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GENERAL UROLOGY

Original Article

Intravesical silver nitrate for refractory hemorrhagic cystitis

Refrakter hemorajik sistitte intravezikal gümüş nitrat

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ABSTRACT

Objective: Hemorrhagic cystitis is a challenging clinical entity with limited evidence available to guide treatment. The use of intravesical silver nitrate has been reported, though supporting literature is sparse. Here, we sought to assess outcomes of patients treated with intravesical silver nitrate for refractory hemorrhagic cystitis.

Material and methods: We identified nine patients with refractory hemorrhagic cystitis treated at our institution with intravesical silver nitrate between 2000-2015. All patients had failed previous continuous bladder irrigation with normal saline and clot evacuation. Treatment success was defined as requiring no additional therapy beyond normal saline irrigation after silver nitrate instillation prior to hospital discharge.

Results: Median patient age was 80 years (IQR 73, 82). Radiation was the most common etiology for hemorrhagic cystitis 89% (8/9). Two patients underwent high dose (0.1%-0.4%) silver nitrate under anesthesia, while the remaining seven were treated with doses from 0.01% to 0.1% via continuous bladder irrigation for a median of 3 days (range 2-4). All nine patients (100%) had persistent hematuria despite intravesical silver nitrate therapy, requiring additional interventions and red blood cell transfusion during the hospitalization. There were no identified complications related to intravesical silver nitrate instillation.

Conclusion: Although well tolerated, we found that intravesical silver nitrate was ineffective for bleeding control, suggesting a limited role for this agent in the management of patients with hemorrhagic cystitis.

Keywords: Bladder; hematuria; hemorrhagic cystitis; intravesical; silver nitrate.

ÖZ

Amaç: Hemorajik sistit tedaviyi yönlendiren kısıtlı sayıda kanıtla zorlayıcı bir klinik durumdur. Destekleyici az sayıda literatüre rağmen intravezikal gümüş nitrat kullanımı bildirilmiştir. Burada refrakter hemorajik sistit için intravezikal gümüş nitratla tedavi edilen hastaların sonuçlarını değerlendirmeyi araştırdık.

Gereç ve yöntemler: Enstitümüzde 2000-2015 yılları arasında intravezikal gümüş nitratla tedavi edilen refrakter hemorajik sistitli dokuz hasta saptadık. Hastaların tümünde önceden yapılan pıhtı tahliyesi ve normal salinle sürekli irrigasyon tedavisi başarısız olmuştu. Tedavi başarısı hastaneden taburcu olmadan önce gümüş nitrat instilasyonu sonrası normal salin irrigasyonunun ötesinde herhangi bir ek tedavi gerekmemesi olarak tanımlanmıştır.

Bulgular: Ortanca hasta yaşı 80 yıl (IQR 73, 82) idi. Hemorajik sistitte en sık etyolojik neden radyasyondu (%89; 8/9). İki hastaya anestezi altında yüksek doz (%0,1-%0,4) gümüş nitrat uygulanırken geri kalan 7 hasta ortalama 3 (2-4 gün) gün sürekli mesane irigasyonuyla %0,01-%0,1 arası dozlarla tedavi edilmiştir (range 2-4). Dokuz hastanın tümünde (%100) intravezikal gümüş nitrat tedavisine rağmen hematüri sebat etti ve bu hastalar hastanede yatışları sırasında ilave girişimlere ve eritrosit transfüzyonlarına gerek duymuştur. İntravezikal gümüş nitrat instilasyonuyla ilişkili herhangi bir komplikasyon tanımlanmamıştır.

Sonuç: İyi tolere edilmiş olmasına rağmen intravezikal gümüş nitratın kanama kontrolünde etkisiz olduğunu saptamış olmamız hemorajik sistit hastalarının tedavisinde bu maddenin kısıtlı bir rolü olduğunu düşündürmektedir.

