Ureteroscopic evaluation and treatment of benign essential hematuria: a systematic review

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Introduction: *The advent of ureteroscopy has revolutionized the treatment many urologic diseases, including benign essential hematuria. This systematic review examines the treatment of benign essential hematuria (BEH) with ureteroscopic interventions.*

Materials and methods: *We performed a systematic review of the literature from 1977 to May 2020. We included studies that evaluated the use of ureteroscopy to diagnose or treat BEH. Demographics, follow up, findings, treatment method and success rate were extracted from each identified paper. Quality analysis was performed independently by both authors.*

Results: *Our search resulted in 587 articles. Fifteen of these studies met inclusion criteria and were included in the final analysis. No randomized controlled trials were found. All 15 studies were case series. Nine studies were graded as good, five as fair, and one as poor. Follow up ranged from 2 to 108 months. A total of 307 patients underwent ureteroscopy for suspected BEH; 223 (73%) were diagnosed with a discrete lesion, 33 (11%) with a diffuse lesion, and 44 (14%) had no lesions seen on ureteroscopy. Of those diagnosed with discrete lesions, the most common was minute venous ruptures (35%), followed by hemangiomas (26%). Ureteroscopic treatment successfully relieved the hematuria and symptoms in most patients, and was more successful in those treated for discrete lesion (115/120, 96%) than diffuse (10/19, 53%).*

Conclusions: *Ureteroscopic treatment of BEH yields excellent outcomes. In this systematic review, 96% of patients with discrete lesions and 53% of patients with diffuse lesions had resolution of their hematuria after ureteroscopic interventions.*

Key Words: essential hematuria, ureteroscopy, hemangioma, minute venous rupture

Introduction

Evaluating patients with hematuria is a common urologic consultation. Patients will usually undergo a standard urologic evaluation including upper urinary tract imaging, cystoscopy, and cytology if indicated. Often, this evaluation will diagnose tumors, stones, anatomic abnormalities or urinary tract infections. Occasionally, the cause cannot be determined through conventional radiologic and hematologic studies and is referred to by the general term, benign essential hematuria (BEH). If the hematuria is found to originate from only one kidney, it may be called lateralizing hematuria.

These patients can have frequent bouts of gross hematuria with clots and renal colic but generally follow a benign course. Rarely a patient will have serious bleeding requiring transfusions and partial or total nephrectomy. Improvements in ureteroscopic instrumentation have had a significant effect on our ability to evaluate and treat patients with lateralizing hematuria.

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The most common lesions causing BEH are small venous abnormalities and hemangiomas on the urothelial surface that can be missed with many conventional imaging studies. Virchow in 1867 first described renal hemangiomas found during autopsy, and suggested they may be a cause of chronic hematuria. For many years, there were no effective treatments for the condition. In 1900, E. Hurry Fenwick, who dedicated much of his professional career to the diagnosis and treatment of lateralizing hematuria summed it up well, stating these diagnoses have "for so long puzzled and baffled the physician by their obscurity, persistency, and danger".[1] There were only rare reports of renal hemangiomas causing unexplained hematuria until 1941 when Webb-Johnson and Turner-Warwick described two cases of essential hematuria cured by nephrectomy. Lateralizing hematuria then became a more clinically relevant diagnosis.[2]

In the past, computed tomography, angiography, and various retrograde studies were the only tools available for evaluating patients with possible upper urinary tract abnormalities. Ureteroscopy not only allows us to better determine the underlying cause of bleeding in patients with hematuria, it also has greatly improved our ability to treat these patients, allowing nephron-sparing endoscopic treatments with few complications.

We carried out a systematic review of ureteroscopy for BEH with the primary goal to answer two questions: 1. What are the most common diagnosis seen during ureteroscopy? and 2. How effective is ureteroscopic treatment for BEH at resolving hematuria?

Materials and methods

Search criteria

All searches were performed within a date range of January 1977 to May 2020. 1977 was used as the inception year for this search as this is the year that use of a ureteroscope was first reported. We searched the Cochrane Central Register of Controlled Trials, Medline (using both PubMed and Ovid interfaces), and Embase. We also examined the reference lists and related links of retrieved articles in PubMed to detect studies potentially eligible for inclusion. We also evaluated chapters, reviews and editorials published within our time frame. Experts in the field were consulted as well.

We identified relevant studies using the search terms "ureteroscope", or "ureteroscopy", or "ureteroscopic", and "hematuria", "essential", "lateralizing", or "unilateral".

