency ablation; PVCF, pathologic vertebral compression fraction; VHL, vertebral height loss; VHR, vertebral height restoration; Hct, Hematocrit; Hb, Hemoglobin; PBV, patient's blood volume.					

Discussion

A few studies of HBL post cement augmentation surgery focused on the PKP/PVP in the treatment of OVCFs[8–10]. However, no research has been explored the hidden blood loss and its influencing factors post cement augmentation of vertebral metastasis with PVCFs. In this research, the main finding revealed that the amount of HBL was 448.2 ± 267.2 ml, which accounted for 10.8% ± 6.2% of PBV, and the mean

Hb loss of 12.8 g/L in the perioperative period. Our research presented a worse result compared with the results from previous studies in OVCFs, such as, Cao et al[8] and Wu et al[10] found out that 279 ± 120 ml mean HBL accompanied by 8.2 ± 3.9g/L Hb loss, and a mean of 282 mL HBL with 8.7 g/L Hb loss during the perioperative period, respectively. As well, 53 patients with normal preoperative Hb levels developed into anemia, which implied that 46.7% preoperative anemia rate increased to 78.1% post operation (Fig. 1A). Advanced malignant tumor with PVCFs represents a high risk and poor ability to resist bleeding in the perioperative period. Massive blood loss will prolong the post-operative recovery time due to the potential adverse effects of anemia, which delayed the time of comprehensive treatment. However, no study focused on the risk factors of HBL during cement augmentation with or without RFA for the treatment of PVCFs. Hence confirming the amount of HBL and its related influencing variables are crucial for patients of PVCFs.

Up to now, the mainstream mechanisms of HBL that has been proposed was blood penetrating tissues or retained in a dead space and blood hemolysis.[18; 19] However, no the related influencing factors associated with the HBL amount were clearly stated in the therapy of cement augmentation plus or not RFA for PVCFs. In our study, multiple linear regression analysis was employed to investigate the related influencing factors. The study considered that patients with lytic bone destruction, more numbers of PVCF(s), greater percentage of VHL, more bone cement amount, bone cement leakage would have more possibility of HBL.

Our study demonstrated that lytic bone destruction related to more HBL compared with the blastic and mixed lytic/blastic patients during perioperative period (Fig. 1B). Compared with blastic and mixed lytic/blastic spinal metastases, lytic spinal metastases mean more vertebral bone reduction and loss of vertebral structural stability. Vertebral reduction will lead to the “empty shell phenomenon” in the vertebral body[20], which may be a source and reason for more HBL in patients with severe VHL.[10] As the bearing bone, loss of vertebral structural stability is apt to occur the VHL, which was also positively related to the HBL amount in our study ($p = 0.011$, Table 5). In the previous study, HBL was also found a positive correlation related to the number and vertebral fracture severity.[8–10]

In the analysis of the relationship between bone cement leakage and HBL, multivariate linear regression analysis showed that the bone cement leakage was positively correlated with HBL in our study, which also can be confirmed in the other article.[8–10] The occurrence of bone cement leakage was mostly due to the fracture gap of cortical defect,[21] which also can be aggravated by the lytic bone destruction. The cortical defect will lead to persistent bleeding of the vertebra[8; 10] and make it accessible to bone cement leakage during the perioperative period of cement augmentation. What’s more, large bone cement volume was strong predictor of bone cement leakage.[22] In addition, there is a significant evidence that the amount of bone cement is positively associated with HBL in our study. Polymethylmethacrylate (PMMA), the most commonly used bone cement, not only can reconstruct the stability of vertebra, but also induce the tumor cell due to exothermic effect in solidification process and cells toxicity.[10] In the previous study, thermal necrosis was a significant factor of hemolysis during PKP,[10] which was not confirmed by us. In

our study, the temperature in the process of RFA can reach a maximum of 103°C, which is higher than the 55°C of bone–cement interface temperature. However, no association was found between RFA and HBL ($p = 0.413$, Table 5). In summary, thermal necrosis may be not the dangerous factor for HBL, so further study should be to explore the correlation between cement and HBL.

As a retrospective study, there are still many limitations, despite being fully designed and implemented. First, the research results should be verified by multiple centers due to the occluded data in a single-center retrospective study. Second, the HBL was falsely estimated. One reason is that the postoperative Hct was evaluated in the 2 or 3 days of postoperation when the fluid shifts were not completed in this time.[14] Another reason is that intravenous fluid infusion in the perioperative period will lead to the hemodilution. Third, a more specific and detailed measurement method for the degree of vertebral destruction especially for osteolysis should be involved.

