

CLINICAL ARTICLE

Bone Cement Implantation Syndrome in Bone Tumor Surgeries: Incidence, Risk Factors, and Clinical Experience

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Objective: To investigate the incidence and risk factors of bone cement implantation syndrome (BCIS) in bone tumor surgeries.

Methods: This was a retrospective observational study. We investigated patients who underwent bone tumor surgeries requiring cementation as part of the surgery between March 2016 and January 2018. We reviewed medical records, including formal anesthesia records and operation notes. Patients with complete data files were included. To investigate the general incidence of BCIS in tumor surgeries, patients of all ages, genders and tumor types were included. Vital signs, including oxygen saturation, blood pressure, heart rate, and respiratory rate, were checked and recorded once every 1–2 min after cementation. Accurate time points of cementation were recorded on formal anesthesia record sheets by the anesthesiologists. The definition and severity of BCIS were based on the classification system proposed in previous studies: grade I, moderate hypoxia (SpO₂ <94%) or hypotension (fall in systolic blood pressure >20%); grade II, severe hypoxia (SpO₂ <88%) or hypotension (fall in systolic blood pressure >40%) or unexpected loss of consciousness; and grade III, cardiovascular collapse requiring cardiopulmonary resuscitation. We also compared the incidence of BCIS between those patients with and without possible risk factors, including intraoperative blood loss, arthroplasty, use of an intramedullary device, patient age, gender, tumor location, and pre-existing lung cancer or lung metastasis.

Results: A total of 88 patients were included. BCIS occurred in 23 patients, with an incidence of 26.1%. Among them, 19 had grade I and 4 had grade II BCIS. There was no patients with grade III BCIS. The lowest blood pressure occurred within 10 min in 21 (87.5%) patients and within 20 min for all patients. A total of 9 grade I BCIS were self-limiting. The other 10 grade I hypotension cases and all grade II hypotension cases recovered after administration of a vasoconstrictor medication. Preexisting lung cancer or lung metastasis was the risk factor for BCIS; 40.0% of patients (16 in 40 patients) with preexisting lung cancer or metastasis had BCIS, whereas only 14.6% of patients (7 in 48 patients) without lung lesions had BCIS. There was no risk difference in terms of arthroplasty, old age, and increased blood loss. Apart from grades I and II bone cement implantation syndrome, there were no other major complications, including death, cardiovascular events, or cerebrovascular events.

Conclusion: Bone cement implantation syndrome is not unusual in bone tumor surgeries, and preexisting lung cancer or lung metastasis is a risk factor.

Key words: Arthroplasty; Bone cement implantation syndrome; Bone tumor surgery; Hypotension

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Introduction

Bone cement implantation syndrome (BCIS) is an important cause of intraoperative morbidity and mortality in patients undergoing cemented hip arthroplasty, such as total hip arthroplasty and bipolar hemiarthroplasty¹⁻⁹. Although there is no standard definition for BCIS, the classic clinical presentation includes hypotension, hypoxia, arrhythmia, loss of consciousness, and even cardiac arrest². The true incidence of BCIS is not conclusive in the published literature. A few studies have shown that its incidence ranges from 27.8% to 38%^{2,4,10}. The intraoperative mortality rate ranges from 0.06% to 0.12%². Patient and surgical risk factors include old age⁷, osteoporosis^{5,6}, bony metastasis^{1,10}, long femoral stem², and previously uninstrumented femoral canals². However, these studies on BCIS only involved patients who underwent cemented hip arthroplasty^{2-4,7-9}. In addition to cemented hip arthroplasty, bone cement is also widely used in surgeries for bone tumors¹¹⁻¹⁷. Unlike BCIS in cemented hip arthroplasties, BCIS has not been widely discussed for bone tumor surgeries. Patients with bone tumors, especially malignant tumors, are likely to be weaker and vulnerable to hemodynamic instability. Thus, BCIS should also be studied exclusively for these patients. Generally, the two major differences in the procedures for bone tumor surgeries and hip arthroplasties are the distinct bony microenvironment and the necessity of an intramedullary prosthesis. Bone cementation provides immediate structural stability and possibly causes thermal necrosis of tumor cells in the surgical margins. Therefore, cementation is not only used for joint reconstruction procedures but also for tumor curettage and/or internal fixation in bone tumor surgeries. Whether these differences result in different presentations of BCIS remains unknown.