Study selection

We included studies if they evaluated or treated hematuria and included ureteroscopy for diagnosis and/or intervention and included diagnosis and resolution of hematuria as endpoints. Accepted study types were clinical trials, cohort studies, case series, systematic reviews and/or meta-analyses.

All non-English and nonhuman studies were excluded. Any study published outside the review time frame as discussed above was excluded as well as any study that did not include the study population, intervention, or endpoint listed. Single case reports were also excluded.

In total, 587 studies were identified. Twenty-one initially met our inclusion criteria. Six were excluded for the following reasons: two did not include resolution of hematuria as an endpoint,[3,4] two were reviews,[5,6] one was an editorial letter,[7] and one included a large cohort of patients whose subset of essential hematuria patients were published separately.[8]

Validity assessment

Our search identified 587 studies, of which 15 fulfilled our inclusion criteria.[9-23] The Intervention Series Quality Assessment Tool was used to grade all studies using a final grade of good, fair, or poor. Because all included studies were case series and none included a control group, traditional scoring systems could not be used for study quality assessment. We used a tool for grading of intervention studies developed by researchers from the Pacific Northwest Evidence Based Practice Center, Oregon Health & Science University. Two investigators independently scored each included study. Disagreements were resolved by consensus.

Data abstraction

From each study one investigator extracted information on study characteristics, patient data, and outcome measures using a standardized protocol. A second investigator reviewed this data for accuracy. Disagreements were resolved by consensus.

Statistical analysis (list tests) was done using Stata 11.2 (StataCorp LP, College Station, TX, USA).

The PRISMA guidelines were followed when preparing this protocol and manuscript.[24] See Figure 1 for the PRISMA flow diagram.

Results

Diagnosis

Table 1 shows the diagnostic characteristics of the 15 included studies. In total, 307 patients underwent attempted ureteroscopy for possible

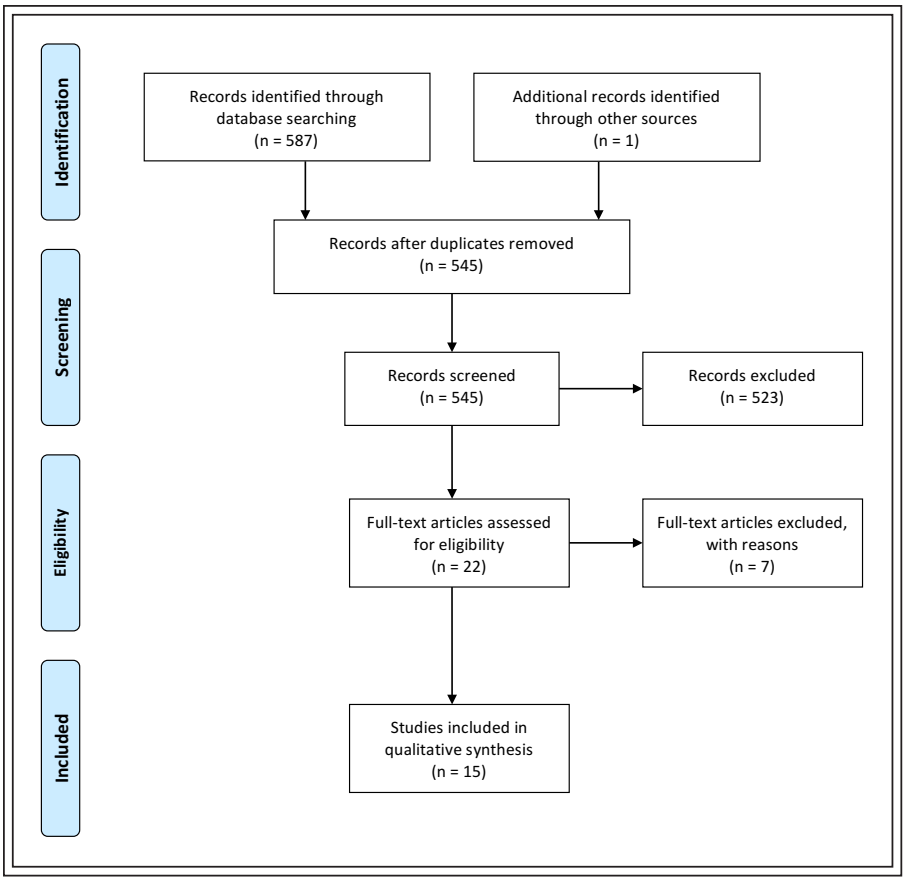

Figure 1. PRISMA flow diagram.

BEH. The procedure was aborted in two patients due to unsuccessful ureteroscope passage in an early series[18] for a total of 395 patients who underwent successful ureteroscopy. In the studies that recorded sex, 43.3% of patients were male. The weighted mean age, when recorded, was 40.8 years old (range: 14-82).

