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ORIGINAL ARTICLE

Superselective vesical artery embolization in the management of intractable hematuria secondary to hemorrhagic cystitis

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Abstract

Purpose To evaluate the efficacy and outcome of superselective vesical arterial embolization in the management of severe intractable hematuria secondary to hemorrhagic cystitis.

Materials and methods We retrospectively reviewed the medical records of nine patients with severe intractable hematuria treated with superselective vesical artery embolization at our institution between March 2003 and February 2015. There were six males and three females with a mean age of 56.1 years. Seven patients had transitional cell carcinoma (TCC) of urinary bladder and had undergone transurethral resection of bladder tumor and pelvic radiotherapy. One patient had synchronous renal pelvis and bladder TCC. One patient had aortoarteritis and was receiving cyclophosphamide therapy and another patient had carcinoma cervix post-pelvic radiotherapy. Following the failure of conservative management, superselective vesical artery catheterization and embolization was performed with 300–500-μ PVA particles in all patients. Coil embolization of inferior gluteal artery followed by particle embolization of vesical arteries was done in one patient in whom superior, inferior vesical and inferior gluteal arteries were arising as a trifurcation.

Results The technical success rate was 100% with complete cessation of hematuria within 48 h in all patients. No significant complications were noted, except for post-embolization syndrome in one patient, which improved on symptomatic treatment. During a mean follow-up period of 14.45 months (ranging from 3–28 months), one patient had mild recurrent hematuria (at 2 months) which resolved spontaneously.

Conclusions Superselective vesical artery embolization is a safe and effective procedure in controlling intractable life-threatening hematuria in a select group of patients who have failed conventional treatment protocols. This procedure may be considered as the treatment of choice since it usually obviates the need for emergency surgery in these severely ill patients.

Keywords Embolization · Therapeutic · Urinary bladder · Hematuria · Cystitis

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Abbreviations

TCC	Transitional cell carcinoma
TURBT	Transurethral resection of bladder tumor
HC	Hemorrhagic cystitis
TA	Takayasu's arteritis
IV	Intravenous
IIA	Internal iliac artery

Introduction

Hemorrhagic cystitis (HC) is defined as acute or insidious diffuse vesical bleeding, with many causes, e.g., chemical toxins (alkylating agents), immune agents, pelvic irradiation, viruses and idiopathic causes. Most cases of hemorrhagic cystitis are secondary to pelvic radiotherapy and chemotherapeutic agents. Less commonly, hematuria may

be an idiopathic response to steroids and may also be seen in children after certain viral infections and in immune-compromised states [1]. According to the amount of hematuria, HC is graded as mild, moderate or severe. Severe intractable hematuria secondary to HC is a potentially life-threatening event that raises major therapeutic challenges [1, 2]. In many patients, bleeding cannot be adequately controlled by conservative measures, such as irrigation with formalin, silver nitrate or alum solution, intravesical hydrostatic pressure, hyperbaric oxygen or endoscopic diathermy, and radical surgery is not always feasible because of high operative risk and associated co-morbidities [3–5]. Angiography with embolization is emerging as a safe and effective measure to control bleeding in this select group of patients. However, only a few reports and small case series are available focusing on the selective embolization of vesical arteries in the management of intractable hematuria secondary to HC [2 ,5–9]. In the present study, we report our experience of superselective embolization of the vesical arteries in nine patients who had severe life-threatening hematuria from HC and evaluate the clinical efficacy, safety and outcome of this procedure in managing such patients.

Materials and methods

We retrospectively reviewed the medical records of nine patients who underwent superselective vesical arterial embolization for severe intractable hematuria secondary to HC, in our hospital, between March 2003 and February 2015, after obtaining approval of institutional ethics committee (Table 1). There were six male and three female patients, with a mean age of 56.1 years (range 21–76 years). Seven patients had transitional cell carcinoma (TCC) of urinary bladder and had undergone transurethral resection of bladder tumor (TURBT) and pelvic radiotherapy. One patient had synchronous renal pelvis and bladder TCC. One patient was diagnosed with Takayasu's arteritis (TA) (aortoarteritis type-3) and was receiving cyclophosphamide and steroid therapy, and another patient had carcinoma cervix post-pelvic radiotherapy, as summarized in Table 1.

