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Selective embolization of the internal iliac arteries for the treatment of intractable hemorrhage in children with malignancies

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Purpose: Acute internal hemorrhage is an occasionally life-threatening complication in pediatric cancer patients. Many therapeutic approaches have been used to control bleeding with various degrees of success. In this study, we evaluated the efficacy of selective internal iliac artery embolization for controlling acute intractable bleeding in children with malignancies.

Methods: We retrospectively evaluated the cases of 6 children with various malignancies (acute lymphoblastic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, T-cell prolymphocytic leukemia, Langerhans cell histiocytosis, and rhabdomyosarcoma), who had undergone selective arterial embolization (SAE) of the internal iliac artery at the Chonnam National University Hwasun Hospital between January 2004 and December 2009. SAE was performed by an interventional radiologist using Gelfoam® and/or Tornado® coils.

Results: The patients were 5 boys and 1 girl with median age of 6.9 years (range, 0.7–14.8 years) at the time of SAE. SAE was performed once in 4 patients and twice in 2, and the procedure was unilateral in 2 and bilateral in 4. The causes of hemorrhage were as follows: hemorrhagic cystitis (HC) in 3 patients, procedure-related internal iliac artery injuries in 2 patients, and tumor rupture in 1 patient. Initial attempt at conservative management was unsuccessful. Of the 6 patients, 5 (83.3%) showed improvement after SAE without complications.

Conclusion: SAE may be a safe and effective procedure for controlling acute intractable hemorrhage in pediatric malignancy patients. This procedure may obviate the need for surgery, which carries an attendant risk of morbidity and mortality in cancer patients with critical conditions.

Key words: Therapeutic embolization, Pediatric patient, Neoplasms

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Introduction

Acute hemorrhage can be a life-threatening complication in cancer patients and is a significant cause of morbidity and mortality[1-3]. It occurs in approximately 6-10% of cancer patients[3, 4]. Medical treatment for acute hemorrhage includes compression, drug therapy, blood transfusion, hydration and other supportive care. Other therapeutic strategies include radiotherapy, surgical therapy, such as vessel ligation or the resection of hemorrhagic tissue[3]. However, the inherent morbidity of the surgical procedures in debilitated patients, and the efficacy of medical treatment may make this approach problematic[3, 5]. Therefore, selective arterial embolization (SAE) is increasingly preferred as a therapeutic procedure for controlling hemorrhage, normally in adults. Furthermore, SAE is applied increasingly in conditions, such as hemorrhage, arterio-venous malformation, arteriovenous fistula, aneurysm and tumors[6-9]. However, SAE is performed less frequently in pediatric patients. This may be secondary to the stress of the procedure itself, lack of doctor's experience and possible long-term side effects[8]. Therefore, the aim of this retrospective study was to determine the efficacy and safety of SAE in the treatment of intractable hemorrhage in pediatric patients with malignancies.

Materials and methods

From January 2004 to December 2009, the medical records of 6 pediatric patients with a malignancy who underwent SAE of the internal iliac artery at Chonnam National University Hwasun Hospital were analyzed retrospectively. All patients presented with intractable hemorrhage, which had not responded to earlier conservative measures. Data on the following items were documented: general characteristics, underlying disease, treatment of underlying disease, number of SAE performed, response to SAE, side effects related to the procedure and follow-up duration. The complications related to the SAE procedure, including nausea, vomiting, fever, development of hematoma, infection, vascular perforation, ischemia, and pain were also examined. SAE was performed by an interventional radiologist under fluoroscopic guidance after patients had been appropriately sedated. The Gelfoam® (Pfizer Inc., New York, NY, USA) and/or Tornado® coils (Cook Inc., Bloomington, IN, USA) were used as embolic agents.

In cases of hemorrhagic cystitis (HC), the onset time and duration of HC before SAE were reviewed. HC was graded according to the criteria previously reported[9]: grade 1, continuation of microscopic hematuria for more than 2 days; grade 2, gross hematuria; grade 3, gross hematuria with a clot; grade 4, gross hematuria with renal impairment due to urinary tract obstruction with a clot.

