Endoscopic injection sclerotherapy control of intractable hematuria following radiation-induced hemorrhagic cystitis. A novel approach.

HARI SIVA GURUNADHA RAO TUNUGUNTLA, MS, M Ch, MAHENDRA BHANDARI, MS, M Ch, ALOK SRIVASTAVA, MS, M Ch, RAKESH KAPOOR, MS, M Ch and TAPAS KUMAR SAHA, MS, M Ch.

Department of Urology and Renal Transplantation. Sanjay Ghandi Postgraduate Institute of Medical Sciences. Lucknow, Uttar Pradesh, India.

Summary.- OBJECTIVE: To establish the utility of endoscopic sclerotherapy using 1% ethoxysclerol for the control of intractable hematuria following post-irradiation telangiectatic cystitis (PTC).

METHODS: Our experience of treating 4 patients (one female and three male) with massive exsanguinating hematuria resulting from PTC, using a combined intralesional and perilesional injection of 1% ethoxysclerol, is presented. Observation on the distribution, grading of telangiectasis and pattern of bleeding are made.

RESULTS: A dramatic and lasting cessation of the hematuria in all the 4 patients was achieved during the follow-up period varying from 1 month to 4 years.

CONCLUSION: Endoscopic injection sclerotherapy is a simple, highly effective, less invasive new technique in the management of massive and intractable hematuria due to radiation-induced telangiectasia of the urinary bladder.


Address correspondence to:
Dr. Hari Siva Gurunadha Rao T
Assistant Professor of Urology and Renal Transplantation
Sanjay Gandhi Postgraduate Institute of Medical Sciences
Raebareli Road, Lucknow-226014
Uttar Pradesh, India
e-mail: siva@sgpgi.ac.in
hotmail: hsgrao@hotmail.com
Accepted for publication February 10, 1999.
INTRODUCTION

Post-irradiation telangiectatic cystitis (PTC) is seen most often after treatment for pelvic malignancies, especially prostate and cervical cancers, with approximately 20% of patients receiving definitive radiation therapy for gynecological, genitourinary and rectal cancers experiencing bladder complications due to a direct or incidental damage to the bladder (1, 2).

Clinically, PTC is often a desperate and exsanguinating situation and the patient presents with an intractable hematuria and at times hemorrhagic shock. The patient requires multiple sessions of evacuation of the bladder of clots for the management of bladder distention resulting from frequent clogging of the catheter by the clots. Multiple units of blood transfusion often fail to maintain the hematocrit and hemodynamic stability.

Although the exact pathophysiological mechanism responsible for the bleeding from the radiation-induced "vesical telangiectasia" is not known, it is most likely that an increase at the intraluminal venous pressure during voiding leads to a rupture of these delicate veins beneath the bladder mucosa, resulting in an increase in the pressure in the esophageal telangiectasia in case of portal hypertension, which leads to hematemesis (3). This increase in the intraluminal venous pressure becomes more evident in the presence of bladder outlet obstruction which may be present in some of these patients.

The hematuria promptly reappearing after each session of clot evacuation can be explained by the fact that intravascular pressure within the "vesical telangiectasia" exceeds the intravesical pressure, leading to a rupture of these delicate veins. As long as the irrigant inflow continues (i.e., during cystoscopy), the intraluminal pressure undergoes a relative tamponade due to the irrigant pressure within the bladder. This could be fairly confirmed by the reappearance of the bleeding from the telangiectasia as the cystoscope is withdrawn towards the bladder neck with a gradual slowing of the inflow.

The overall results of management of PTC have been poor. Several reports have been published addressing the treatment of hematuria following PTC, using steroid (4, 5), vitamin E (4, 5), trypsin, orgotein (6), hyperbaric oxygen (7, 8) and sodium pentosulfanpolysulfate (9). There is a paucity of data to show a definite role of these agents in the treatment of PTC excepting hyperbaric oxygen and sodium pentosulfanpolysulfate. While several local therapies are available, for example, intravesical instillations of formalin, silver nitrate, alum (4, 5), hydrostatic dilation and fulguration, none has demonstrated consistent therapeutic success. Even the results with selective embolization of hypogastric arteries are disappointing. Palliative cystectomy as a definite modality of treatment, is often difficult to execute in a sick patient.

