MANAGEMENT OF INTRACTABLE HAEMATURIA IN CARCINOMA BLADDER

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ABSTRACT

Introduction: Intractable haematuria is a common and severe complication in patients with inoperable bladder carcinoma. Various options are available to treat haematuria in patients with inoperable bladder cancer; these include orally administered epsilon-aminocaproic acid, tranexamic acid, intravesical formalin, alum or prostaglandin irrigation, hydrostatic pressure, urinary diversion, radiotherapy, embolization and intra-arterial mitoxantrone perfusion. These treatment options are associated with different prospects of success, risks and side-effects. Well-designed and large studies comparing options are completely lacking. Despite various treatment options, management of intractable haematuria in patients with inoperable bladder cancer remains a challenge, and most of the reported methods are seen as experimental. Interventional radiology-selective embolization, haemostatic/hypofractionated radiotherapy and alum instillation seem to be suitable alternative options for patients who, after critical consideration, cannot be treated by irrigation, transurethral resection or palliative cystectomy.

Objectives: 1. To elaborate different methods used to control haematuria in advanced carcinoma of bladder patients. 2. To identify the effectiveness of each method.

Methods: All patients of carcinoma of urinary bladder who had intractable haematuria and admitted to our hospital for palliative treatment from August 2016 to July 2019 were retrospectively selected for the present study. These were the patients who were either diagnosed and received primary treatment at our hospital and later on came with recurrence of tumour and/or metastases or referred from other hospitals for palliative care. Different methods used to control haematuria were recorded and their effectiveness was evaluated.

Results: A total of thirteen patients were treated and included in the study. Of these eight patients were male and five patients were female. The mean age of patient was 67.7 years. Youngest patient was 55 years old and oldest patient was 85 years old. In four patients haematuria was controlled with EACA/tranexamic acid. Another four patients got relief with alum irrigation. Two patients underwent selective embolization, but one had partial relief and relapse within a week. Three patients were treated with radiotherapy and there was no relapse in this group.

Conclusion: There is no best method to control haematuria in carcinoma bladder. However, a systematic approach with large bore catheterisation and clot evacuation initially followed by cold saline irrigation should be done till initial work-up is done. Then as per the patient condition tranexamic acid, alum irrigation, selective arterial embolization and radiotherapy are the options to control haematuria. Further controlled trials are needed to label one therapy as the best therapy.

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INTRODUCTION

Intractable haematuria is defined as a severe form of haematuria where there is continuous loss of blood in urine with passage of clots and the haematuria/ bleeding cannot be controlled by simple means. Blood transfusion fails to keep pace with the rate of blood loss. It requires urgent intervention to control the haematuria. Irrigation of the bladder through a three-way catheter and fulguration of the bleeding lesions fail to stop the haematuria. Intractable haematuria from the bladder can be life-threatening and its management remains a difficult clinical problem. Patients with such uncontrollable haematuria are usually elderly and unfit for any major surgical intervention as a treatment. Various reasons for bleeding are sloughing of tumour mass, side-effects of radiation, cyclophosphamide-induced haemorrhagic cystitis and

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simultaneous ureteropelvic cancer or severe infection. The situation is further complicated by antplatelet drugs as the most of the patients are elderly and have associated comorbidities. Most of these patients are for palliative care. The situation worsens when these patients develop intractable haematuria as stopping the antplatelet drug and starting the antifibrinolytics drugs increase the chances of cardiac complications. We here will discuss various management options of intractable haematuria in carcinoma bladder patients with the aim to provide an overview of therapeutic options for such cases.

METHODS

All patients of carcinoma of urinary bladder who had intractable haematuria and admitted to our hospital for palliative treatment from August 2016 to July 2019 were retrospectively selected for the present study. These were the patients who were either diagnosed and received primary treatment at our hospital and later on came with recurrence of tumour and/or metastases or referred from other hospitals for palliative care. A total of thirteen patients were managed in different manner in a stepwise approach. Whatever the method, the management of intractable haematuria began with evacuation of all clots from the bladder before initiating any of the treatments. The evacuation was done by bladder irrigation through a large-bore three-way catheter in the ward, or by cystoscopic bladder irrigation in the operation theatre, if needed. Simultaneously blood samples were send for complete blood counts, serum creatinine levels, liver function tests, coagulation profile, urine routine microscopy and culture & sensitivity and blood grouping.