HC was diagnosed on the basis of clinical history, physical examination and cystoscopy findings. HC was graded as previously reported [10], and all patients in the present series had grade 3 or 4 HC. Before embolization, a mean of 9 units of packed red blood cells (range 0–24) were transfused. 1 patient refused transfusion of blood products on religious grounds, and plasma expanders were transfused, as needed. The mean hemoglobin was 7.1 gm/dl (range 5.2–11.1 gm/dl) and the coagulation parameters were normal in our patient cohort, at the time of hospital admission.

Cystoscopy was performed prior to embolization in all patients. In patients with TCC, there was no recurrence of the primary tumor and no discrete bleeding site was observed. However, telangiectasias were seen in all patients (Fig. 1). Urinalysis (routine and microscopic) was normal in all patients, with sterile culture, and urine cytology was negative for malignant cells.

Technique

All patients were initially managed conservatively with general measures such as bladder irrigation with saline, alum and formalin, all of which are known to control hematuria—as per urology protocol for such patients. Initial control on hematuria was obtained in eight out of nine patients but the relief was short term (1–4 days), following which the hematuria recurred. These measures were of no relief in one patient (case-2), Table 1. Vascular embolization was subsequently performed for these patients. All patients were counseled about the potential risks of the procedure and written informed consent was obtained. Pre-procedural intravenous (IV) antibiotics were administered to all patients. Under all aseptic measures and under local anesthesia, right femoral arterial retrograde approach was taken in all patients, and a 6 F arterial access sheath was placed. A 5 F pigtail catheter (Cook Bloomington, IN, USA) was positioned in the lower abdominal aorta and baseline pelvic aortogram performed on a monoplane DSA equipment (G.E. Medical Systems, Milwaukee, WI, USA). Internal iliac arteries (IIA) were then selectively catheterized using 5 F Cobra catheter (Cook Bloomington, IN, USA). Ipsilateral IIA catheterization was performed using the same catheter by Waltman's loop technique. IIA angiography was then performed to identify the abnormal vessels supplying the urinary bladder. In two patients, microcatheter, microferret 2.5F (Cook Bloomington, IN, USA), mounted over a 0.014-inch micro guidewire was used for superselective catheterization of vesical arteries. Arteriography was then performed which showed hypervascularity and contrast blush in the region of urinary bladder (Figs. 2a, b, 3a, b). No discrete bleeding point or contrast extravasation was appreciated. Under continuous X-ray fluoroscopy, the embolization was then performed. Embolic agents used, arteries embolized and other technical details are summarized in Table 2. The goal of the procedure was complete embolization of the vesicular branches not necessarily the entire internal iliac vessel. All patients were advised lower limb immobilization for 6 h after the procedure.

Results and follow-up

Post-embolization pelvic angiography revealed pruning of the arteries supplying the urinary bladder, with preservation of the remaining internal ilac artery branches (Figs. 2c. d, 3c,

