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Original Research Article

Management of late hemorrhagic radiation cystitis in patients of carcinoma cervix with special reference to 1% alum irrigation and its safety: a clinical study in a tertiary care centre

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ABSTRACT

Background: Radiation cystitis is a well-known complication arising from radiation therapy in pelvic malignancies. Haematuria is usually the main presenting symptom of radiation cystitis, which can range from mild to severe refractory and life-threatening forms. There are various forms of treatment ranging from intravesical instillations like alum, formalin, prostaglandins and pentosan sulphate; hyperbaric oxygen therapy to surgical treatment like cystoscopic fulguration, arterial ligation and cystectomy.
Here authors aimed to find the efficacy of 1% alum irrigation in controlling haematuria due to radiation cystitis and to correlate its use with change in clinical status and biochemical parameters.
Methods: This retrospective study was done for a period from July 2010 to July 2017 which included all female cervical cancer patients with intractable haematuria due to radiation cystitis. Only patients with normal renal function were included. Irrigation with 0.9% NS, hem coagulase and subsequently 1% alum irrigation were given. Failed cases underwent cystoscopic fulguration.
Results: Average age of presentation was 59.79 years. Of the 34 patients 20 (64.51%) patients showed complete response, 4 (12.9%) patients showed partial response and 7 (22.58%) patients had no response to alum irrigation and cystoscopic fulguration were done in these cases. There was no significant change in vital parameters and biochemical parameters except increased prothrombin time (<0.001).
Conclusions: No standard of care therapy is presently available for patients with hematuria following radiation cystitis although there is big armamentarium of therapies. Authors found that 1% alum irrigation is safe and efficacious for these patients although normal renal function is a prerequisite.

Keywords: Cervical cancer, Hematuria, 1% alum irrigation, Radiation cystitis

INTRODUCTION

Radiation cystitis is a well-known complication arising from radiation therapy to pelvis in pelvic malignancies. Uterine cervical carcinoma is a major health problem which accounts for death of around 500,000 women globally every year.[1] Radical hysterectomy, radiation therapy and combined chemo radiotherapy are considered effective modality of management in cervical carcinoma.[2]

The aim of radiotherapy is to deliver high radiation doses to target tissues while minimizing the exposure to normal tissues. Despite advances in delivery techniques like high energy linear accelerators, IMRT and conformal radiotherapy (CRT), injury to normal tissue still occur.[3]

Radiation cystitis can be acute onset or late onset. Acute form occurs during or soon after initiation of radiotherapy which is usually self-limited. The late onset form can occur from 6 months up to 20 years. Hematuria is usually the main presenting symptom, which can range from mild to severe refractory and life-threatening forms.[4]

After exposure to radiation, intermediate cells and basal cells of urinary bladder are show disruption by 3 months. At 6-12 months, radiation dose dependent proliferation of bladder epithelium is evident with loss of barrier between urine and bladder correlating with the onset of irritative lower urinary tract symptoms. Proliferation of endothelial cells is seen >6 months after radiation. The damage to vascular endothelial cells seems to be the pathology of late onset cystitis. Changes in endothelial cells are seen months to years.[4]

The features of late onset radiation cystitis are mainly irritative symptoms with hematuria.[5] The radiation therapy oncology group has devised a scoring system for late onset radiation cystitis (Table 1).[6]

There are various ways to control hematuria following radiation cystitis. Intravesical instillation like 1% alum solution, prostaglandins, formalin, placental extract are used in many studies. Systemic therapies like pentosan polysulfate, conjugated estrogen, WF10 are mentioned in literature.[7-15]

Local therapies include intravesical instillation of botulinum toxin A and the most commonly used cystoscopic fulguration.[16,17] Hyperbaric oxygen therapy is now being increasing used to control hematuria.[18]

When all these fail, surgical interventions like selective ligation of ligation of iliac arteries percutaneous embolization of both vesical arteries and even urinary diversion with or without cystectomy can be the only saviour.[19-21]

Most of the time hematuria is controlled by continuous irrigation with 0.9% normal saline. This method may fail many a time and one may need to resort to transurethral fulguration of bleeding points. However, in selected cases there is a simple and safe method of continuous irrigation of the bladder with 1% alum solution without anesthesia, which may prevent the need for fulgaration of the bleeding points or delay it for some time. Reports of toxicity due to systemic absorption of aluminium following alum irrigation are rare.[8,22]

The aims and objective of this study was this study has been performed to find the efficacy of 1% alum irrigation in controlling hematuria due to radiation cystitis and to correlate its use with change in clinical status and biochemical parameters like hemoglobin, BUN, serum creatitine, prothrombin time, APTT, Platelet count, pH, SGOT, SGPT and total leukocyte count.