Results

1. General characteristics of the patients

Six patients with various malignancies were enrolled in this study: acute lymphocytic leukemia, acute myelogenous leukemia, chronic myelogenous leukemia, T-cell prolymphocytic leukemia, Langerhans cell histiocytosis and rhabdomyosarcoma. The median age was 6.9 years (range, 0.7–14.8 years). Five were males (83.3%). The median follow-up period was 9.5 months (range, 0.3–24 months). The patient with rhabdomyosarcoma was treated by chemotherapy consisting of vincristine, dactinomycin and cyclophosphamide. The other 5 patients (83.3%) received allogeneic hematopoietic stem cell transplantation (HSCT). The stem cell sources for transplantation were umbilical cord blood, unrelated bone marrow and unrelated peripheral blood for 1 patient each and haploidentical bone marrow for 2 patients (Table 1).

2. The causes of hemorrhage and initial treatment

In 3 of the 6 patients (50%), the cause of the hemorrhage was HC, which developed after allogeneic HSCT. Two patients (33.3%)

Table 1. General Patient Characteristics and the Cause of Internal Pelvic Cavity Hemorrhage

UPN	Gender	Age (years)	Underlying disease	Treatment for underlying disease	HSCT donor	Cause of internal pelvic cavity hemorrhage
1	M	14.8	AML	HSCT	Haploidentical BM+ Mismatched UCB	HC
2	M	9.4	CML	HSCT	Matched unrelated BM	HC
3	M	10.2	T-PLL	HSCT	Haploidentical BM	HC
4	M	1.8	LCH	HSCT	Matched UCB	Injury of Rt. internal iliac artery
5	F	0.7	ALL	HSCT	Unrelated matched PB	Injury of Lt. internal iliac artery
6	M	7.6	Rhabdomyosarcoma	IRS-IV chemotherapy	(-)	Rupture of tumor

Abbreviations: UPN, unique patient number; M, male; F, female; AML, acute myelogenous leukemia; CML, chronic myelogenous leukemia; T-PLL, T-cell prolymphocytic leukemia; ALL, acute lymphocytic leukemia; LCH, Langerhans cell histiocytosis; IRS, Inter-group rhabdomyosarcoma study; HSCT, hematopoietic stem cell transplantation; BM, bone marrow; UCB, umbilical cord blood; PB, peripheral blood; HC, hemorrhagic cystitis.

had an iatrogenic iliac artery injury and the last patient had a tumor rupture (Table 1). For the children with HC, the median day of onset was 15 days after allogeneic HSCT (range, 13–47 days), and the median duration of HC was 15 days (range, 9–33 days) before SAE. Two patients had grade 3 HC and 1 had grade 4. For transplant conditioning, intravenous busulfan and cyclophosphamide were used in 2 patients with HC, and cyclophosphamide and total body irradiation were used in 1. Two patients were positive for both adenovirus type 2 and the BK virus in blood and urine, which are associated with HC.

Before SAE was performed, numerous therapeutic approaches had been attempted. In cases of HC, all the measures, such as forced hydration over 3000 mL/m^2 per day, platelet or red cell and fresh frozen plasma transfusions, Foley catheter insertion, instillation of sodium hyaluronate within the bladder, diuretics and antiviral agents were not able to control the bleeding (Table 2). Three patients with refractory hemorrhage due to internal iliac artery injury or tumor rupture did not respond to medical treatments including hydration, administration of blood products, inotropic agents and vitamin K administration, resulting in hypotension and markedly decreased hemoglobin (Hb) concentration (mean value, 5.1 g/dL). Surgery was generally not attempted because of high risk conditions, such as, low platelet counts less than 20,000/mm^3, prolonged PT/PTT and decreased neutrophil counts. In addition, active bleeding sites were able to be localized by angiography. Thus, SAE was attempted instead of surgery.

3. Results of selective internal iliac artery embolization

Of the 6 patients, 4 (66.7%) underwent bilateral SAE, and 2 (33.3%) had unilateral SAE. Gelfoam® and/or Tornado® coils were used for embolization (Gelfoam® alone in 4 patients; Tornado® coils alone in 1; both Gelfoam® and Tornado® coils in 1). Five (83.3%) patients responded to SAE initially but repeat SAE was needed because the hemorrhage reappeared in 2 patients. There were no more recurrences after the repeated procedures. After SAE, it took a median interval of 6 days (range, 3-12 days) to control the bleeding. One patient who did not respond to SAE in addition to supportive measures died of hypotension caused by the uncontrolled bleeding 3 days after the procedure. During follow-up period, two more patients died from causes not related to bleeding: chronic graft-versus-host disease 14 months after HSCT; and sepsis 3 months after transplantation.