Table 1 Summary of demographics for patients with Hemorrhagic Cystitis

Case	Age/sex	Primary disease	Treatment given	Mean radiation dose	Interval between RT and onset of hematuria	HC grade	Cystoscopy	Conservative M/M
1.	37/F	Ca cervix	Total abdominal hysterectomy & Radiotherapy	50 Gy/25 fx 0.5 weeks to whole pelvis + 6 Gy × 2 fx to vault by brachytherapy	15 months	3	Urethra—N Bladder mucosa—pale, frosted B/L ureteric orifices—N efflux	Bladder irrigation, saline irrigation, 3 intravesical instillations of (1%) alum
2.	76/M	Ca bladder	TURBT twice & Radiotherapy	RT details not available	24 months	4	No active bleeding, no growth. Diffuse telangiectasis present.	Bladder irrigation, saline irrigation, 1 intravesical alum (1%), 1 formalin (1%) instillation
3.	21/F	Takayasu's arteritis	Cyclophosphamide & Steroids	N.A.	N.A.	3	Urethra—N Bladder mucosa—N B/L ureteric orifices—N efflux	Bladder irrigation, saline irrigation, 2 intravesical alum (1%), 2 formalin (1%) instillations
4.	53/M	Ca bladder	TURBT & Radiotherapy	RT details not available	17 months	3	No active bleeding, no growth. Scattered telangiectasis	Bladder irrigation, saline irrigation, 3 intravesical alum (1%), 2 formalin (1%) instillations
5.	45/M	Ca bladder	TURBT & Radiotherapy	(2 Gy/d × 5 day) × 5 weeks for a total of 50 Gy	20 months	3	No active bleeding, no growth. Few telangiectatic spots	Bladder irrigation, saline irrigation, 2 intravesical alum (1%), 2 formalin (1%) instillations
6.	76/M	Rt. renal pelvis & ureteric TCC	Rt. nephroureterectomy & partial Cystectomy, BCG & Radiotherapy	(2 Gy/d × 5 day) × 5 weeks for a total of 50 Gy	12 months	4	No active bleeding, no growth, telangiectasis hyperemia & bullous edema of left lateral wall	Bladder irrigation, saline irrigation, 1 intravesical alum (1%), 2 AgNO3 instillations
7.	67/M	Ca bladder	TURBT & Radiotherapy	(2 Gy/d × 5 day) × 5 weeks for a total of 50 Gy	18 months	3	No active bleeding, no growth. Few telangiectatic spots	Bladder irrigation, saline irrigation, 2 intravesical alum (1%), 2 formalin (1%) instillations
8.	71/M	Ca bladder	TURBT & Radiotherapy	(2 Gy/d × 5 day) × 5 weeks for a total of 50 Gy	14 months	3	No active bleeding, no growth. Few telangiectatic spots	Bladder irrigation, saline irrigation, 2 intravesical alum (1%), 2 formalin (1%) instillations
9.	59/F	Ca bladder	TURBT & Radiotherapy	(2 Gy/d × 5 day) × 5 weeks for a total of 50 Gy	16 months	3	No active bleeding, no growth. Few telangiectatic spots	Bladder irrigation, saline irrigation, 2 intravesical alum (1%), 2 formalin (1%) instillations

HC hemorrhagic cystitis, *M/M* management, *B/L* bilateral, *N* normal, *RT* radiation therapy, *TURBT* trans urethral resection of bladder tumor, *N.A.* not applicable, *TCC* transitional cell carcinoma

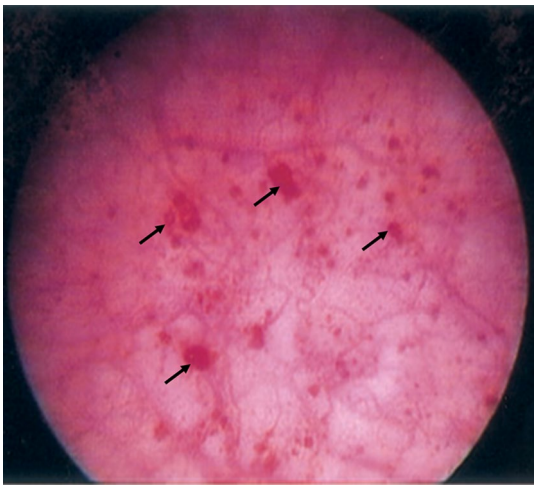

Fig. 1 **37**-Year-old woman with carcinoma cervix and radiation cystitis (case 1). Cystoscopy demonstrating multiple hyperemic telangiectatic areas (black arrows)

d). Bladder catheterization was maintained, and once clear urine was confirmed catheter was removed in an average time of 2.5 days. There was complete control of hematuria (macroscopically clear urine) in all nine patients within 48 h post-procedure. No patient required blood transfusion after the procedure. In case 2, hematuria recurred after 2 months of the procedure. Cystoscopy demonstrated no evidence of hyperemia, telangiectasias, or bullous edema that was present pre-procedure. In this patient, hematuria spontaneously resolved without any active intervention.

There were no major complications, with no reported bladder or sexual dysfunction. Two patients complained of dull deep gluteal pain, which resolved in a few days requiring no medication while one patient had moderate buttock and thigh pain which required analgesics. One patient developed fever 24 h after the procedure. This patient recovered fully within 2 days with symptomatic treatment. All patients were discharged, in good general condition, with no hematuria and with normal hemoglobin values. All patients were followed up regularly to verify the absence of macroscopic hematuria, with follow-up period ranging from 3