Anahtar kelimeler: Mesane; hematüri; hemorajik sistit; intravezikal; gümüş nitrat

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Introduction

Hematuria is one of the most common reasons for urological consultation.[1] Hemorrhagic cystitis is a challenging clinical entity due to the diffuse nature of bleeding from the urothelium, and is most commonly secondary to pelvic radiation therapy.[2,3] Over time, radiation therapy can cause obliterative endarteritis which in turn results in bladder mucosa ischemia, tissue breakdown, and hemorrhage.[4,5] The degree of hematuria in patients with hemorrhagic cystitis can be highly variable, but in its most severe form, the hematuria can require blood transfusions, be refractory to intravesical therapies and may require urinary diversion.[6]

Notably, there are a number of treatment options commonly reported for hemorrhagic cystitis (e.g. saline irrigation, alum irrigation, silver nitrate irrigation, formalin instillation, cystoscopic fulguration, bilateral nephrostomy tubes, hyperbaric oxygen therapy, cystectomy, etc.), with several treatment algorithms that highlight a step-wise progression from least invasive to more invasive therapies having been proposed.[2,7] One of the frequently referenced options is intravesical silver nitrate instillation.[2,7,8] The use of intravesical silver nitrate for radiation cystitis was first reported in the 1960s.[9] The proposed mechanism of action involves conversion of silver nitrate into nitric acid which causes chemical cauterization of urothelium.[10,11] Unfortunately, since that report data regarding the effectiveness of silver nitrate remains scarce, with less than 20 total cases reported and the most recent publication being from the 1980s.[9,12-14]

Therefore, we assessed the outcomes of patients treated with intravesical silver nitrate for refractory hemorrhagic cystitis, in a contemporary cohort of patients.

Material and methods

Following Institutional Review Board approval, we identified nine patients who underwent intravesical silver nitrate treatment for hemorrhagic cystitis between 2000 and 2015 at our institution. All patients were 18 years or older at the time of treatment, and all had failed initial measures including indwelling large-bore catheter placement with continuous normal saline bladder irrigation and cystoscopic clot evacuation.

Intravesical silver nitrate was delivered either under anesthesia (n=2) or during general floor care (n=7), depending on the concentration instilled. For those treated during regular floor care, the concentration of silver nitrate was gradually increased from 1:7500 (0.01%) to 1:1000 (0.1%) over the course of two to four days. Irrigation was discontinued if hematuria did not improve after reaching the 0.05% or 0.1% concentration. Two patients underwent multiple intraoperative instillations under general anesthesia after rigid cystoscopy with clot evacuation and fulguration of any discrete bleeding vessels. A large bore catheter was then placed and cystogram performed to ensure no evidence of bladder perforation. Silver nitrate solution (0.1% or 0.4%) was instilled into the bladder under gravity with a dwell time of 15 minutes. After draining the silver nitrate from the bladder, the bladder was copiously irrigated with sterile water and continuous bladder irrigation with normal saline was initiated.

Patient charts were reviewed for clinicopathologic variables including gender, age at the time of silver nitrate therapy, etiology for hemorrhagic cystitis, medical comorbidities, previous therapies for hemorrhagic cystitis, peri-instillation complications (during hospitalization), blood transfusion after silver nitrate therapy, hematuria resolution, and subsequent therapies for hemorrhagic cystitis. Treatment success was defined as requiring no additional therapy beyond normal saline irrigation after silver nitrate instillation prior to hospital dismissal.

Continuous variables are summarized with median and interquartile range; categorical variables are summarized by number count and percentage. Statistical analyses were performed using the JMP Pro 11 software package (SAS Institute, Cary, NC).