Following were the methods that we used to control intractable haematuria:

**Continuous bladder irrigation:** Initially all patients were catheterised with a wide bore catheter and bladder wash given to remove the clots in the bladder. This was followed by continuous irrigation of the bladder with normal saline.

**Orally antifibrinolitics (epsilon-aminocaproic acid [EACA] or tranaxemic acid):** EACA is a synthetic lysin that competitively inhibits fibrinolysis induced by plasminogen and plasmin. When given orally, the drug is absorbed rapidly and 80% is secreted unchanged in the urine within 24 hour. We used it in the dose of 150mg/kg/day for 2-3 weeks. Tranaxemic acid is a synthetic derivative of the amino acid lysine that exerts its antifibrinolytic effect through the reversible blockade of lysine binding sites on plasminogen molecules. We used tranaxemic acid 500 mg twice or thrice daily for 2-3 weeks. The haematuria was controlled effectively in four cases without any clinical side effects.

**Intravesical cold saline irrigation:** This method was used either alone or in combination with alum irrigation. Cold saline helps by mechanism of vasoconstriction locally to decrease haematuria temporarily.

**Our protocol:** We used sterile normal saline ice water slush for irrigation. First one/two/three litres of NS bottles, as per the availability in the hospital, were refrigerated to form ice. Ice slush was then made and mixed with cold normal saline. Irrigation was then started immediately so that the temperature remains low till the bag was finished and next started.

**Embolization:** Therapeutic embolization for the control of bladder haemorrhage was first reported in 1974 by Hald and Mygiand. This procedure has the advantage of doing it under local anaesthesia.

The internal iliac artery on either side is catheterised from the ipsilateral or contralateral femoral artery. The axillary artery can also be used but is difficult to puncture and has its own surgical problems. However, it gives good approach to the pelvic vessels because of its ease to enter both the internal iliac arteries and their main branches. We use the femoral approach. Various arteries can be embolised depending on the ease of catheterisation. Grossly we can do therapeutic embolization by completely occluding the internal iliac artery, or by selectively catheterising the anterior division of the internal iliac artery, or more selectively embolising the superior and inferior vesical arteries or super selectively embolising the specific small vessels that supply the specific regions. The material used could be coils, blood clot, gelfoam, histoacryl or isobutyl-2-cyanoacrylate. We used coils and gelfoam. We embolised the particular artery depending on the ease in that patient. In one patient we embolised superior vesical artery and in the other we embolised the anterior division of the internal iliac artery (Figure 1 & 2).

**Hypofractionated radiotherapy:** Irradiation has been used for the control of haematuria in patients with bladder carcinoma since 1960s. Various regimes have been used to control bleeding viz. 10 Gy with 12 x 12 cm portals or 30 Gy x 10 over two weeks. We used 30 Gy x 10 over two weeks and 6MV energy. All the patients tolerated the procedure well with minimal or very few side effects.

**Other described methods in literature:** these include

1. Hydrostatic bladder distension
2. Intravesical instillation of prostaglandins
3. Hyperbaric oxygen therapy
4. Urinary diversion.

RESULTS

A total of thirteen patients were treated and included in the study. These were the patients who were either diagnosed primarily with advanced carcinoma bladder or referred to us for tertiary/palliative care.

Of these eight patients were male and five patients were female. The mean age of patient was 67.7 years. Youngest patient was 55 years old and oldest patient was 85 years old. In all these patients after initial work-up, a large bore three way catheter was kept and bladder wash was given to remove all the clots. This was followed by continuous irrigation with normal
saline. Simultaneously all the patients were started intravenous epsilon-aminocaproic acid/tranexamic acid two to three times daily. Cold normal saline was also started in all the patients after 3-4 hours of admission, taking care to avoid hypothermia in already compromised elderly patients. If the bleeding doesn’t stop/decrease in 24 hours, then other methods to stop the haematuria were adopted. Haematuria stopped with EACA/tranexamic acid in four patients.

In four patients alum irrigation was sufficient to stop the haematuria.

Therapeutic embolization helped to control haematuria in two patients. In one patient we embolised vesical arteries and in the other we embolised the anterior division of the internal iliac artery (Figure 1&2).