Several mechanisms have been proposed for the etiology and pathophysiology of BCIS². These mechanisms include monomer-mediated vasoconstriction, emboli formation, histamine release, and complement activation. In the emboli model, the debris from the medulla embolizes to the lungs, heart, and other circulation organs. The pulmonary emboli cause characteristic hypoxia and right ventricular dysfunction, which leads to hypotension². The extent of embolization is correlated to the intramedullary pressure². The peak and mean intramedullary pressures have been shown to be much higher in cementation with prosthesis insertion. In unvented femurs, the peak pressure and mean pressure can reach 4931 and 3140 mm Hg, respectively, during prosthesis insertion, whereas the pressure is less than one-fifth without prosthesis insertion². Therefore, the incidence of BCIS during cementation without an intramedullary device should be relatively low. In bone tumor surgeries, cementation is frequently used after tumor curettage for aggressive benign bone tumors and malignant bone tumors, while intramedullary prosthesis is not always necessary (Figs 1 and 2). However, bony metastasis has been shown to be a risk factor of BCIS in cemented hip arthroplasties^{1,10}. Compared to normal bones, the relative hypervascularity of bone metastasis may result in easier

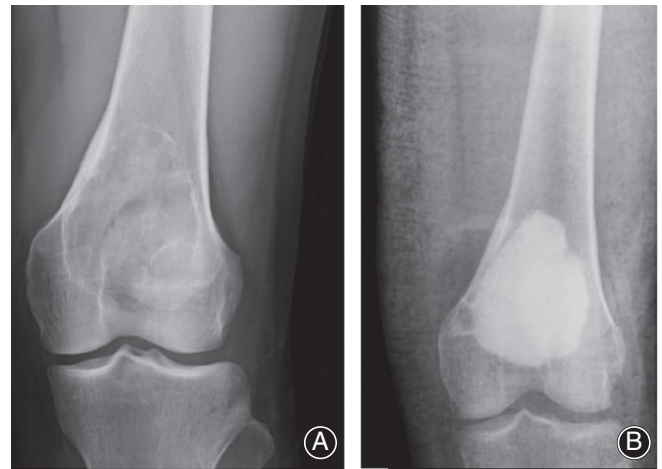


Fig. 1 A 30-year-old woman with giant cell tumor of the left femur. (A) Preoperative plain film. (B) Status post-tumor curettage and cementation alone.

access of the cement, air, or fat particles into the systemic circulation and provoke further physiologic responses. Aggressive benign bone tumors and primary bone malignancies may have the same characteristic. Taking all these factors into account, we speculated that cementation in bone tumor surgeries may still result in a considerable incidence rate of BCIS even without an intramedullary device.

To lower the incidence or lessen the severity of BCIS, some strategies have been developed to eliminate the effects of the abovementioned mechanisms¹⁸⁻²¹. For the emboli model, venting the distal canal is a commonly used method to decrease the intramedullary pressure^{2,22}. By drilling a hole in the cortical bone, the air can escape from the end of the cement plug, which prevents the formation of air emboli. Physiologic responses also play an important role in BCIS.

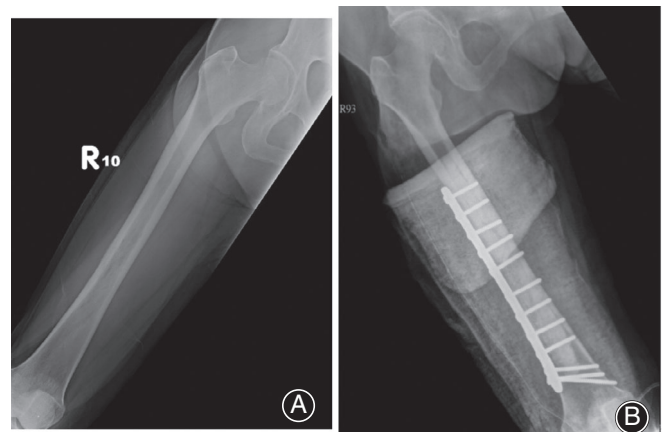


Fig. 2 A 51-year-old man with pathologic fracture of the left femur (metastasis from hypopharynx carcinoma). (A) Preoperative plain films. (B) Status post-tumor curettage, cementation, and internal fixation.

