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Transarterial Embolization in the Management of Intractable Haemorrhage

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Keywords
Bladder haemorrhage · Haematuria · Embolization · Internal iliac artery · Selective transarterial embolization

Abstract
Introduction: The purpose of this study was to evaluate the effectiveness and long-term results of selective transarterial iliac embolization (STIE) in patients with intractable bladder haemorrhage (IBH). ***Methods:*** Twenty-five patients with a median age of 84 (range 65–94) years underwent STIE because of IBH between 2002 and 2020. The median follow-up time was 3 (mean 13.9) months. Patients were treated because of bleeding bladder or prostate cancer, radiation-induced haemorrhagic cystitis, and other conditions. Success was defined as technical success (feasibility to embolize bilateral hypogastric arteries or neoplastic arteries) and as clinical success (absence of further or additional therapy). ***Results:*** Twenty-five patients with a median age of 84 years with a median hospital stay of 7 days were embolized at our institution. In total, 60% required additional therapy. Only 20% had minor complications, but no complication major was seen; 60% needed an additional therapy because of continuous bleeding. Our 30-day, 90-day, 6-month, and 12-month mortality rates were 28, 44, 64, and 76%, respectively. ***Conclusions:*** STIE in IBH is a safe, well-tolerated, and feasible procedure for palliating haematuria patients in poor general condition. Major complications are very rarely seen. However, patients often need additional therapy after STIE.

Introduction

Intractable bladder haemorrhage (IBH) is a serious urological emergency and can potentially be life-threatening. IBH arises as a result of bladder cancer progression, advanced prostate cancer, radiation-induced haemorrhagic cystitis, cyclophosphamide-induced cystitis, or other infiltrating locally advanced pelvic neoplasms; severe infections can also trigger IBH in a pre-damaged tissue [1–3].

The management of IBH is a challenging clinical problem as most IBH patients are multimorbid or elderly in bad overall condition, often on blood-thinning medication, and/or are not eligible for surgery. Initial management of IBH is always conservative [1, 3]. At our institution, we are following a protocol previously described by

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Lodde et al. [4] and Pycha et al. [5], with cystoscopic clot removal, a large bore 3-way Foley catheter placement, and continuous bladder irrigation with saline as first conservative steps. If resolution is not achieved, a transurethral resection is performed to remove the tumour or to maintain haemostasis. If this fails and the patient refuses or is not eligible for cystectomy with urinary diversion, a selective transarterial iliac embolization (STIE) of the hypogastric artery is performed. If haemostasis is still not achieved, a salvage cystectomy (RC) is then performed as a last resort. The purpose of this retrospective study was to report the short- and long-term results of STIE in IBH, which we performed over the course of 18 years at our institution.

Materials and Methods

Between October 2002 and May 2020, 25 patients underwent STIE for IBH and were enroled in this current study. We collected data prospectively and evaluated patient charts retrospectively. Ethics/institutional review board approval was not required. The inclusion criteria were IBH after treatment for bladder cancer, prostate cancer, radiation-induced haemorrhagic cystitis, or complications of secondary malignancies involving the bladder.

The reviewed data comprise gender, age, manifestation of the disorder, adult comorbidity evaluation index (ACE-27), length of hospital stay, pre-embolization therapy/treatment, additional therapy after embolization, minor and major complication rate, and mortality rate (30 days, 90 days, 6 months, and 12 months). The ACE-27 index has been applied in all patients [6].

Success was defined as technical success (feasibility to embolize hypogastric arteries or neoplastic arteries bilaterally) and as clinical success (absence of further or additional therapy). If there was no clinical success after STIE, a second-line alternative therapy was proposed, like salvage RC, formalin bladder instillation, or haemostatic radiotherapy. If formalin instillation was proposed, a preoperative cystogram was performed to exclude vesico-ureteric reflux. In case of reflux, formalin instillation was not performed, and another alternative method was applied.