Results

We identified nine patients managed with intravesical silver nitrate between 2000-2015 at our institution. Patient demographics are provided in Table 1. Notably, the majority of patients 89% (8/9) were male, and pelvic radiation therapy was the most common etiology for hemorrhagic cystitis (89%, 8/9). Median patient age at the time of presentation was 80 years (Interquartile range 73; 82). The median time from radiation therapy to hospitalization for hemorrhagic cystitis was 7 years (Interquartile range 3.6; 11.7). All patients were hospitalized at the time of silver nitrate instillation, and the average length of hospitalization including silver nitrate therapy was 39.4±16.8 days.

All patients were initially treated with cystoscopy, clot evacuation, and continuous normal saline bladder irrigation. Additionally, eight patients (88.9%) underwent cystoscopic fulguration of bladder mucosa at least once. Seven patients (77.8%) underwent intravesical alum irrigation and two patients (22.2%) underwent hyperbaric oxygen therapy prior to silver nitrate instillation. The mean number of interventions prior to intravesical silver nitrate therapy was 3.3±1.7 (Table 2).

Seven patients (77.8%) underwent continuous intravesical silver nitrate irrigation without anesthesia for a median of 3 days (range 2-4 days). Irrigation concentrations were progressively increased from 0.01% (1:7500) to 0.1% (1:1000). Two patients (22.2%) underwent instillations under anesthesia for 15 minutes

Table 1. Patient clinical and demographic features

	Intravesical silver nitrate instillation (n=9)
Median age (yrs), (IQR)	80 (73, 82)
No. Gender (%)	
Male	8 (89)
Female	1 (11)
Hemorrhagic cystitis etiology (%)	
XRT† for PCa‡ or GYN Ca*	8 (89)
Idiopathic	1 (11)
Median BMI, (IQR)	29 (25.5, 31.5)
No. diabetes mellitus (%)	2 (22.2)
No. hypertension (%)	8 (88.9)
No. coronary artery disease (%)	6 (66.7)
No. current or previous smoker (%)	5 (55.6)

† XRT: External Beam Radiation; ‡Prostate Cancer; *Gynecologic cancer

Table 2. Prior hemorrhagic cystitis treatment

	Intravesical silver nitrate instillation (n=9)
Continuous saline bladder irrigation (%)	9 (100)
Cystoscopy + clot evacuation (%)	9 (100)
Intravesical alum (%)	7 (77.8)
Formalin (%)	0 (0)
Aminocaproic acid (%)	0 (0)
Hyperbaric oxygen therapy (%)	2 (22.2)
No. Pre-interventions, mean, (SD)	3.3 (1.7)

at a maximum concentration of 0.4% (1:250). No complications were noted following intravesical silver nitrate therapy.

Intravesical silver nitrate therapy was unsuccessful at stopping hematuria in all nine patients (100%). Likewise, all patients required transfusion of at least one unit of packed red blood cells due to continued bleeding following intravesical silver nitrate. Furthermore, a mean of 3.4±1.5 additional interventions after intravesical silver nitrate therapy were required prior to cessation of hematuria. Five patients (55.6%) proceeded to intravesical formalin instillation, five patients (55.6%) underwent bilateral nephrostomy tube placement, and one patient (11.1%) ultimately underwent cystectomy with urinary diversion (Table 3).

Table 3. Perioperative and postoperative outcomes

	Intravesical silver nitrate (n=9)
Method of silver nitrate instillations	
Continuous irrigation without anesthesia	7 (77.8%)
Intraoperative instillation (15 min.)	2 (22.2%)
Length of hospitalization (days), mean (SD) (%)	39.4 (16.8)
No. units pRBC transfused during hospitalization, mean (range)	16 (1-36)
Resolution of hematuria (%)	0 (0)
Patients requiring transfusion after therapy	9 (100)
No. interventions after silver nitrate, mean, (SD)	3.4 (1.5)
Additional procedures (%)	9 (100)
Hyperbaric oxygen therapy	2 (22.2)
Aminocaproic acid	1 (11.1)
Formalin	5 (55.6)
Bilateral nephrostomy tube placement	5 (55.6)
Cystectomy with urinary diversion	1 (11.1)
Complications following Silver Nitrate therapy	None