One of the responses is increased plasma histamine concentration²⁰. Although controversy exists^{23,24}, antihistamine medication may reduce cardiovascular reactions during cementation²⁰. We attempted to prevent BCIS by executing these two strategies. However, we still observed that a period of hypotension or hypoxia occasionally occurred after cementation, and vasoconstrictors are needed in some cases. In the published literature, there was no information about the frequency and severity of BCIS in bone tumor surgeries. Adding this information to the literature would help orthopaedic surgeons and anesthesiologists to be wary of this syndrome and understand more about its clinical course and outcomes.

Therefore, we conducted this retrospective observational study on BCIS in bone tumor surgeries. The purpose of this study was: (i) to investigate the general incidence of BCIS in bone tumor surgeries; (ii) to identify the severity and the clinical course of BCIS according the preexisting classification, and (iii) to clarify whether there is any risk factor of BCIS for bone tumor surgeries. The hypothesis is that the general incidence and severity of BCIS in bone tumor surgeries are similar to those results reported for cemented hip arthroplasties. Furthermore, we share our experience and strategies to lessen the severity of BCIS in bone tumor surgeries. To our knowledge, this is the first study to address this issue.

Methods

We performed a retrospective observational study at the corresponding author's hospital. We include patients who underwent bone tumor surgeries requiring cementation as part of the surgery between March 2016 and January 2018. We reviewed medical records, including formal anesthesia records and operation notes. Patients with complete data files were included. To investigate the general incidence of BCIS in tumor surgeries, patients of all ages, genders, and tumor types were included.

Pre-cementation Medication

Aiming to lower the effect of plasma histamine release, we routinely administered 30 mg of intravenous diphenhydramine within 1 h before cementation.

Cementation Technique

To lower the intramedullary pressure, we attempted to vent the medullary canal through an intramedullary tube. We did not drill the bone to create a vent because of the concern of creating a weak point. An unnecessary weak point should be avoided in bone tumor surgeries to decrease the risk of further pathologic fractures. Instead, we inserted a long tube into the distal canal and maintained a constant suction force. The bone cement was then manually impacted and pressurized beside the tube into the medullary space. When adequate bone cement was applied, the suction tube was pulled out. By doing this, trapped air and small medullary contents

could move out, potentially lowering the intramedullary pressure.

Review of Medical Records

We reviewed medical records, images, and pathology reports to investigate the possible risk factors of BCIS for each patient. These factors included intraoperative blood loss, arthroplasty, use of an intramedullary device, patient age, gender, tumor location, and preexisting lung cancer or lung metastasis. We compared the incidence of patients with and without these risk factors.

Monitoring of Intraoperative Vital Signs

Given the concern regarding BCIS, we always informed the anesthesiologists before cementation and requested frequent physiological monitoring. Generally, vital signs, including oxygen saturation, blood pressure, heart rate, and respiratory rate, were checked and recorded once every 1–2 min after cementation. Accurate time points of cementation were recorded on formal anesthesia record sheets by the anesthesiologists. The definition and measurements of these parameters of vital signs and severity of BCIS are described in what follows. The severity of BCIS was classified using a pre-existing system². Blood pressure and oxygen saturation were the two parameters in the classification system

Blood Pressure

The blood pressure is the pressure of the blood in the circulatory system, measured by arterial line pressure monitoring or cuff pressure manometer during the operation. Compared to the pre-cementation blood pressure, a fall in systolic blood pressure >20% was classified as grade I BCIS and a fall in systolic blood pressure >40% was classified as grade II BCIS. Cardiovascular collapse requiring cardiopulmonary resuscitation was classified as grade III BCIS².

Oxygen Saturation

The oxygen saturation is defined as the fraction of oxygen-saturated hemoglobin relative to total hemoglobin (unsaturated + saturated) in the blood, measured by pulse oximeter. During the operation, oxygen saturation <94% was classified as grade I BCIS, and oxygen saturation <88% was classified as grade II BCIS².