Ureteroscopic inspection revealed 227 discrete (74.4%) and 33 diffuse lesions (10.8%). No causative lesion was seen in 45 patients (14.8%), Figure 2. Discrete lesions included previously undiagnosed renal calculi found in 8 patients (2.6%) and transitional cell carcinoma found in 8 patients (2.6%). Two patients had ureteral strictures that were thought to be the cause of the hematuria. The majority of the lesions identified were minute venous ruptures, seen in 107 patients (35.1%) and hemangiomas, seen in 81 patients (26.6%). Diffuse lesions, such as large or multiple venous abnormalities or hemangiomas, made up 10.8 % of the total lesions seen. The remainder of the less common findings are listed in Table 1.

Treatment

Endoscopic treatment was attempted in 200 of the 227 discrete lesions identified (88.1%). Endoscopic treatment was attempted less frequently in patients with diffuse lesions with 16 of the 33 lesions undergoing treatment (47%).

In the Gittes and Varady study,[22] ureteroscopy was only used for diagnosis followed by total nephrectomy (12/13 patients) or partial nephrectomy (one patient). In the remainder of the studies, endoscopic treatment included fulguration (63.8%), laser ablation (13.7%), nitrate cautery (0.44%), or some combination of these modalities (15.9%). Two calculi were treated with ureterolithotomy and one with percutaneous nephrolithotomy.

Success rate

The overall success rate (resolution of hematuria at

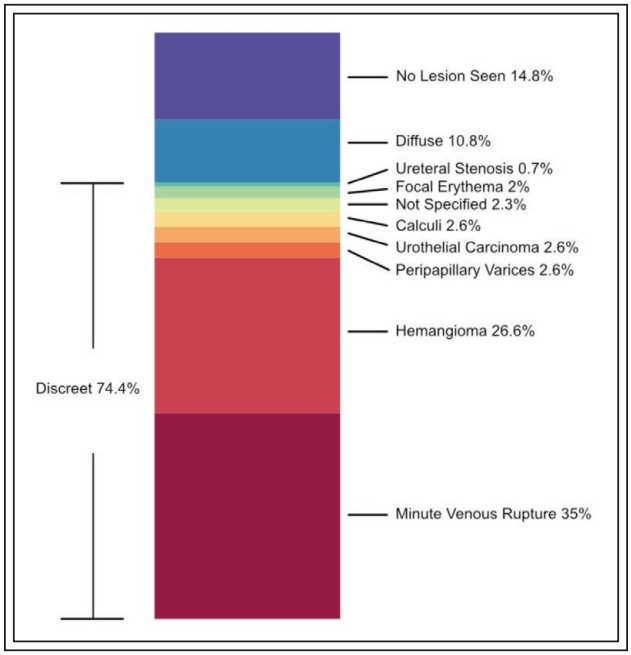

Figure 2. Ureteroscopic findings.

Study and Year	n	Mean Age (yrs) (range)	Sex Ratio (Male: Female)	Endoscopic Findings: Discrete					Diffuse	No Lesion Found	Success (%)				Mean Follow up (months)
				Hemangioma	Minute Venous Rupture	Other Discrete Lesions	Tumor	Stone			Discrete Lesions	Diffuse Lesions	No Lesion	Total	
Gittes and Varady. 1981	13	31 (15-39)	4:9	5	0	0	0	0	8	0					
Patterson et al. 1984	4	36.5 (20-73)	2:2	0	2	0	0	0	2	0	2/2	2/2	0/0	4/4	5.5
McMurtry et al. 1987	8	31 (5-54)	4:4	0	4	0	0	1	3	0	5/5	1/3	0/0	6/8	11
Kavoussi et al. 1989	8			0	0	6	0	0	0	2	5/6	0/0		5/6	11
Bagley and Allen. 1990	32	38 (14-67)	12:20	11	2	1	1	1	9	5	12/13	0/4	5/5	17/22	
Desgrandchamps et al. 1994	8	50.6 (24-70)	2:6	0	0	3	0	0	4	1	0/0	4/4	0/1	4/5	16
Nakada et al. 1997	17	44 (21-67)		5	0	4	1	1	3	3	9/11	0/3	1/3	10/14	60
Tawfiek and Bagley. 1998	23	60.5 (36-80)	14:9	7	3	0	3	2	3	5	14/14	3/3	4/5	21/22	8
Yazaki et al. 1999	15	NR (26-73)	7:8	1	2	1	1	0	1	4					
Mugiya et al. 1999	4	53 (32-84)		1	0	3	0	0	0	0	4/4	0/0	0/0	4/4	
Daneshmand and Huffman. 2002	15	37.5 (NR)		15	0	0	0	0	0	0	11/12	0/0	0/0	11/12	20.2
Mugiya et al. 2007	23	48 (18-82)	15:8	2	14	0	0	2	0	5	9/9	0/0	0/0	9/9	73
Brito et al. 2009	13	37.2 (27-66)	2:11	9	4	0	0	0	0	0	13/13	0/0	0/0	13/13	26
Mugiya et al. 2010	20	41 (18-82)	9:11	4	15	0	0	0	0	1	19/19	0/0	0/0	19/19	16
Araki et al. 2012	104	37 (14-80)	56:48	21	61	3	0	1	0	18		0/0		97/104	139
Total	**307**	**40.8**	**127:136**	**81**	**107**	**21**	**6**	**8**	**33**	**44**	**115/120**	**10/19**	**10/14**	**220/242**	