Conclusion

In conclusion, the present study indicates that the HBL in patients with PVCFs is much greater than generally considered in OVCFs. Orthopedic surgeons should be on guard against those patients with lytic vertebral destruction, the greater amount of bone cement, bone cement leakage, more numbers of PVCF(s), higher percentage of VHL. Further in-depth clinical research should be performed especially for patients with preoperation anemia to assure the safety in the perioperative period of cement augmentation.

Declarations

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

All authors were involved in the preparation of this manuscript. Conception and design: SGZ and SJY; Analysis and interpretation: SGZ and SJY；Data collection: SGZ；Writing the article: SGZ；Critical revision of the article: ZGZ, LBX, SFX, XXZ,TL and SGY. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Conflict of interest

We declare that we have no conflicts of interest.

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Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

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Figures

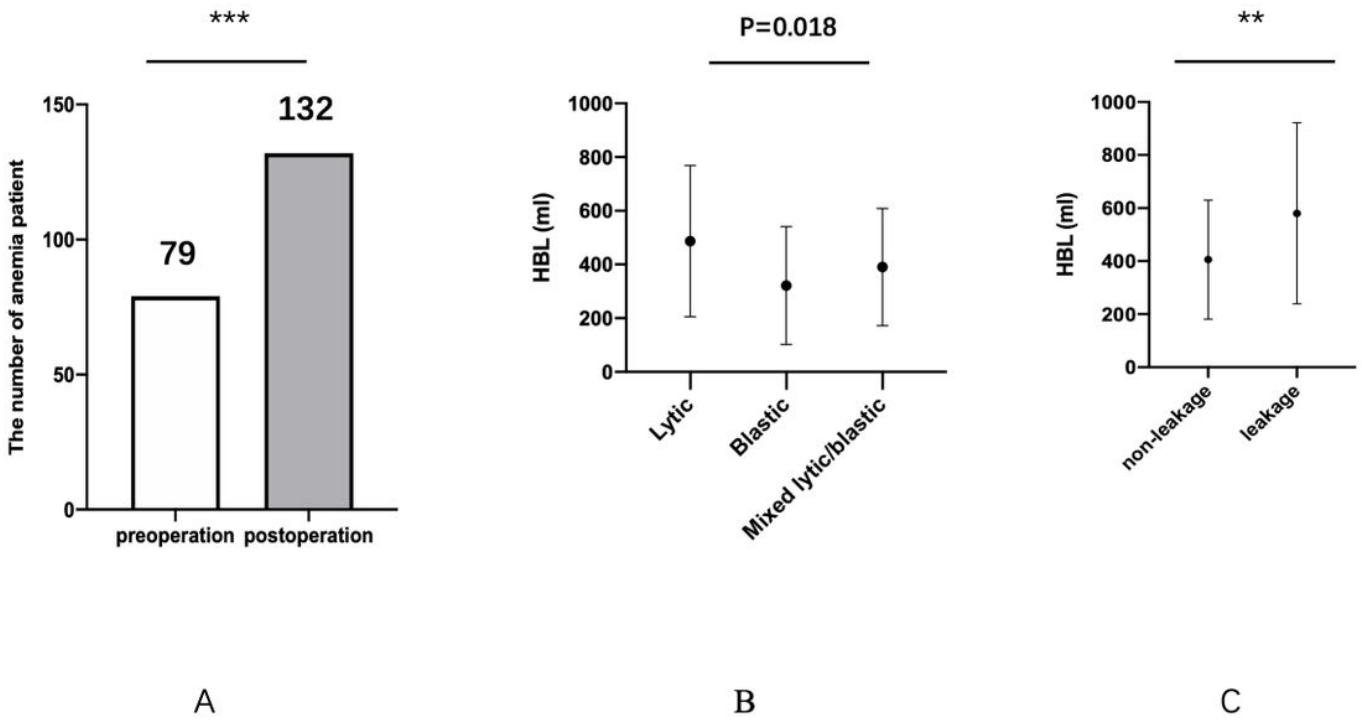

Figure 1

Our study demonstrated that lytic bone destruction related to more HBL compared with the blastic and mixed lytic/blastic patients during perioperative period