Statistical Analysis

Before starting the current study, we determined the sample size needed for the χ^2 -test, while the power, degrees of freedom, effect size, and significant level were set as 0.8, 1, 0.3, and 0.05, respectively. After calculation, at least 87 participants were needed. The comparison of the incidence in patients with and without each risk factor was analyzed with the χ^2 -test. Statistical analysis was conducted using SPSS software (version 20, IBM) on a Microsoft Windows computer.

The current study was approved by the Ethics Committee of the National Taiwan University Hospital with a

waiver of informed consent for the retrospective use of patient data (approval number: 201805071RIND).

Results

Series Characteristics and Surgery Types

A total of 88 patients were included in the study. The characteristics of bone tumors and types of surgery are shown in Table 1. Generally, there were three types of bone tumor surgeries in this series: (i) 12 patients underwent tumor curettage of bone tumors and cementation without any implants (Fig. 1); (ii) 42 patients underwent tumor curettage of bone tumors with prophylactic fixation or fixation of pathologic fractures (Fig. 2); and (iii) 34 patients underwent tumor wide excision with prosthesis insertion (Fig. 3). The locations of the operation were illustrated in Fig. 4.

The average age of patients was 55.0 ± 16.3 years. The average operation time was 105.3 ± 44.6 min and the average blood loss was 225.0 ± 261.5 mL.

Clinical Presentation and Incidence of Bone Cement Implantation Syndrome

Bone cement implantation syndrome occurred in 23 patients, with an incidence of 26.1%. Among these patients, 19 had grade I BCIS and 4 had grade II BCIS. None had grade III BCIS. Only 1 grade I patient presented with hypoxia and the others presented with hypotension.

Among the hypotensive events, the lowest blood pressure occurred within 10 min in 21 patients (87.5%) and within 20 min for all patients. A total of 9 grade I BCIS cases were self-limiting. The other 10 grade I hypotension cases and all grade II hypotension cases recovered after administration of a vasoconstrictor medication.

Risk Factors

A comparison of the incidence in patients with and without each risk factor is shown in Table 2. The occurrence rate of BCIS was significantly higher when there was a preexisting lung cancer or lung metastasis ($P = 0.008$); 40.0% of patients (16 in 40 patients) with preexisting lung cancer or metastasis had BCIS, whereas only 14.6% of patients (7 in 48 patients) without a lung lesions had BCIS. Other factors, including age, gender, tumor location, implant type, gender, and blood loss, did not affect the incidence of BCIS.

Complications

Apart from grade I and grade II bone cement implantation syndrome, there were no other major complications, including death, cardiovascular events, or cerebrovascular events.

Discussion

In numerous previous studies, BCIS has been discussed in patients undergoing hip arthroplasties¹⁻⁹. However, there has been no detailed information available about the frequency and severity of BCIS in bone tumor surgeries. The present study revealed an incidence of BCIS in bone tumor surgeries of 26%. Thus, caution is necessary to decrease intraoperative and postoperative morbidity and mortality in these patients.

Because different definitions have been used, the incidence of BCIS in cemented hip arthroplasties varies widely in the published literature. The incidence has been reported as over 25%^{2, 4, 10}. Prosthesis insertion into a cemented medullary canal generates significantly higher intramedullary pressure, which may result in increased emboli formation². Therefore, cementation with prosthesis insertion is supposed to have higher risk than cementation alone. However, in this study, the incidence of BCIS in bone tumor surgeries was similar even without prosthesis insertion compared to

TABLE 1 Characteristics of bone tumors and types of surgery

Variables		BCIS grade*			Total
		N/A	Grade I	Grade II	
Tumor type	Bone metastasis	40	15	3	58
	Primary bone cancer	10	2	1	15
	Benign bone tumor	11	2	0	15
Types of surgery	Cementation alone	10	2	0	12
	Cementation + plate and screws	29	10	1	40
	Cementation + intramedullary nail	2	0	0	2
	Cementation + arthroplasty	24	7	3	34
Tumor location	Femur	39	13	3	55
	Humerus	9	5	1	15
	Tibia	9	0	0	9
	Acetabulum	3	1	0	4
	Acetabulum+femur	2	0	0	2
	Radius	2	0	0	2
	Foot	1	0	0	1

* There was no grade III BCIS; BCIS, bone cement implantation syndrome; N/A, not applicable.