Discussion

We found that none of our patients experienced resolution of their hematuria following intravesical silver nitrate for the treatment of refractory hemorrhagic cystitis. On average, these patients required approximately three additional interventions in an escalating fashion prior to hematuria cessation. Interventions commonly used include cystoscopic clot evacuation with electrical fulguration of areas of bleeding, saline irrigation, alum irrigation, formalin installation, urinary diversion via nephrostomy tubes, and hyperbaric oxygen therapy.[2] Even though intravesical silver nitrate is a commonly cited treatment in therapeutic algorithms,[2,5,7,8] there is a paucity of data supporting its use for refractory hemorrhagic cystitis secondary to radiation in adult patients.

Silver nitrate is a cauterizing agent commonly utilized for control of epistaxis.[15-17] In the case of epistaxis, dry silver nitrate is directly applied to tissue via an applicator stick. When combined with water, silver nitrate produces nitric acid which is a highly corrosive mineral acid capable of a chemical cauterizing effect.[10,11] Delivery of silver nitrate into the bladder requires dilution of silver nitrate in water to create an irrigant. A literature search revealed data on approximately sixteen patients who had been

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treated with intravesical silver nitrate for hemorrhagic cystitis, with the majority of these patients being children with cyclophosphamide induced hematuria.[9,12-14] It should be noted that in the largest series, response to silver nitrate was not durable and bleeding recurred in the majority (6/8, 75%) of children.[13] Only one previous publication commented on effectiveness of intravesical silver nitrate for radiation cystitis in an adult population, and found that it was not effective in their three cases.[9] These results are consistent with our findings of limited efficacy in this patient population.

We did not identify any specific complications related to intravesical silver nitrate therapy. To date, the only published complication is anuria developing after intravesical instillation of 1% silver nitrate solution, which was thought to be secondary to ureteral obstruction as a result of mucosal ulceration/edema and silver salt deposition.[14] Notably, the highest concentration utilized within our patient population was 0.4% and prior to instillation of normal saline a thorough bladder rinse with sterile water was performed in an effort to decrease silver salt deposition.

Limitations of our series include the small cohort size, variable silver nitrate concentrations utilized, and retrospective design. It should be noted that given the retrospective nature of the series and timeframe of patients included, no standardized treatment algorithm for hemorrhagic cystitis was utilized and the decision to proceed with intravesical silver nitrate was at the discretion of the treating physicians. However, as noted by the treatment of these patients, management proceeded with a stepwise fashion with all patients failing conservative measures (saline irrigation, clot evacuation, etc) prior to intravesical instillation and many had failed other intravesical agents prior to silver nitrate instillation. Lastly, while our data augments the sparse available literature on intravesical silver nitrate instillation, it is still limited in scope. Ideally, further larger studies, potentially in a multicenter setting, may better define the utility of silver nitrate instillation in this challenging clinical entity.

In conclusion, intravesical silver nitrate was ineffective for treating hemorrhagic cystitis and should have a limited role in the management of adult patients with hemorrhagic cystitis. Ultimately, additional data is required for further refinement of hemorrhagic cystitis treatment algorithms.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Mayo Clinic (IRB Application #: 14-009325).

Informed Consent: Informed consent was not obtained for this study due to its retrospective nature and minimal risk to patients. Its retrospective nature made obtaining informed consent impractical as many subjects were lost to follow up, no longer seen regularly in clinic, or deceased.

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Hasta Onamı: Retrospektif doğası ve hastalara minimal riski nedeniyle bu çalışma için bilgilendirilmiş onam alınmamıştır. Retrospektif doğası nedeniyle, birçok hasta takipten kaçtığı, düzenli olarak klinikte görülmediği veya öldüğü için bilgilendirilmiş onam alınmasının pratik onemi yoktur.

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