We report our experience of treating 4 consecutive patients with PTC using 1% ethoxysclerol injection sclerotherapy with a successful outcome.

TECHNIQUE OF INJECTION

A meticulous, careful and watchful endeavor is needed to detect the areas of the vesical telangiectasia to effect their obliteration by the injection sclerotherapy. The bladder is first evacuated of all the clots until the returns are clear. The cystoscope is then gradually withdrawn towards the bladder outlet with a slowing of the inflow, which immediately reveals a streaking of blood through some of the telangiectasia and the appearance of ooze emanating from the areas of underlying submucosal vesical telangiectasia (evidenced by the overlying petechiae and swarming smoothly over the rest of bladder mucosa and rapidly conglomerating with the others from the rest of the telangiectasia and configuring into the larger sized clots rapidly filling the bladder (Fig. 1). After taking multiple biopsies of the bladder mucosa, the telangiectatic areas are sclerosed with 1% ethoxysclerol

Fig. 1: Endophotograph depicting the successive stages of formation of clots and pattern of bleeding.
using an endoscopic needle negotiated through a 21 Fr. cystoscopic sheath, using a 30 degree Hopkins II telescope. A combination of intralesional (Fig. 5) and perivascular injection (Fig. 6) is used to effect the injection sclerotherapy depending upon the grade and type of the telangiectasia.

The actual injection procedure includes identification of the telangiectasia; raising a bleb of the mucosa by a submucosal injection of the sclerosant; puncturing the telangiectasia injection of the sclerosant intralesionally in a small (less than 5 mm) isolated telangiectasia; not confluent with the other (grade I) (Fig. 2). Fulguration of the puncture site using the ball electrode is required in case of a larger (equal to or more than 5 mm) varix, the puncture site of which may bleed (grade II) (Fig. 3). A perivascular injection is used if the telangiectasia is very much dilated, prominent (i.e., more than 5 mm) and tortuous (grade III (Fig. 4). A total of about 20-25 ml of the sclerosant may be needed to be injected obliterating all the telangiectasia with about 0.5 ml injected into each telangiectasia. The bladder irrigation with saline is continued for 48 hours postoperatively.

PATIENTS AND METHODS

Case No. 1:
A 50-year-old female patient received radical radiotherapy using a combination of intracavitary

Fig. 2: Endophotographic appearance of grade I "vesical telangiectasia"; also seen in the surrounding bladder mucosa studded with petechial hemorrhages which often lead to the detection of the underlying "telangiectasia".

Fig. 3: Endoscopic appearance of grade II "vesical telangiectasia".

Fig. 4: Endoscopic appearance of grade III "vesical telangiectasia".

Fig. 5: Endophotograph showing the intralesional injection of 1% ethoxysclerol.
(7500 cGy over one week) and external beam (3500 cGy over 4 weeks) irradiation for squamous cell carcinoma of cervix (stage II A) in December 1992. One year later, the patient started having frequency, dysuria and hematuria which increased rapidly over a period of 3 months. The patient then presented to the Emergency Room with giddiness, sweating, hemoglobin at the time of admission was 6 mg/dl. The serum creatinine was 1.6 mg/dl. The patient required evacuation of the bladder of clots 5 times to dispel the clogging of the perurethral catheter leading to distention of the bladder. Contrast enhanced CT scan of the abdomen and pelvis did not reveal any evidence of recurrence from carcinoma of cervix.

The cystoscopic examination after clot evacuation revealed multiple telangiectatic lesion (of all grades) over the posterior wall trigone, both lateral walls of the bladder and around the bladder neck. At the end of each session of the cystoscopic clot evacuation from the bladder, clear returns could be achieved with a running irrigant, prompting a conclusion of the procedure. However, hematuria promptly returned in the immediate postoperative period following the clot evaluation.