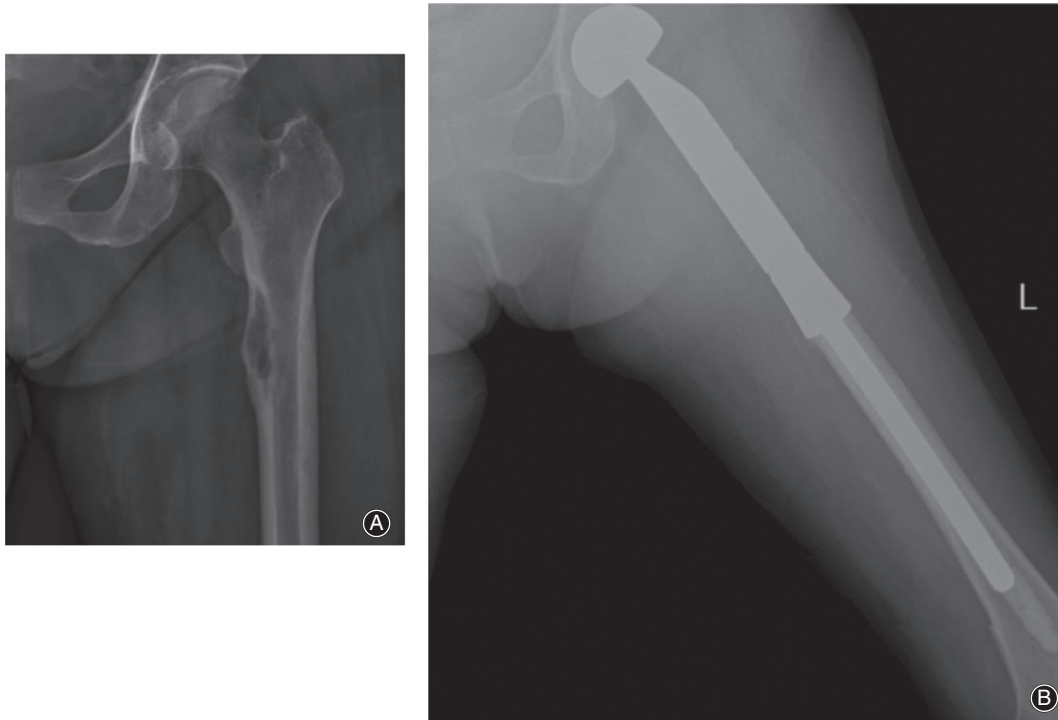


Fig. 3 A 72-year-old woman with pleomorphic sarcoma of the left femur. (A) Preoperative plain film. (B) Status after wide excision and custom-made bipolar hemiarthroplasty.

reported incidence. The possible reason is that the bony environment is usually hypervascular with aggressive bone tumors. This makes the medullary content and cement particles highly accessible to the circulation. This effect may lower the threshold of intramedullary pressure because the prosthesis group did not have increased BCIS occurrence in this study. Therefore, appropriate anesthesia preparation and attentive hemodynamic monitoring are necessary before and during cementation in bone tumor surgeries regardless of the presence of prostheses. In addition, preexisting lung cancer or metastasis was found to be a risk factor for BCIS in bone tumor surgeries; they increase the incidence to 40%. In previous studies on arthroplasties, impaired cardiopulmonary function has also been shown to a risk factor^{5,10,17}. In our experience of treating bone tumors, pulmonary metastasis is not unusual once there is bone metastasis. Therefore, BCIS can affect many patients when treating bone malignancies. Careful preoperative staging is very important to determine the risk before surgery.