METHODS

This is a retrospective study done for a period from July 2010 to July 2017. All female patients with intractable hematuria were investigated with proper history, physical examination and ultrasound or CT-IVU. The patients who were known case of carcinoma of uterine cervix, had taken pelvic radiotherapy in form of EBRT and had presented with features of late onset radiation cystitis were analyzed. A thorough analysis was done to exclude any other identifiable lesion causing hematuria.

The patients were graded as per RTOG/EORTC late radiation morbidity scoring system of urinary bladder (Table 1).[6]

Only those with grade 2, grade 3 or grade 4 were included in the study. Renal function (serum creatinine and blood urea nitrogen), blood glucose, liver function tests, coagulation profile and arterial blood gas analysis were performed.

Only those with parameters in normal range were included in study. All patients with CKD, T2DM, and deranged LFT and with features suggestive of underlying sepsis and allergic diathesis were excluded from study.

Table 1: RTOG/EORTC late radiation morbidity scoring system.

Grade	Presentation
Grade 0	Normal
Grade 1	Slight epithelial atrophy
	Minor telangiectasia
	Microscopic haematuria
Grade 2	Moderate frequency
	Generalised telangiectasia
	Intermittent macroscopic haematuria
Grade 3	Severe frequency and dysuria
	Severe generalised telangiectasia with petechiae
	Frequent haematuria
	Reduction in bladder capacity (<150 cc)
Grade 4	Necrosis
	Contracted bladder (<100 cc)
	Severe haemorrhagic cystitis

Initial clot evacuation and cystoscopy was done in all cases and irrigation with 0.9% normal saline was started. Those who did not respond to irrigation within 6 hours were given 100 ml of hem coagulase (Botroclot) diluted to 200 ml and catheter was clamped for 1 hour. Those whose hematuria continued intravesical instillation 1% alum was then instilled. 1% alum solution was prepared using 50 gm of alum in 5000ml of 0.9% normal saline and then irrigation was started in a closed system using 22Fr Triway Foley's catheter. The rate of irrigation was kept between 6-8 ml/min up to maximum of 15ml/min.

Those who responded to the alum irrigation were continued on the 1% alum irrigation for 8 hours. After alum irrigation was stopped irrigation with normal saline (0.9%) was continued till 24 hours. The response were categorized as complete response when gross hematuria settled until next therapeutic step or for a period of 1 month, partial response when reduction of hematuria to the extent that blood transfusions were not required and failure when no decrease in hematuria or there aroused the need to suspend alum irrigation due to uncontrollable adverse effects.[7,8]

In the patients undergoing alum irrigation symptoms and signs of encephalopathy were closely monitored which included the consciousness level, orientation to time place and person and any cognitive deficits. Vitals like pulse rate, blood pressure, temperature and respiratory rate were recorded before the start of alum irrigation and were monitored 6 hourly during irrigation.

Local irritative symptoms like suprapubic pain and vesical tenesmus were taken into account. These symptoms were graded as mild (those that did not require medication), moderate (those that required analgesics and antispasmodics) and severe (those that did not respond to analgesics).[8]

Blood samples for pH, hemoglobin, serum creatinine, blood urea nitrogen, prothrombin time, activated partial thromboplastin time and platelet count analyses were drawn before the beginning of the alum irrigation and then at 12 hourly intervals.

Those patients had partial response or no response to alum irrigation were submitted for cystoscopy fulguration of bleeding points under anesthesia. All the vital parameters and blood parameters before and after start of 1% alum irrigation were statistically compared using paired student t test.

RESULTS

Authors enrolled 34 patients in present study. These patients were having gross hematuria of bladder origin. The causes of hematuria in our cases were late onset radiation cystitis following external beam radiotherapy for carcinoma cervix. The average age of patients was 59.79 years (IQR =53-60). When RTOG scoring system for grading radiation cystitis was used our patients were graded from grade 2 to grade 4. Twenty-two cases had grade 2, 8 cases had grade 3 and 4 cases had grade 4 lesions.

Initial cystoscopy and clot evacuation were performed in all cases. In 28 patients' flat hemorrhagic lesions involving mainly posterior wall and trigone up to bladder neck were seen. Nodular lesions were seen in 6 cases. All of these 34 these patients were subjected to continuous bladder irrigation using 0.9% normal saline for 24 hours. Hematuria stopped in 3 cases.

In the remaining 31 cases where hematuria continued, authors instilled 200 ml hem coagulase (botroclot) in sterile (1:1 proportion) and blocked the catheter for 2 hours. None of the 31 patients responded to it and hematuria restarted.