Saline irrigation of the bladder was instituted after clot evacuation along with irrigation of the bladder with 1% alum. Hemodynamic stability could not be maintained despite all possible supportive measures including 16 units of blood transfusion. One percent ethoxysclerol was then injected into these telangiectatic lesions by a flexible endoscopic needle. Postoperatively the hematuria stopped dramatically and the patient was discharged on the 6th postoperative day. She is free from hematuria at the present time, years after the sclerotherapy.

**Case No. 2:**
A 42-year-old male patient underwent transurethral resection of a 5 x 4 cm papillary bladder tumor involving the left lateral wall on September 6, 1996. The histopathology of the tumor revealed a grade II transitional cell carcinoma of the bladder with invasion of the superficial muscle. He received radical external beam radiotherapy with 5500 cGy in 20 fractions over four weeks. One year later, the patient started having gross hematuria, severe urgency, dysuria and suprapubic discomfort requiring multiple blood transfusions. An ultrasound examination of the KUB region revealed normal upper tracts and the bladder filled with multiple homogeneous echogenic areas, suggestive of blood clots. He required evacuation of the clots from the bladder on 4 occasions to maintain the patency of the perurethral catheter. One per cent alum and silver nitrate failed to control bleeding. All the while the hemoglobin continued to be low (4.5 to 5 gm/dl). The serum creatinine was 1.3 mg/dl. The patient was hemodynamically unstable despite all possible supportive measures including 14 units of blood transfusion. Therefore, he underwent cystoscopy and injection sclerotherapy of the multiple, active, bleeding "vesical telangiectasia" (of all grades) involving the trigone, bladder neck and the posterior wall of the bladder using 1% ethoxysclerol (as described above). A total of 20 ml of the sclerosant was injected. The bladder irrigation was continued for 48 hours postoperatively. Multiple biopsies of the bladder mucosa did not reveal any evidence of tumor recurrence. The hematuria stopped after two days and the patient was discharged on the fourth postoperative day. The patient is free from hematuria to date.

**Case No. 3:**
A 52-year-old male patient underwent transurethral resection of a solid-looking (i.e., endoscopic appearance) 5 x 6 cm bladder tumor of the right lateral wall of the bladder on November 9, 1996. The histopathology revealed a grade III transitional cell carcinoma of the bladder with invasion of the deep muscle layer. He received radical external beam...
radiotherapy with 6000 cGy in 20 fractions over a period of four weeks. Nine months later, the patient started having recurrent gross hematuria. An ultrasound examination of the KUB region revealed normal upper tracts and the bladder filled with multiple homogenous echogenic areas, suggestive of blood clots. The serum creatinine was 1.4 mg/dl. The blood hemoglobin level dropped to 7.5 gm/dl. He required a total of 12 units of blood transfusion to maintain the hemodynamic stability along with the other supportive measures. The intractable hematuria continued defying all possible measures including saline irrigations of the bladder, 4 sessions of clot evacuation, 1% alum and silver nitrate. He therefore underwent cystoscopy which revealed multiple areas of telangiectasia (mainly of grade II and grade III) involving the trigone and both the lateral walls of the bladder with active bleeding. The telangiectatic area were injected with a total 22 ml of 1% ethoxysclerol (as described above) and a continuous bladder irrigation was started which was continued for 48 hours postoperatively. The hematuria stopped after 72 hours and the patient was discharged on the 5th postoperative day. Biopsy of the bladder mucosa taken from multiple sites did not show any tumor recurrence.

