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Successful Use of Renal Denervation in Patients With Loin Pain Hematuria Syndrome—The Regina Loin Pain Hematuria Syndrome Study

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Introduction: Loin pain hematuria syndrome (LPHS) is characterized by severe unilateral or bilateral loin pain that suggests a renal origin but occurs in the absence of identifiable or relevant urinary tract disease. Hematuria can either be microscopic or macroscopic, but the renal abnormalities responsible for the hematuria are unexplained. Debilitating pain refractory to conventional pain medications is the main cause of morbidity.

Methods: We conducted a single-arm, single-center study. Twelve patients between the ages of 21 and 62 years (11 female, 1 male) with LPHS underwent endovascular ablation of the renal nerves between July 2015 and November 2016, using the Vessix renal denervation system. The primary objective was to achieve 30% reduction in self-reported pain with the McGill Pain Questionnaire (MPQ) at 6 months. The secondary objectives were to measure changes in disability (Oswestry Disability Index [ODI]), mood (Geriatric Depression Scale [GDS]), and quality of life (EuroQol-5D [EQ-5D] and the MOS 36-Item Short Form Survey [SF-36]) scores from baseline to 6 months postprocedure.

Results: Ten of 12 patients at 3 months and 11 of 12 patients at 6 months reported a >30% reduction in pain based on the MPQ at 3 and 6 months. We found consistent improvements in MPQ, ODI, GDS, EQ-5D, and SF-36 scores from baseline to 6 months postprocedure.

Conclusion: We conclude that renal denervation is associated with a considerable improvement in pain, disability, quality of life, and mood. Our results suggest that percutaneous catheter–based delivery of radiofrequency energy is a safe, rapid treatment option that should be considered in all patients with LPHS.

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Loin pain hematuria syndrome (LPHS) is a rare clinical disorder with a reported prevalence of 0.012%[1] and typically affects younger women. Since its initial description in 1963,[2] it has remained a poorly understood clinical condition characterized by severe, unilateral or bilateral loin pain localized to the kidney but in the absence of identifiable urinary tract disease.[2] Hematuria can be either microscopic or macroscopic, and the renal abnormalities responsible for both pain and hematuria are often unexplained.[3] Debilitating pain refractory to conventional pain medications is the main cause of morbidity.[4] LPHS imposes a significant health and economic impact in terms of loss of productivity and quality of life in a young population as these patients are shuffled among numerous health care providers in search of a diagnosis.[5] Multiple visits to the emergency departments add to the significant burden of investigations and consultations.

It is likely that multiple, as-yet-unrecognized stimuli are responsible for the agonizing and unrelenting pain. Nociceptive fibers are transmitted in afferent Aδ and C

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fibers from the kidney, coursing through the periarterial nerves, ascending by way of renal and intermesenteric plexi to the lowest splanchnic nerve, and passing via the dorsal roots of T11 through L1 to the spinothalamic tracts.[6,7] The presence of these pain-carrying fibers in the renal arterial adventitia presents a unique opportunity to interrupt the pathways by using percutaneous intravascular ablation by thermal ablation as a practical superior alternative. Recent case reports[8] and small case series[9,10] have shown successful renal denervation (RDN) to be a potent therapeutic target for patients with LPHS. It has the advantage of being catheter based, safe, rapid, and minimally invasive.[8,9]

We present 12 cases of patients who underwent successful RDN as part of our Prairie renal denervation study using the Vessix renal denervation system, leading to significant improvement in pain relief.

MATERIALS AND METHODS

Study Design and Participants

We conducted a single-center, single-arm, pre−post design study, consisting of 12 patients with LPHS who were referred for bilateral endovascular ablation of the renal nerves for pain relief across western Canada. Individual patient consent was obtained prior to the procedure. RDN was performed after seeking Health Canada approval. The results of this study include findings from 4 patients of our previous study.[9]

Inclusion Criteria

Patients were included if they had flank and loin pain expressed at the costovertebral angle, unilateral or bilateral, and described as "deep pain." Pain was required to be chronic, severe, recurrent for 6 months or more, and exacerbated by a gentle punch to the costovertebral angle. It was required to be sufficiently severe to prompt the patients' health care providers to prescribe or consider narcotic therapy. If urolithiasis had occurred in the past, the absence of obstruction was confirmed by 1 or more consecutive imaging procedures obtained during episodes of flank pain. For the LPHS cohort, hematuria was defined as more than 5 red blood cells (RBCs) per high-power field (HPF).