Then authors started 1% alum irrigation in these patients. Authors had given alum irrigation maximum up to 48 hours. After instillation of 1% alum irrigation, 20 (64.51%) patients completely responded (hematuria settled in 24 hours in 14 cases; 36-48 hours in 6 cases). 4 (12.9%) patients had a partial response (hematuria decreased but continued even after 48 hours, blood transfusions could be avoided; hematuria settled in less than 72 hours). Seven (22.58%) patients had no response to alum irrigation and authors had performed cystoscopic fulguration under anaesthesia in these patients. Authors observed that 85.7% (6 out of 7 patients) who did not respond to alum irrigation had nodular lesions. The average duration of alum irrigation in the patients was 26.4 hours (IQR: 27-48). Average amount of alum solution used was 158.4 grams for each patient.

All the patients had hypogastric discomfort during irrigation. Twenty patients had mild, 7 patients had moderate and 4 patients had severe form of suprapubic pain. Though only 4 patients had severe suprapubic pain which responded only party to analgesics and antispasmodics it subsequently subsided after stoppage of irrigation when hematuria stopped. Sodium pentosan sulphate was given to patients with severe symptoms 75% (3 patients) of whom responded. None of them had symptoms of encephalopathy.

Authors observed changes in vital parameter during the period of alum irrigation which is depicted below in (Table 2). Except mild increase in systolic blood pressure other parameters did not show any statistically significant change.

Table 2: Changes in vital parameters during alum irrigation.

Parameter	Start of irrigation (average)	At 48 hours following irrigation (average)	P value
Pulse rate	80.29/min	82.03/min	0.311
Blood pressure (systolic)	125.88 mmHg	128.59 mmHg	0.024
Blood pressure (diastolic)	80.41 mmHg	81.35 mmHg	0.292
Temperature	98.8 F	99.1 F	0.234
Respiratory rate	20.41 /min	19.85/min	0.385

Table 3: Average blood parameters of patients during alum irrigation.

Parameter (Average value)	0 hour	48hours	p value
Hb	7.04 g/dl	7.13 g/dl	0.083
BUN	30.74 mg/dl	30.97 mg/dl	0.445
S.creat	1.00 mg/dl	0.95 mg/dl	0.173
PT	14.64 sec	15.02 sec	0.000384
APTT	35.76 sec	35.96 sec	0.481
Platelet count	3.08 lakhs/cumm	3.14 lakhs/cumm	0.069
pH	7.40	7.39	0.283
SGOT	48.5 U/L	52.3 U/L	0.172
SGPT	30.56 U/L	31.35 U/L	0.246
Total leukocyte count	8647 /cumm	8475 /cumm	0.198

The average blood parameters during alum irrigation are depicted below in (Table 3). Except increase in prothrombin time authors did not find any statistically significant change in the parameters (p value <0.05).

DISCUSSION

Alarming hematuria as a sequel to pelvic irradiation in carcinoma cervix patients is a common clinical problem with no definite recommended method of treatment. Intravesical agents, systemic therapies, hyperbaric oxygen and cystoscopic fulguration have been described. If these therapies do not suffice, then selective arterial embolization or cystectomy can be taken as last resort.

Ostroff EB et al, and Chenault OW et al, introduced a simple and effective method of 1% alum irrigation to control vesical hemorrhage and has been confirmed by many studies.[8,22,23]

Alum is classified chemically as an astringent. Potash alum is potassium aluminum sulphate or ammonium aluminum sulphate which is readily available in the market. The accepted mechanism by which 1% alum irrigation acts in controlling bleeding vessels is involvement in precipitation of protein in the interstitial spaces and cell membranes. This results in contraction of extracellular matrix proteins and tamponade of hemorrhagic areas. Local inflammatory response is prevented as there is sclerosing of exposed capillary endothelium and thereby minimizing aluminum absorption.[22,23]

Hem coagulase is an enzyme isolated from poison of Parmar B et al, which has got coagulative and anti-hemorrhagic properties.[24] It has thrombin and thrombosplastin like action on coagulation profile, transforming fibrinogen into fibrin.[25]

In present study authors used hemcoagulase (Botropase) solution in 1:1 proportion with normal saline as an intravesical agent prior to alum irrigation. However, authors did not find any patient responding to this therapy. A possible reason for this could be dilution of hemocoagulase. Additionally, large amount of this solution would be needed for irrigation which prevented its use. No literature was found regarding use of hemocoagulase in treatment of hemorrhagic cystitis.