**Case No. 4:**
A 50-year-old male patient underwent transurethral resection of the bladder tumor at the Institute of Medical Sciences, Banaras Hindu University, Varanasi, U.P. India, in September 1996. He was symptomatic for 1 1/2 years (prior to the resection with gross painless and total hematuria. The histopathological examination revealed a grade III transitional cell carcinoma of the bladder with superficial muscle invasion. He received radical external beam radiotherapy with 6000 cGy in 20 fractions over a period of four weeks and was advised regular follow-up every 3 months with urine cytology and cystopanendoscopic examination. Seven months later, the patient started having recurrent gross hematuria. The blood hemoglobin was 9.5 gm/dl. The urine cytology did not reveal any malignant cells. A cystopanendoscopic examination revealed telangiectatic areas on the trigone and around the bladder neck, which were fulgurated. Multiple biopsies of the bladder mucosa did not show any recurrent tumor. An ultrasound examination of the KUB region revealed normal upper tracts and the bladder filled with multiple echogenic areas, suggestive of blood clots. The serum creatinine was 1.6 mg/dl. The blood hemoglobin level dropped to 8 ml/dl. He required a total of 10 units of blood transfusion to maintain the hemodynamic stability along with the other supportive measures. The intractable hematuria continued defying all possible measures including saline irrigations of the bladder, 2 sessions of clot evacuation, 1% alum and silver nitrate. He therefore underwent cystoscopy, which revealed multiple areas of telangiectasia (mainly of grade II) involving the trigone and bladder neck (11 o’clock position) with active bleeding. The efflux was clear from both the ureteric orifices. There was also a bilobar obstructive prostatomegaly. There were also multiple bleeding grade II "vesical telangiectasia" on the floor of the prostatic urethra. The telangiectatic areas were injected with a total of 12 ml of 1% ethoxysclerol (as described above). A transurethral resection of the prostate was also performed along with the injection sclerotherapy. A continuous bladder irrigation was started which was continued for 48 hours postoperatively. The hematuria stopped after 72 hours and the patient was discharged on the 4th post-operative day. Biopsy of the bladder mucosa taken from multiple sites did not show any tumor recurrence.

**RESULTS**

The hematuria subsided in all the patients 48 to 72 hours after injection sclerotherapy. Two of the three patients are free from hematuria after the first session of sclerotherapy and did not require any intervention for recurrent hemorrhagic cystitis to date during a follow-up ranging from 1 month to 4 years. The 3rd patient had recurrent hematuria one month after the first session of sclerotherapy and required a second session of injection for its control. This patient has most prominently, multiple and tortuous grade III "vesical telangiectasia" around the bladder neck at
about 11 o’clock and 2 o’clock positions.

These vesical telangiectasias were reinjected with a total of 15 ml of 1% ethoxysclero, which controlled the hematuria. This patient is free of hematuria to date.

The symptoms (frequency, dysuria and urgency) are being managed with good hydration and urinary analgesics such as phenazopyridine hydrochloride, oxybutynin chloride, propantheline bromide, flavoxate hydrochloride. All patients were started on a course of low dose chemoprophylaxis with fluoroquinolones for a period of 3 months postoperatively.

**DISCUSSION AND CONCLUSION**

Currently under clinical investigation for the treatment of PTC are hyperbaric oxygen (7, 8), sodium sulfanpolysulfate (9), and conjugated estrogen (10), each of which attempts to stabilize the damaged urothelium and promote healing.

The urinary bladder has a radiotolerance up to 6 000 cGy in 20 fractions over 4 weeks (11). Radiation-induced bladder injury became apparent with the wide clinical experience gained through treatment of cervical carcinoma and other pelvic malignancies, particularly with radium therapy.

Approximately 20% of the patients who undergo pelvic irradiation suffer bladder complications, half of these being hemorrhagic cystitis (2, 12). Cystoscopically, there is telangiectasia of the vessels in the region of the trigone.

We did not observe any mucosal ulceration in our patients, although it is identified and believed to be the cause of bleeding in most of the reports (12-14). The specific areas of the bladder which are prone to radiation injury include the posterior wall trigone, area of the bladder neck and around the area of the previous tumor, if the radiotherapy was given for bladder carcinoma (11). The dome of the bladder is usually resistant to radiation injury (Fig. 2).

We do not observe any mucosal ulceration in our patients, although it is identified and believed to be the cause of bleeding in most of the reports (12-14). The specific areas of the bladder which are prone to radiation injury include the posterior wall trigone, area of the bladder neck and around the area of the previous tumor, if the radiotherapy was given for bladder carcinoma (11). The dome of the bladder is usually resistant to radiation injury (Fig. 2).