Technique of Embolization

All endovascular procedures were performed through a 5 French or a 6 French right common femoral artery retrograde access. After the initial distal abdominal aortogram using a 5 French pigtail catheter, right and left internal iliac artery angiographies were performed using a 5 French diagnostic catheter (Contra or Cobra shape), in order to detect the arterial supply to the neoplastic tissue. After that, afferent vessels were catheterized using a 2.4 French microcatheter and a 0.016″ or 0.018″ guidewire. The target was confirmed by means of selective angiography, and embolization was performed using different agents, according to angiographic findings and the patient's clinical status. The embolic agents used were Gelfoam particles alone or in association with metallic coils or non-resorbable polyvinyl alcohol (PVA) particles, and PVA particles alone or in association with metallic coils, metallic coils alone, or glue.

Table 1. Demographical data: factors that lead to haematuria

Cause of haematuria	Patients, *n* (%)
Bladder cancer	13 (52)
Radiation-induced haemorrhagic cystitis	9 (36)
Prostate cancer	2 (8)
Bladder infiltrating sarcoma of the pelvis	1 (4)

Table 2. Histology of bladder cancer and cause of radiotherapy

Bleeding bladder cancer, *n* = 13/25	Radiation-induced haemorrhagic cystitis, *n* = 9/25
pT2, *n* = 9	Prostate cancer, *n* = 4
pT4, *n* = 1	Bladder cancer, *n* = 3
pT1 + Cis, *n* = 2	Endometrium cancer, *n* = 1
pTaG2, *n* = 1	Colon cancer, *n* = 1

Results

A total of 25 patients (23 males and 2 females) with a median age of 84 years (range 65–94 years, mean 83 years) were included in this retrospective observational study. All patients were admitted for IBH and all patients had an ACE-27 index grade 3. Eight patients (32%) had blood-thinning medication for cardiac or vascular comorbidities.

The cause of bleeding was bladder cancer in 13 patients, radiation-induced haemorrhagic cystitis in 9, bleeding prostate cancer in 2, and a bladder infiltrating sarcoma of the small pelvis in 1 patient (Tables 1 and 2). All patients had conservative treatment before STIE, as described above [4, 5].

The median time between hospital admission and STIE was 2 days (range 0–25 days, mean 6 days). The median haemoglobin level before embolization was 10 g% (range 4–14 g%, mean 10 g%), and the median haemoglobin level after embolization was 10.2 g% (range 8.7–14.1 g%, mean 10.4 g%).

Prior to the intervention, a mean of 2 blood units (range 2–12 units, median 0 units) was given in 12/25 patients (48%) and after embolization the other 12 patients (48%) needed a mean of 1.7 units (range 0–8 units, median 0 units). The median hospital stay was 7 days (1–32 days, mean 9 days).

In 17 cases (68%), the interventional radiologist was able to perform a bilateral STIE and in 8 (32%), a unilateral STIE. Technical success, with complete neoplastic tissue devascularization, was achieved in 22/25 (88.0%)

Table 3. Analysis in detail of the 2 major bleeding cohorts and their additional therapy after STIE

Bleeding bladder cancer, n = 13 patients	Radiation-induced haemorrhagic cystitis, n = 9 patients
3/13: formalin bladder instillation	1/9: formalin bladder instillation
3/13: salvage RC	2/9: salvage RC
3/13: haemostatic TUR-bladder	1/9: haemostatic bladder irradiation plus formalin bladder instillation
Survival Mean 94 days (range 11–468 days) Median 63 days	*Survival* Mean 27.6 months (range 16–2,933 days) Median 10 months

STIE, selective transarterial iliac embolization; TUR, transurethral resection.

Table 4. Detailed information about post-operative mortality with cause of death (n = 25 patients)

	Still alive (2/25)	Died from a heart attack (2/25)	Died of tumour progression or general health detoriation (21/25)
Median	3.9 yr	3 months	3 months
Mean (range)	3.9 yr (3.8–4.1 yr)	3 months (61–67 d)	12 months (9 d–8.3 yr)

patients, whereas devascularization was only partial in the remaining 3/25 (12%).