There were no significant immediate or late side effects associated with the SAE procedures, such as nausea, vomiting, fever, infection,

Table 2. Characteristics of Patients with Hemorrhagic Cystitis

UPN	HC (Grade)	HC onset from HSCT (days)	HC duration before SAE (days)	Conditioning regimen	Virus		Initial treatment
					Adenovirus Type II	BK Virus	
1	4	13	9	Busulfan (iv) Cyclophosphamide	Blood PCR Urine culture	Blood/Urine PCR	Supportive care SH instillation
2	4	47	33	Busulfan (iv) Cyclophosphamide	Blood PCR	(-)	Supportive care
3	3	15	15	TBI Cyclophosphamide	Blood PCR	Urine PCR/culture	Supportive care SH instillation
Median		15	15				

Supportive care: hydration, transfusion, Foley catheter insertion, diuretics
Abbreviations: UPN, unique patient number; HC, hemorrhagic cystitis; SAE, selective arterial embolization; HSCT, hematopoietic stem cell transplant; TBI, total body irradiation; PCR, polymerase chain reaction; SH, sodium hyaluronate.

Table 3. Outcomes of Selective Internal Iliac Artery Embolization

UPN	Site	Materials	Time to response (days)	Follow-up duration (months)	Number of procedures (times)	Side effect	Outcome
1	Bilateral	Gelfoam®	7	7	2	No	Controlled
2	Bilateral	Gelfoam®	12	24	1	No	Controlled
3	Bilateral	Gelfoam®	5	3	2	No	Controlled
4	Unilateral	Tornado® coils	6	14	1	No	Controlled
5	Unilateral	Gelfoam®	NR	0.3	1	No	Uncontrolled
6	Bilateral	Gelfoam® Tornado® coils	3	12	1	No	Controlled
Median			6	9.5			

Abbreviations: UPN, Unique patient number; NR, no response.

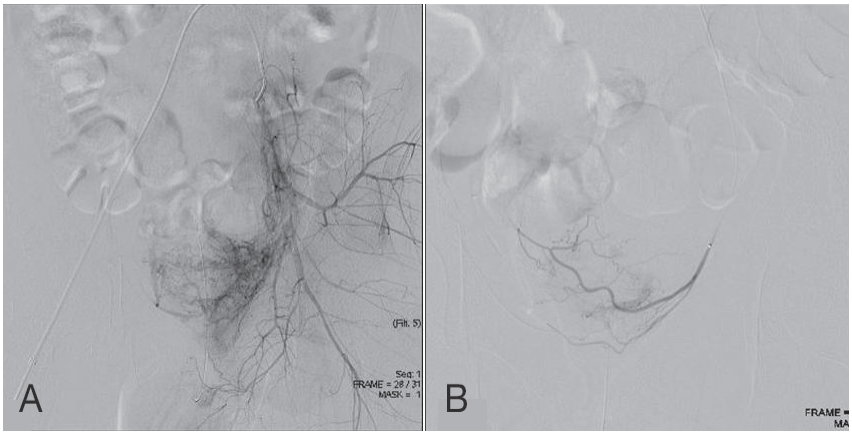

Fig. 1. Image of the vesical arteries before and after embolization (Patient 1). A) Selective angiography of the right internal iliac artery before embolization shows prominent hypervascularization at the level of the left vesical arteries. B) Angiography findings of the internal iliac artery after embolization with Gelfoam® show improved hypervascularization of the left vesical arteries.