Strategies to prevent or lessen the severity of BCIS have been proposed in the published literature¹⁸⁻²¹. By venting the medullary canal in a modified way and giving antihistamine before cementation, no grade III BCIS has been reported, and most BCIS cases were grade I in this study. Previous studies have shown that the peak and mean pressures can reach 881 and 229 mmHg, respectively, for cementation in unvented femurs. The pressure increases by 5 to

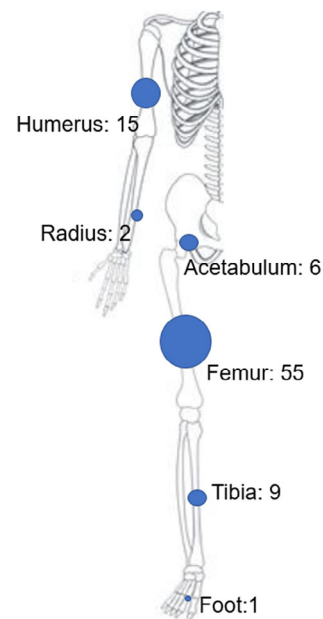


Fig. 4 Locations of the bone tumor surgeries.

10 times with prosthesis insertion^{2,22}. The elevated intramedullary pressure can increase the risk and severity of BCIS. Venting the canal by drilling a hole in the bone may

TABLE 2 Comparison of BCIS incidence in patients with and without possible risk factors

Indexes	Bone cement implantation syndrome		P-value
	Yes	No	
Age (≥ 60 years)			0.333
Yes	13	28	
No	10	37	
Arthroplasty			0.624
Yes	10	24	
No	13	41	
IM device*			0.809
Yes	10	26	
No	13	39	
Lung morbidity†			0.008
Yes	16	24	
No	7	41	
Blood loss (≥ 200 mL)			0.141
Yes	13	24	
No	10	41	
Tumor location			0.622
Femur	16	41	
Non-femur	7	24	
Gender			0.326
Male	11	23	
Female	12	42	

* Any intramedullary device, including prosthesis and intramedullary nail; † Primary lung cancer or lung metastasis; BCIS, bone cement implantation syndrome.

significantly lower the pressure¹⁹. We modified the venting method by inserting a soft tube distally with a constant suction force to remove trapped air and medullary contents and lower the intramedullary pressure. This method produces a negative pressure and also helps the bone cement to fill the canal easily and more evenly. In addition to the intramedullary pressure, physiological response plays an important role in BCIS. A significant increase in plasma histamine concentration after cementation has been reported²⁰. Although controversy exists^{23,24}, antihistamines may reduce cardiovascular reactions during cementation²⁰. Because patient-related risk factors such as age, cardiopulmonary function, osteoporosis, and preexisting pulmonary hypertension are unchangeable facts, surgeons need to implement strategies to lessen the adverse effects.

In the present study, the lowest blood pressure occurred within 10 min for most BCIS cases (87.0%). Nine grade I BCIS courses were self-limiting. A peripheral vasoconstrictor was administered for 10 grade I patients and every grade II patient. Interestingly, only 1 BCIS case was characterized by desaturation in the present study. This differs from previous studies on cemented arthroplasties^{2,10,25}. The possible inference is that the medullary composition in bone tumors is largely different from that of healthy bones. In addition, delicate tumor curettage and thorough irrigation were performed prior to cementation in bone tumor

surgeries, which created a larger medullary cavity. Both factors may affect the content of emboli after cementation alone or following prosthesis insertion. Further studies are required to elucidate the underlying mechanism.

The present study has several limitations. First, the types of bone tumor differed among the patients, and different tumor types may affect the incidence of BCIS. However, this study still provided useful information about BCIS in bone tumor surgeries. Further studies may be needed to investigate BCIS in certain tumor types. Second, we could only share our clinical experience to prevent or lessen the severity of BCIS. Further studies are necessary to prove its clinical effectiveness. Finally, we could not analyze delayed presentation of BCIS, which has been previously reported²⁶. Prospective studies are needed to obtain more thorough information.

Conclusion

Bone cement implantation syndrome is not unusual in bone tumor surgeries, even without prosthesis insertion. Its incidence is similar to that of cemented arthroplasties. Having preexisting lung malignancy further increases the risk. Surgeons and anesthesiologists should keep an eye out or for this condition and be well prepared before and during the operation.

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