Gelfoam particles alone were used in 10/25 (40.0%) cases, Gelfoam particles in association with metallic coils in 7/25 (28.0%), Gelfoam particles in association with non-resorbable PVA particles in 2/25 (8.0%), PVA particles alone in 2/25 (8.0%), PVA particles in association with metallic coils in 2/25 (8.0%), metallic coils alone in 1/25 (4.0%), and glue in 1/25 (4.0%).

We had a clinical success rate of 40%. In total, 15 patients (60%) required an additional therapy after STIE. Of the 15 patients who received an additional therapy after STIE, 5/15 patients (33.2%) received a salvage RC, 4/15 patients (26.7%) received a formalin bladder instillation, 26.7% (4/15 patients) had to be treated endoscopically again (intravesical resection or diathermocoagulation), 1/15 (6.7%) received a haemostatic bladder irradiation plus formalin bladder instillation, and 1/15 patients (6.7%) was managed with haemostatic bladder irradiation. An additional analysis is shown in Table 3. No second session of STIE was performed.

The median time between STIE and the second additional therapy was 7 days (range 3–173 days, mean 21 days). Intraprocedural complications occurred in 1/25 (4%) of the patients with non-target embolization into the superior gluteal artery without long-term complications.

Only 5 patients (20%) developed fever after the procedure and were classified as Clavien-Dindo grade I. No major complications after STIE were observed. Nevertheless, the 30-day mortality rate was 28% (7/25) due to the grade 3 ACE-27 index, the tumour progression, and the detoriation of the general patients' condition. The 90-day mortality rate was 44% (11/25). The 6- and 12-month mortality rates were 64% (16/25 patients) and 76% (19/25 patients), respectively.

The median follow-up time was 3 months (mean 13.9 months) (range 11 days–8 years). Only 8 patients (32%) had survived 6 months after therapy. As of May 2020, 2 patients (8%) are still alive in discrete general condition and without recurrence of disease, with a median follow-up of 3.9 years (see Table 4 for detailed information about post-operative mortality with cause of death).

Discussion

IBH is a serious urological emergency which can be a life-threating condition and remains a challenge for all clinicians. IBH arises as a result of bladder cancer progression, advanced prostate cancer, radiation-induced haemorrhagic cystitis, cyclophosphamide-induced cystitis, or other infiltrating locally advanced pelvic neoplasms; severe infections can also trigger IBH in pre-dam-

aged tissue [1–3]. Additionally, the management of IBH is complicated by patients' comorbidities or by blood-thinning medication.

At our institution, an RC is proposed to every patient affected by muscle invasive non-metastatic bladder cancer. However, not every patient accepts this radical surgical concept, and some candidates are not eligible for surgery due to severe concomitant disease and the resulting high ACE-27 index. In some cases, it is a combination of high ACE-27 index, advanced age, and the patient's will impeding an RC. In this case, we manage the patients with a bladder preserving strategy [4, 5]. Many of the patients in this study were readmitted due to haemorrhage of recurrent or progressing tumours often in precarious conditions. If the conservative management of IBH fails, STIE permits to control an acute emergency and saves time by bridging the patient until he or she is in an adequate condition for further decisions and/or treatment (e.g., cystectomy). In terminal patients, STIE may constitute a definitive solution.

Various alternative therapeutic options for IBH [3, 7] were published: intravesical irrigation (formalin, alum, or prostaglandin irrigation), orally administered epsilon-aminocaproic acid, hyperbaric oxygen therapy, hydrostatic pressure (Helmstein balloon compression), hypofractionated radiotherapy or interventional radiology with embolization, or chemoperfusion with mitoxantrone [3].

Embolization of the internal iliac artery was first described by Hald and Mygind in 1974 [8]. It is a well-tolerated technique with low risk of serious complications and is performed under local anaesthesia. As the success rate (technical success rate and clinical success rate) is defined differently in the studies, it is difficult to compare them. Our technical success rate was 88%, which is the same as stated by Korkmaz et al. [7]. However, his clinical success rate reached 100%, which is much higher than our clinical success rate of 40%. Our clinical success rate of 40% (10/25 patients needed no additional therapy) could be due to the fact that only 68% were embolized on both sides.