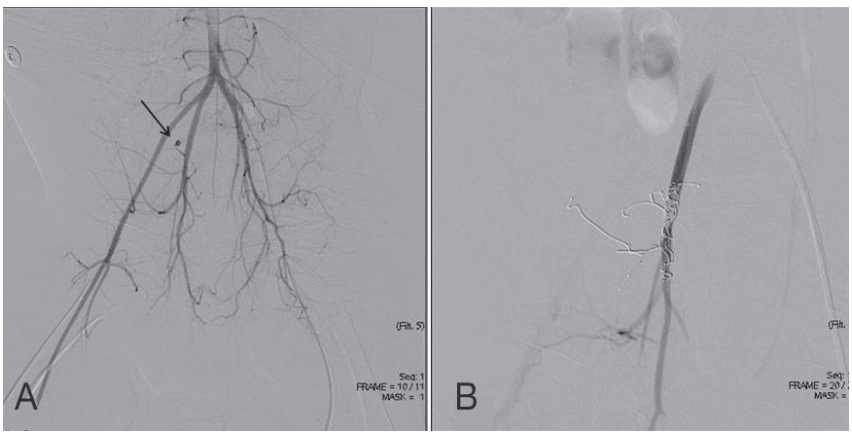

Fig. 2. Angiography showing the right internal iliac artery in patient 4. A) Selective angiography revealed active bleeding from the right internal iliac artery (arrow) before embolization. B) The bleeding was markedly reduced after selective internal iliac artery embolization with multiple microcoils.

hematoma, vascular perforation, ischemia, paresthesia, claudication and pain in buttock or procedure site (Table 3, Fig. 1-3).

Discussion

In cancer patients, acute hemorrhage is a well-known complication that is associated with high morbidity and mortality[3, 5]. Various therapeutic approaches have been attempted including intensive supportive care with compression, hydration, blood transfusion, drug therapy and surgical care[3, 5, 9]. However, there is no specific and effective treatment. Some patients do not respond to medical care[5, 11]. Surgical treatment is the ultimate therapeutic approach for controlling refractory hemorrhage but is associated with high morbidity and mortality because of the poor general condition of the cancer patients or underlying disease as well as the complications arising from treatment of the underlying disease[2, 12]. SAE is a minimally invasive procedure with a lower rate of morbidity, having obvious advantages over surgery. Therefore, it is an accepted approach and is used more often to treat intractable hemorrhage[5, 12, 13].

The SAE of the internal iliac artery was first reported in 1973 as a mean to control the bleeding associated with pelvic fractures[16]. In 1974, Halad and Myging[17] were the first to describe the use of SAE of the internal iliac artery to control HC secondary to radiation therapy for bladder cancer. Since then, the indications for SAE of the internal iliac artery to control intractable hemorrhage have widened[18], including the management of hemorrhage resulting from trauma, iatrogenic or obstetrical causes, and pelvic or urological neoplasm[2, 5, 9, 14, 15, 19]. In this study, all 6 children had an acute pelvic cavity hemorrhage resulting from HC, iatrogenic vascular injuries or rupture of a retroperitoneal tumor, which could not be controlled

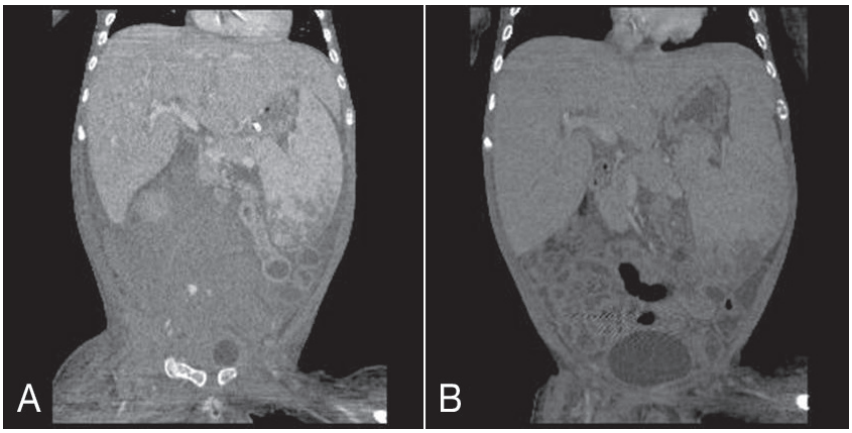

Fig. 3. A) Abdominal computerized tomography scan showing a large retroperitoneal hematoma and active bleeding in the iliopsoas area of the right pelvis due to an iatrogenic internal arterial injury (patient 4). B) Fourteen days after selective internal arterial embolization, right pelvic and lower abdominal retroperitoneal hematoma was markedly reabsorbed.

by medical treatment. SAE of the internal iliac artery was attempted as surgical therapy was impossible due to the poor general condition of the patients and their low platelet counts. The bleeding was brought under control in 5 of the 6 patients (83.3%) after SAE. The remaining one patient died of uncontrollable bleeding despite the SAE procedure because of poor general condition associated with underlying hypotensive shock. These results are similar to those of previous studies showing the efficacy of SAE[2, 5, 9, 11, 12, 14, 15].