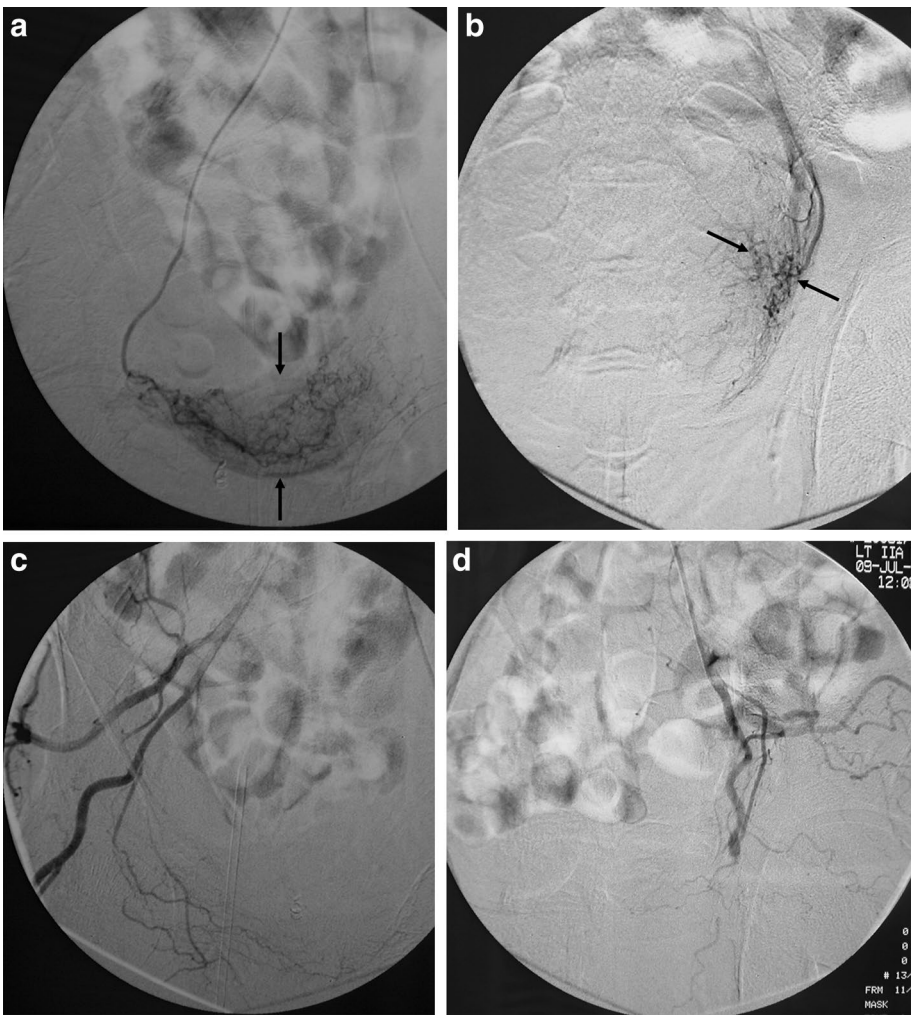

Fig. 2 **37**-Year-old woman with carcinoma cervix and radiation cystitis (case 1). Superselective right (**a**) and left (**b**) vesical artery angiograms showing hypervascularity and contrast blush in the region of urinary bladder (black arrows), with no discrete bleeding point or contrast extravasation. Post-embolization right (**c**) and left (**d**) vesical artery angiogram revealed pruning of the arteries supplying the bladder, with preservation of the remaining internal ilac artery branches