If technically or anatomically feasible, embolization should always be bilateral. In our study, 17 of 25 patients (68%) underwent bilateral STIE, and of these, 9/17 (53%) needed a second alternative therapy because of bleeding recurrence. Three patients underwent salvage RC, 4 received a formalin bladder instillation, and 2 were managed endoscopically.

Of the 8 patients who received unilateral embolization, 75% (6/8 patients) needed a second therapy: endoscopic coagulation in 2 patients, haemostatic radiotherapy in 1 patient; 2 patients underwent a salvage RC and 1 patient underwent haemostatic radiotherapy plus formalin instillation. These results underline the basic necessity to treat both hypogastric arteries to obtain a reliable result.

The influence of the type of embolic agent on the clinical outcome is a controversial discussion. In most series, the number of patients was too low to allow conclusions about the best embolic agent [2, 9, 10]. The same is the case in our series. Due to the low number of patients, it is not possible to determine a difference in effectiveness between the various embolic agents.

Most patients have to be transfused with blood units before and after embolization. In our patient cohort, 12 patients (48%) received a mean of 2 units (range 2–12 units, median 0 units) prior to embolization. After embolization, another 12 patients (48%) needed a mean of 1.7 units (range 0–8 units, median 0 units). Our results are comparable with the results of Nabi et al. [11] with 3.2 units overall and also the results of with Liguori et al. [12]. He reported a transfusion rate before and after embolization of 55 and 30%, respectively.

STIE is a well-tolerated procedure with a low complication rate. The most common complications are minor ones, like gluteal pain, fever, nausea, vomiting, or pain in the back of the thigh [3]. We observed post-interventional fever in only 5 patients (20%). This is comparable with the study of Liguori et al. [12], which showed 27% minor complications. Also, in terms of major complications, our results (0%) correspond to those of Korkmaz et al. [7] and Nabi et al. [11]. Currently, there is only one case report [13] about gluteal necrosis after embolization in a patient with haemorrhage in bladder cancer. It appears that the complication rate was reduced by selective and super-selective embolization and the technical improvement of catheters and occlusion material over the last years [3].

Compared to the literature [1, 7, 12] with a success rate of 43–100%, we have slightly worse results in terms of the clinical success rate with 40% (10/25 patients). This could be explained by all the patients in this cohort being in bad general condition (all patients had grade 3 ACE-27 index), with a high median age of 84 years, but perhaps also with the technique, the laterality of the performed embolization technique, and the used embolic agents: only in 17 patients (68%) the embolization was feasible on both sides and Gelfoam alone or in combination was used in a total of 76% (19/25 patients). Of the bilaterally embolized patients, 53% received a second-

line therapy in contrast to almost 75% of patients with a monolateral embolization.

There are only few studies which examined the survival rate after embolization. Liguori et al. [12] reported a 6-month mortality rate of 66%. These results are comparable with our 6-month mortality rate of 64% (16/25 patients). Appleton et al. [14] reported a 30-day mortality rate of 30%, which is the same as we found (28%). Of the 2 patients still alive today, 1 has undergone a salvage RC with urinary diversion because of a bladder and prostate infiltrating sarcoma of the pelvis and the other 1 is under anti-hormonal therapy for prostate cancer.

Conclusion

STIE in IBH is a safe, well-tolerated, and feasible procedure for palliating haematuria in terminally ill patients and patients in bad general condition. Major complications are very rare. However, most patients need an additional interventional therapy for definitive resolution of IBH.

Statement of Ethics

Ethics/institutional review board approval was not required. It is a prospective retrospective original article with review of patient charts and patient consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

E. Comploj: project development, data analysis, data collection, and manuscript writing. A. Pycha: manuscript editing. E. Trenti: data management. S. Palermo: data management. M. Bonatti: data collection and data analysis. P. Krause: data collection. D.M. Folchini: data collection. A. Pycha: project development and manuscript writing/editing.

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