According to Han et al.[5], 10 patients with grade 3–4 HC following allogeneic HSCT underwent SAE of the internal iliac artery. The unsuccessful medical treatments performed before SAE included the following: hyperhydration, blood transfusion, intravesical instillation of granulocyte, monocyte-colony stimulating factor, bladder irrigation, and antiviral agents. Eight patients responded to SAE within 15 days. Surgical treatment, such as cauterization with cystoscopy or cystectomy, was not necessary[5]. There were several reports about successful SAE; 2 adults with HC who received an allogeneic HSCT[2] and 6 patients (mean age 80 years) with bladder or prostate carcinoma, who all patients were embolized successfully within 8 days and without complications[12]. SAE was also performed successfully in instances of severe postpartum hemorrhage, pelvic fracture or trauma[15, 20].

During the follow-up period, 2 children underwent a second SAE due to a relapse of the hemorrhage but there were no recurrences after the second procedure. This finding is comparable to that of other studies. In the recent study, 6 adult patients were reported who underwent selective embolization of the bladder arteries for treatment of incoercible hematuria. All patients with hematuria responded within 48 hours after the procedure, but two patients had a recurrence of the bleeding that required a second procedure[21]. In 2007 report, among 7 patients with intractable bladder hemorrhage who underwent internal iliac artery embolization, but bleeding was controlled permanently in 4 (57%) patients and a second embolization was required in 1 patient[22]. In the other study of 44 patients with an advanced pelvic tumor (mean age 79 years; range 51–95), the initial embolization produced complete control of the bleeding in 36 of the 44 patients (82%). However, subsequent arterial embolization was required in 5 patients (11%) and was successful[23]. In addition, this procedure can also be used to diagnose and treat aneurysms, arterio-venous malformation or tumors[6, 24, 25].

However, SAE is performed less frequently in children, particularly in pediatric cancer patients[6-8, 24]. A search of the literature on SAE in the pediatric population revealed only a few reports. Legge et al.[8] performed SAE in 5 pediatric patients suffering from hypersplenism, hemobilia, sigmoid hemangioma and aneurysmal bone cysts in the iliac bone. Embolization provided definitive treatment in all cases without complications. Bilateral internal pudendal artery embolization was performed for intractable priapism in a 14- year-old boy with chronic myelogenous leukemia[7]. A month-old baby with a mycotic internal iliac aneurysm underwent successful coil embolization[6]. Erkan[24] also carried out SAE for the treatment of pelvic aneurysmal bone cysts in two children. Along with the reported cases, our data on 6 patients support the effectiveness of SAE for the treatment of refractory hemorrhage in children with a malignancy.

A range of materials have been used for embolization including muscle, autologous clots, gelatin, coil, and balloon[26]. Gelfoam® and/or coil were used for embolization. Gelfoam®, a gelatin sponge, is a water-insoluble hemostatic material that is easy to handle. It is biodegradable or absorbable, and the vessel recanalizes within a few weeks. Consequently, it has fewer complications of vascular occlusion than using coil or surgical vessel ligation[8, 26]. A coil is effective

either for fast flowing vessels or when needed to occlude a vessel permanently[23].

The complications associated with SAE include nausea, vomiting, fever, infection, pain, hematoma, vascular perforation, chills, claudication, erectile dysfunction, urinary retention, and paresthesia[5, 12, 17, 26-28]. However, serious side effects are rare[26, 29] and can be reduced by precise placement of the coil or Gelfoam® to preserve tissue perfusion[12, 21, 30]. In the current study, there were no side effects encountered during the follow-up period, but it will be necessary to carefully observe these patients for possible long-term complications, such as claudication, sexual dysfunction and paresthesia[26-28].

In conclusion, bleeding was controlled in 5 out of 6 children (83.3%) after SAE of the internal iliac artery without side effects. The results suggest that SAE of the internal iliac artery is an effective and safe therapeutic approach in pediatric cancer patients with hemorrhage who do not respond to supportive care. SAE can also reduce the patients` exposure to the risks inherent with the surgical procedures. Further clinical trials involving a larger number of patients will be needed to evaluate the potential role, safety and possible long-term side effects of SAE in children with malignancies.

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