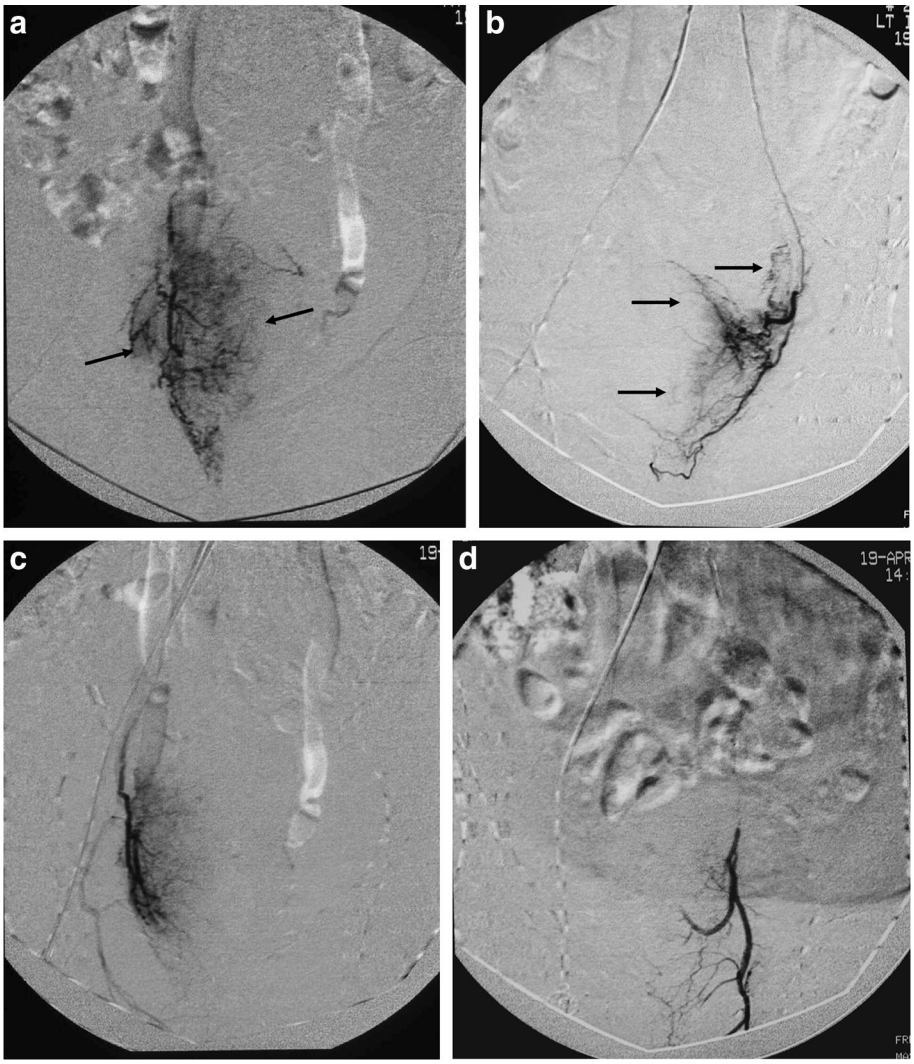

Fig. 3 45-Year-old male with carcinoma of the urinary bladder, post-TURBT and radiotherapy (case 5). Superselective right (**a**) and left (**b**) vesical artery angiograms showing hypervascularity and contrast blush in the region of urinary bladder (black arrows), with no discrete bleeding point or contrast extravasation. Post-embolization right (**c**) and left (**d**) vesical artery angiogram revealed pruning of the arteries supplying the bladder, with preservation of the remaining internal ilac artery branches

to 28 months (mean 14.45 months). The longest follow-up available was in $n=2$ patients (case 2 and case 3), with follow-up period of more than 2 years. In $n=2$ patients (case 4 and case 9), the follow-up period was about 1½ years. In $n=3$ patients (case 5, case 7 and case 8), the follow-up period was about 1 year, and in $n=2$ patients (case 1 and case 6) the follow-up period was the shortest, less than 6 months, as detailed in Table 2. The two patients with shortest follow-up (case 1 and case 6) did not visit our hospital during the follow-up period, as they transferred their care to a different institution.

Discussion

Our study demonstrates the safety and efficacy of superselective vesical artery embolization in nine patients with intractable life-threatening hematuria who have failed prior conventional treatment protocols. There was complete control of hematuria in all nine patients within 48 h post-procedure with no significant post-procedural complications.

HC is a known complication of pelvic irradiation, administration of chemotherapeutic agents, e.g., cyclophosphamide, etc., and occurs as an end result of obliterative endarteritis, which causes mucosal sloughing, vascular telangiectasis and ulcerations [1,11–13]. The cytology and histology of cyclophosphamide toxicity and irradiated patients is the same [1,14,15]. Painless persistent profuse hematuria is the common denominator, which at times becomes life threatening, may not respond to conservative management and require aggressive intervention.