There are many studies related to 1% alum irrigation. Arrizabalaga M et al, in their 15 patients of vesical hematuria found a complete response in 66 %, partial response in 15% and failure of response in 20% of the cases with 1% alum solution.[7]

Goswami AK et al, in their 12 patients found that 50% of the patients had complete response, 33% of patients had a partial response and 17 % of patients had failure of response.[8]

Authors found complete response in 20 (64.51%) patients, partial response in 4 (12.9%) patients and no response in 7 (22.58%) patients. All the patients had some form of hypogastric discomfort during irrigation. Twenty patients had mild, 7 patients had moderate and 4 patients had severe form of suprapubic pain. These spasmodic pains noted in our patients were probably the result of acidic pH of the solution. Most of these patients responded well to antispasmodics.

Among our 31 patients in whom alum irrigation was instilled, none of them exhibited statistically significant change in pulse rate, respiratory rate and temperature (Table 3). However, although there was no significant change in diastolic blood pressure, authors found a statistically increase in systolic blood pressure (p=0.024). Similarly, many studies commented on the safety profile in vital parameters when 1% alum irrigation is used.[7,8,22,23,26]

The mean irrigation time in our cases was 26.4 hours (IQR: 27-48). The average amount of alum used was 158.4 grams for each patient. Arrizabalaga M et al, and Goswami AK et al, reported average irrigation time of 21 hours and 36.5 hours respectively and the mean amount

of alum used in each patient were 6L and 10.48 L respectively.[7,8]

Although in this study authors did not measure the pre and post alum irrigation serum aluminum levels, authors closely monitored for any change in consciousness, cognition or any form of delirium throughout the procedure. Authors did not find any neurological symptoms in the 31 patients, suggesting the safety from systemic aluminum toxicity while using 1% alum irrigation. Aluminum from alum is absorbed via mucosal surface and is then excreted by kidneys which has a potential to excrete up to 30 times the normal values. Goswami AK et al, found a significant difference in pre and post alum irrigation serum level of aluminium of 1.68µmol/L and 3.36µmol./L ($p<0.001$) respectively.[8] Similarly other studies also found increase in post irrigation serum aluminium levels.[27] However, similar to present study, none of these studies had reported signs and symptoms aluminum toxicity following 1% alum irrigation although their post irrigation levels of serum aluminum was significantly higher. This is probably because aluminum level was lower than that which causes toxicity. Aluminum toxicity affects the CNS causing neurofibrillary degeneration which can cause difficulty in speech, dementia and rarely convulsions.[8]

In the blood parameters, authors found significant increase in prothrombin time from 14.64 sec to 15.04 sec ($p=<0.001$). Waldron-Edward D et al, found that the increase in prothrombin time in their patients exposed to alumina dust showed positive correlation with increase in serum aluminum levels.[28] This may be due to binding of aluminum to serum proteins which disturbs one or more of coagulation factors (I, II, V, VII or X).[28] Similar increase in prothrombin time 13.91 to 16.25 seconds was noticed by Goswami AK et al.[8] Kavoussi et al, found post irrigation serum aluminium level of 17µmol/L (normal 3 to 10µg/L) and increase in prothrombin time up to 23 seconds.[27] Such a massive increase in PT could be due to very high blood aluminum levels due presence of renal impairment in a few of their patients.

During cystoscopy authors have noticed that most of the lesions which responded to irrigation were flat in comparison to the nodular lesions that did not respond. Most of the lesions of radiation cystitis in this series were located in the posterior wall of bladder including trigone up to bladder neck. Posterior wall of bladder is nearer to the cervix than the anterior wall or dome, where EBRT is focused. This may be the reason for such site predilection. When 1% alum irrigation has failed, cystoscopic fulguration using monopolar diathermy has been used successfully in 7 patients.

This is an effective method of treating hemorrhagic radiation cystitis that is unresponsive to conservative measures.[29] Various methods of fulguration can be used like electrocoagulation and several types of lasers.[30]

CONCLUSION

Radiation cystitis following external beam radiotherapy to pelvis in uterine cervical cancer is a rare but serious disease. No standard of care therapy is presently available for such patients. The initial step in the management of hematuria in radiation cystitis is directed towards cystoscopy and clot evacuation, improvement of hematocrit. If hematuria persists in spite of irrigation with 0.9% normal saline, one can safely resort to 1% alum irrigation in patients with normal renal function for at least up to 36 hours. However, careful monitoring of clinical parameters during irrigation is advisable. Hemocoagulase instillation is ineffective in management of hematuria in radiation cystitis. Increase in prothrombin time during irrigation with 1% alum irrigation can be taken as an indirect parameter of serum aluminum levels. In case of incomplete response, cystoscopic fulguration is always an important saviour. Authors noticed that most of these hemorrhagic lesions were distributed in posterior bladder wall up to neck. Nodular lesions did not respond to 1% alum irrigation. To conclude, although there are many methods in the armamentarium to control hematuria in radiation cystitis, 1% alum irrigation is still an efficacious and safe time proven method.

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