Hypofractionated radiotherapy was needed in other three patients to control the bleeding. Ten cycles in two weeks helped the patient.

No major surgery was done at our centre, neither urinary diversion was done.

**DISCUSSION**

Massive and potentially life threatening haemorrhage secondary to bladder malignancy is a serious clinical problem owing to its morbidity. Most haematuria episodes due to advanced bladder malignancy can be controlled by continuous normal saline irrigation using three-way catheters and by endoscopic cauterization of bleeders. When these measures fail to control bleeding, the urologist then faces a difficult clinical situation. Potential causes of bleeding in bladder tumour could be the sloughing of the tumour, radiation cystitis, simultaneous prostate pathology in males and advanced cervical malignancy in females.

Many different methods have been described to control the haematuria. Comparison of the success rates of the different methods is limited due to relapse and the difficulty in assessing the severity and cause of bleeding. Moreover, there are no randomised control trials that can justify which method is the best in controlling the haematuria.

We used EACA/ tranexamic acid in all the thirteen patients alongside the normal saline/ cold saline irrigation. These oral measures stop bleeding completely in 30.77% of the patients. Rest of the patients had partial response. Stefanini et al. described nine patients with haematuria of various causes. They treated their patients with approximately 150 mg/kg/day EACA for up to 21 consecutive days. The authors reported that haematuria was controlled effectively in all cases without overt clinical reactions. In our study though the success was very less but we came to a conclusion that oral therapy with EACA/ tranexamic acid is definitely effective in controlling the haematuria.

We used alum irrigation in our patients where oral therapy with EACA/ tranexamic acid failed. Alum irrigation achieved success in four (44.44%) out of the nine remaining patients. Various studies have reported variable success rates 66% to 100% using 1% alum solution. Arribalagha et al. reported 66% success with complete response and 15% rate of partial response. Goswami et al. reported 50% complete response rate and 33% partial response rate. Ghahestani and Shakhsalim in their study also concluded that alum instillation is very effective and inexpensive method to control haematuria with the least morbidity in carcinoma bladder patients.

Therapeutic embolization is in use to control severe haematuria since 1974. Selective, super selective, unilateral or bilateral embolization can be done as per the expertise available. We did selective embolization in two patients. Different materials are used for embolization. We used gelfoam/coils for embolization. Pain in the gluteal region and fever were the main complications that our patients had. They subsided with symptomatic treatment. Hald and Mygindalso reported similar minor side effects. We had partial response in one patient. The haematuria recurred after 7 days. Ahmed El-Assmy also had 57% response rate with internal iliac artery embolization.

Radiation therapy for control of haematuria in carcinoma of the bladder has been in use since 1960. Various studies have been done to look for the benefits of radiotherapy in carcinoma bladder patients since then. We used hypofractionated radiotherapy in three patients. One of them had a partial relapse after selective embolization. All the patients had complete response. Chan et al had 100% response rate while Jose et al had 50% response rate in their studies. No recurrence of haematuria and any serious effects were noted. Chan et al reported no long term complications. We used 30 Gy x 10 over two weeks and 6MV energy. Chan et al used up to three doses of 10 Gy with 12 × 12 cm portals in 7 patients and got 100% response. Fossa and Hosbach used 3 Gy x 10 over 2 weeks in 39 patients and reported a marked improvement of haematuria. Jose et al used weekly 6-Gy fractions up to a total of 30–36 Gy in seven patients and had 50% response rate. Lacarrrière E et al in their study showed that 79% of patients undergoing hypofractionated regimen were haematuria-free.

**CONCLUSION**

Various treatment modalities are available to treat intractable haematuria in advanced carcinoma bladder patients. As most of the patients are elderly with or without co-morbidities and with a limited life expectancy, the choice of treatment for each patient differs. We should use the method that is minimal invasive and benefits the patient most. We recommend using cold saline irrigation first in all the patients, followed by oral antifibrinolytics. Alum irrigation comes next. This should be followed by embolization and hypofractionated radiotherapy respectively. Formalin should be used with caution due to need of anaesthesia and serious side effects of formalin. Finally, further randomised or case control studies are needed to find out the final solution for the problem.

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