Vela-Ojeda et al. [10] classified HC in four grades. In grade 1, there is microscopic hematuria on more than two consecutive days; grade 2, macroscopic hematuria; grade 3, macroscopic hematuria with clots; grade 4, macroscopic hematuria with clots and impaired renal function secondary to urinary tract obstruction. Clinically, De Vries and Freiha divided bladder hemorrhage into three categories: mild,

Table 2 Summary of procedural and other technical details

Case	Internal Iliac branches occluded		Agent used	Complications	Post-embolization result	Bleeding free follow-up period
	Right	Left				
1.	Superselective vesical artery	Superselective vesical artery	PVA particles 300–500 µ	Major- none moderate buttock and thigh pain	One episode of hematuria that cleared spontaneously	5 months
2.	Superselective vesical artery	Superselective vesical artery	1-PVA particles 300–500 µ	Major- none dull deep gluteal pain	Complete cessation of hematuria	26 months
3.	Superselective vesical artery feeders	Superselective vesical artery	PVA particles 300–500 µ	None	Complete cessation of hematuria	28 months
4.	Superselective vesical artery	Superselective vesical artery	PVA particles 300–500 µ	Major- none mild fever	Complete cessation of hematuria	17 months
5.	Superselective vesical artery	Superselective vesical artery	PVA particles 300–500 µ	None	Complete cessation of hematuria	11 months
6.	No feeders	Inferior gluteal artery- coil embolised Selective vesical artery- PVA particles	1-Coils 2- PVA particles 300–500 µ	Major- None dull deep gluteal pain on the left side	Hematuria recurred after 2 months, which then responded to intravesical instillation of 1% formalin	3 months
7.	Superselective vesical artery	Superselective vesical artery	PVA particles 300–500 µ	None	Complete cessation of hematuria	12 months
8.	Superselective vesical artery	Superselective vesical artery	PVA particles 300–500 µ	Major- None mild pain	Complete cessation of hematuria	10 months
9.	Superselective vesical artery	Superselective vesical artery	PVA particles 300–500 µ	None	Complete cessation of hematuria	18 months

moderate and severe [1]. Mild hematuria does not decrease the hematocrit and can be controlled by simple measures [16]. Moderate hemorrhage decreases the hematocrit and requires 6 units or less of transfused red blood cells. Severe hematuria is defined as hemorrhage refractory to simple irrigations and instillations, and requires more than 6 units of packed red blood cell transfusions. All patients referred for angiography and embolization in our series had grade 3 or 4 HC, with severe hematuria requiring a mean of 9 units of packed red blood cells.

Management of intractable hematuria secondary to HC requires a rational plan including detailed clinical history, physical examination, urinalysis, urine culture and assessment of baseline renal function with serum creatinine and cystoscopy. Treatment consists of a series of measures beginning with the most conservative and only a minor proportion requires aggressive intervention [1,2]. Various surgical procedures including cystectomy remain as the final treatment option, but are associated with high morbidity and mortality [2, 17–19].

Transcatheter arterial embolization is an accepted approach for intractable hemorrhage from pelvic organs [20] which offers the obvious advantage of a lower rate of morbidity over surgery. Non-selective embolization of the internal iliac arteries has been described in the past to stop bleeding from branches of these arteries in situations such as pelvic malignancies, obstetric and gynecological emergencies, blunt pelvic trauma, in control of internal iliac aneurysms and in the treatment of arterio-venous malformations [21, 22], but only a few articles are available emphasizing the role of selective vesical artery embolization or internal iliac artery embolization in the management of HC [2, 5–9].

Hald and Mygind were the first to demonstrate a role of internal iliac artery embolization in the treatment of such patients [23]. Mc Ivor et al. [24] and Gujral et al. [25] have also reported the effectiveness of this technique with no side effects. Appleton et al. have reported its use in the treatment of post-pelvic radiotherapy severe hematuria in patients with invasive bladder cancers [21]. Massive bladder hemorrhage was successfully treated by selective embolization of vesical arteries in patients with vesical neoplasms by Kobayashi et al. and Ozono et al. [26, 27]. De Berardinis E performed superselective embolization of the bladder arteries to control severe intractable bleeding in a patient post-bladder irradiation for an infiltrating TCC [6].

Han et al treated ten HC patients with selective vesical artery embolization, where all the conservative measures for controlling hematuria had failed. Eight of ten patients (80%) achieved complete response and no further therapy was required in all the patients [2]. No apparent adverse effect was observed except transient buttock pain in two

patients and fever in one patient which was accounted to pulmonary infection.