The mode of treatment of PTC depends upon the degree of hematuria. Mild hematuria does not produce an acute decrease in hematocrit and can be controlled by simple measures like saline irrigation, silver nitrate, PGE1, PGE2, and carboprost tromethamine or alum instillation intravesically and aminocaproic acid. Moderate hematuria results in an acute decrease in hematocrit during several days. Either equal to or less than 6 units of blood transfusion is often required to maintain the hematocrit. Severe hematuria is often refractory to simple irrigations, intravesical instillations of alum and silver nitrate (4). Frequently blood transfusions fail to improve the hemodynamic instability. All our patients belonged to the category of those having severe hematuria. Moderate and severe hematuria are often resistant to measures like saline irrigations of the bladder, alum irrigation, silver nitrate instillation, prostaglandin instillation, formalin instillation, etc. Orgotein has not found a role in preventive or therapeutic treatment of PTC (6). The urologist in the past had a resort to the ultimate measures like placement of percutaneous nephrostomy tubes, ligation of the hypogastric arteries, ileal loop diversion cutaneous ureterostomy, ureterosigmoidostomy and supravesical diversion of the urinary stream (4) with or without cystectomy.

In our experience, none of the conservative measures enumerated above have been satisfactory in the management of radiation-induced hemorrhagic cystitis. Looking for a desperate remedy, we devised a new method in the management of these patients with PTC using 1% ethoxysclerol to obliterate the vesical "telangiectasia" by a transurethral endoscopic approach as described above.

The pattern of bleeding from the "vesical telangiectasia" is very characteristic of this condition (Fig. 1) and requires specific maneuvers for its identification, as described above in the technique of injection. The obliteration of the telangiectasia is effected by a combined intravesical injection (Fig. 5) and perivascular injection (Fig. 6) of the vesical "telangiectasia" with a long flexible, endoscopic needle passed through a 21Fr. cystoscopic sheath. An average of 0.5 ml of the sclerosant is injected into each telangiectasia. Blanching of the mucosal surface around the injection site is invariably observed, which confirms the adequacy of the properly effected sclerotherapy. On average, a total of 20 ml of sclerosant is sufficient for the entire procedure and 8 to 10 variceal sites required the injection in each patient. Perivascular injection appears to be more effective and safe for controlling a larger (grade III) (Fig. 4) telangiectasia in view of the fact that the sclerosant accumulates submucosally around the telangiectasia for a longer period leading to a more effective and lasting fibrosis, which will eventually obliterate the telangiectasia. Some areas of puncture or the large telangiectasia injected with the sclerosant may bleed and require...
fulguration with a ball electrode/vaportrode. During a follow-up period varying from 1 month to 4 years, only one patient required a second session of injection sclerotherapy for the control of recurrent hematuria, one month after the initial session on injection sclerotherapy. All the patients are free from hematuria to date, including the third case who required a second session of injection sclerotherapy.

Intramural fibrosis of the bladder is a logical anticipation of injection sclerotherapy. But this fibrosis is expected to be minimal and is a small price to be paid for the successful management of this clinically desperate situation, with the patients often presenting to the emergency room in a hemodynamic crisis defying all possible supportive treatment. We plan to perform Tc 99m DTPA renograms in these patients during the follow-up to exclude any upper tract obstruction due to sclerosant injection around ureteric orifices. We also plan to perform cystograms every 3 months in these patients during the follow-up period to monitor the fibrosis of the bladder, which may progress to a state of contracted bladder requiring augmentation cystoplasty.

Conventional treatment modalities of severe PTC often are not successful and a urologist is compelled to undertake drastic treatment measures like urinary diversion with or without cystectomy. The new technique of injection sclerotherapy using 1% ethoxysclerol, as described herein, was effective and successful in all 4 of our patients in whom it was undertaken, with the longest follow-up being years. This approach may salvage the bladder with a lasting symptom relief.

REFERENCES