TABLE 1. **Diagnosis and treatment of benign essential hematuria.**

follow up) was 91%. Treatment of discrete lesions causing hematuria was uniformly high in all the studies with a pooled success rate (defined as the absence of gross hematuria at follow up) of 95.6%. Follow up was reported in thirteen of the fifteen studies and ranged from 2-277 months.

Of the nineteen patients with diffuse lesions that were treated, ten (53%) had resolution of their hematuria.

One of the three patients with a discrete lesion that was not treated had resolution of their gross hematuria as well. Similarly, where success rates were reported for patients with no lesion seen, ten of the fourteen patients (71%) had resolution of their hematuria.

None of the studies in this systematic review reported complications.

Quality assessment

The grading system used was developed by researchers from the Oregon Evidence Based Practice Center and based on the United States Preventative Services Task Force Cohort Tool for grading of intervention studies as all studies were case series and none contained a control group. Of the fifteen studies included in this review, nine studies were graded as good, five as fair, and one as poor.

Discussion

BEH is a relatively rare but difficult to diagnose urologic problem. Improvements in ureteroscopic instrumentation and technique have helped tremendously with the diagnosis and treatment of this disease. The most common finding during ureteroscopy for lateralizing hematuria was minute venous ruptures. These venous abnormalities of the calyces have been variously described in the literature as renal forniceal hemorrhages, varices, pyelovenous fistula, and hemorrhagic papillitis as well. Though they may differ slightly, they all seem to share a common pathological basis. Anatomic studies in the past have demonstrated a close relationship between the tributaries of the renal vein and the calyceal fornix.[25] These venous sinuses are so close to the surface of the calyceal fornix that they may erode or rupture through the urothelium. It is postulated that they may develop after periods of elevated pressure within the intrarenal collecting system.[6]

Renal hemangiomas were the second most common finding during ureteroscopy in our study. They most commonly occur on the tips of the renal papilla. Historically, these can be quite large in size but are typically small and occasionally microscopic.[26] They usually appear as small red or blue spots, but can occasionally look like large mulberry-like lesions. The associated hematuria tends to be spontaneous in onset and intermittent in nature, though significant hemorrhage is possible.

When treated endoscopically, discrete lesions had a resolution rate of 96%. Interestingly, 71% of patients had resolution of their hematuria after ureteroscopy even when no lesion was seen. It has been suggested this could be due to closure of unseen venous-caliceal communications because of increased intraluminal pressure during ureteroscopy.

This study was limited by the quality of literature available for the review. Of the fifteen studies, nine studies were graded as good, five as fair, and one as poor. Follow up varied greatly from study to study, but was deemed adequate. All the studies were case series with no randomized studies or case-control series.

Based on our systematic review, we recommend performing ureteroscopy in patients that present with a possible diagnosis of benign essential or lateralizing hematuria. Negative upper urinary tract imaging, cystoscopy, cytology and urine culture are the norm. If an obvious source of the hematuria cannot be determined through conventional workup, ureteroscopy is the next step. Ureteroscopic evaluation and treatment are more successful when the patient is actively bleeding, and when the lesions are discrete rather than diffuse. This should be performed with a "no touch" technique to minimize upper tract irritation which can make it difficult to visualize small vascular lesions or other areas of bleeding.[27] Once identified, these lesions should be treated with fulguration or laser ablation depending on what equipment is available and the surgeon's experience with the technology. Using the above technique, the majority of patients (91%) have an excellent chance of resolution of their hematuria.

Conclusions

BEH is rare and can be difficult to diagnose, but ureteroscopic treatment is successful in most patients. □

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