In our study, nine patients with severe life-threatening hematuria were treated with superselective embolization after all the conservative measures had failed. There was complete control of hematuria in all nine patients within 48 h post-procedure and no patient required blood transfusion thereafter. Han et al. [2] used gelatin sponge particles or pledgets as embolic agent, whereas we used 300–500-μ PVA particles in all of our patients. Coil embolization of inferior gluteal artery followed by particle embolization of vesical arteries was done in one patient in whom superior, inferior vesical and inferior gluteal arteries were arising as a trifurcation. All our procedures were carried out through the right femoral route. McIvor et al used the left axillary approach thinking a catheter passing down the aorta can usually be manipulated into the internal iliac arteries and their smaller branches on both sides without difficulty [24].

Complications, such as ischemic pain, bladder necrosis, bladder infarction, and even inadvertent occlusion of uninvolved vessels by refluxed embolic material have been reported [26]. lschemic pain commonly occurs in this procedure (26), which was probably seen as post-embolization syndrome in one patient in our study which was symptomatically managed with analgesics. However, two patients also complained of dull deep gluteal pain, which resolved in a few days requiring no medication. Superselective vesical artery embolization was performed and no non-target embolization to any intestinal branches occurred. No ischemic sequelae of the embolization procedure were noted with any reported bladder or sexual dysfunction in our patients.

Many authors have stated that occlusion of unilateral or bilateral IIA is well tolerated without severe complications [28, 29]. Urinary bladder has a complex arterial supply with many normal variations, and a greater number of arteries are found supplying the bladder than usually described in the anatomy literature. The complete set of branches consists of the following: (a) one urachal (b) two superior vesical (c) one middle vesical (d) another one or two superior vesical (e) a vesiculo-deferential (f) and one inferior vesical [30]. Thus, bladder infarction remains a rare complication as urinary bladder has an abundant collateral blood flow [28]. This was useful to us as it makes feasible to embolize a branch of an IIA in patients with massive bleeding from the bladder that is impossible to control by other means. Nevertheless, arterial embolization may result in extensive occlusion of peripheral vessels, preventing the development of collateral circulation and potentially giving rise to tissue infarction or even necrosis [28]. To avoid such hazards, we selected the largest vesical artery originating from the anterior trunk of the IIA and embolized it, and a similar embolization was performed on the opposite side. In one patient (case 6, Table 2), no prominent vessel (which could be superselectively cannulated), supplying the urinary bladder was identified on the right side; hence, no embolization was performed on the right side in this patient. No detailed angiographic attempts were made to map or to embolize the whole arterial supply of the urinary bladder in any patient. This may be the reason for having no ischemic complications in our series, as the remaining arterial supply of the urinary bladder was left intact.

Since we did not expect to find any active bleeding, based on the pathophysiology of HC as discussed above [1, 11–13], a clinical decision was made to occlude the most prominent arteries supplying the bladder, even prior to the diagnostic angiogram. The diagnostic angiogram was used to help guide superselective catheterization of the vesical arteries.

In all of our patients, complete hemostasis was obtained without significant complications by selective embolization of the vesical arteries. In case 2, obturator artery was also embolized in addition to the selective vesical arteries, and in case 6 left inferior gluteal artery was embolized along with the vesical artery.

The available literature on endovascular management of hematuria from radiation-induced HC is principally retrospective and involves small numbers of patients who have had several different treatment modalities. In the absence of randomized studies comparing treatments, it is impossible to set definitive rules about management but some patients with this condition may warrant aggressive treatment.

Thus, our series illustrate the value of this procedure in managing these patients when all other conservative measures have failed and hemostasis is proving to be difficult to achieve. Our study suggests that embolotherapy can minimize total blood loss and thereby avoids the morbidities associated with multiple blood transfusions. Thus, we conclude that superselective vesical artery embolization is a safe and effective procedure in controlling hematuria not responding to traditional measures, and we propose this approach as a valid and viable option in patients of HC. For some select cases, this procedure may be considered as the treatment of choice since it usually obviates the need for emergency surgery in these severely ill patients.

Author's contribution SM data collection, manuscript writing. SK protocol/project development, manuscript editing. DD data collection, manuscript editing. RVP protocol/project development, manuscript editing. SSB data collection, manuscript editing. MK protocol/project development, data collection, manuscript editing.

Compliance with ethical standards

Conflicts of interest All the authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institu-

tional and/or national research committee, and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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