Exclusion Criteria

Patients were excluded if the traditional causes of flank pain and hematuria were present: obstructive uropathy, pyelonephritis, polycystic kidney disease, renal artery embolism, renal artery dissection, renal papillary necrosis, renal vein thrombosis, left renal vein entrapment (nutcracker syndrome), trauma, and renal tumor. All patients underwent cystoscopy and triphasic computed tomography of the abdomen and pelvis with delayed images; a MAG3 split-function renogram was arranged to look at split glomerular filtration rate to exclude secondary causes of LPHS. Patients also underwent basic biochemistry tests (including a renal panel and electrolytes) and a complete blood count, and provided urine for cytology and repeated urine microscopic examinations.

Procedure

All patients underwent renal artery radiofrequency ablation using a Vessix catheter, 5- to 7-mm wide, in the angiography suite under general anesthesia. An interventional radiologist gained percutaneous femoral access to introduce the 7Fr Terumo destination sheath under aseptic technique. A 0.035-inch-diameter guide wire was introduced via the arterial puncture. This was followed by insertion of a 5Fr pigtail catheter. An aorto-renal angiogram was performed in 10° Left Anterior Oblique projection. A cobra catheter was used to perform selective individual renal artery catheterization and angiography. A 3000-IU quantity of heparin and 50-μm quantity of Nitrocine (glyceryl trinitrate) were administered into each renal artery. The Vessix catheter (5−7 mm wide, 2 cm long) was selectively introduced into renal arteries sequentially over a 0.018-inch SV5 guide wire. Six bipolar electrodes on a balloon platform enabled firm contact with the renal endothelium, which was confirmed on the generator module. Energy (30 seconds long, 0.7-W radiofrequency energy ablations) was then delivered multiple times across the entire length of the vessel in a fixed helical pattern under radiographic and impedance control, creating between 16 and 24 lesions, depending on the length of the main artery and the presence of accessory vessels. The procedure was then repeated on the contralateral renal artery. A final renal angiogram was then obtained, to check the integrity of the renal artery. A closure device was used for all patients to allow early ambulation.

Data Collection

Once the patient was considered to be suitable for the procedure, the coordinator then interviewed the patient to document the following: pain score (McGill Pain Questionnaire [MPQ]), quality of life scores (EuroQol-5D [EQ-5D] and 36-Item Short Form Health Survey [SF-36]), mood (Geriatric Depression Scale [GDS]), and disability (Oswestry Disability Index [ODI]). The interviews were conducted prior to the procedure and at 3 and 6 months after RDN (±15 days).

McGill Pain Questionnaire

The MPQ provides a quantitative profile of 3 aspects of pain (sensory, affective, and evaluative, to specify subjective pain experiences). It also contains an

intensity scale to determine the properties of pain experience. The minimum and maximum pain scores are 0 and 78, respectively.

36-Item Short Form Health Survey

The SF-36 is a quality-of-life survey that enquires on 8 health concepts: bodily pain, role limitations due to physical problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, physical functioning, energy/fatigue, and general health perceptions.

EuroQol-5D

The EQ-5D questionnaire has 2 different documents, namely, a health state description and an evaluation. The evaluation document records the respondent's self-rated health on a vertical visual analog scale (VAS) on which the end points are "best imaginable health state" and "worst imaginable health state." In the descriptive document, health status is measured in 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). Each dimension has 5 levels (no/slight/moderate/severe, and extreme problems). Patients use a 5-level scale to self-rate their level of severity for each dimension.

Oswestry Disability Index

The ODI is a self-completed questionnaire that contains 10 topics concerning pain intensity, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, and sleep quality. Each topic category has 6 statements describing different potential scenarios in the patient's life relating to the topic. Each question is scored on a scale of 0 to 5, with the first statement being 0, indicating the least amount of disability and the last statement being 5, indicating the most severe disability. Zero is equated with no disability, and 100 is the maximum disability possible.

5-Item Geriatric Depression Scale

The GDS is a simple, 5-question screening and assessment tool that was used in our study for depression. A score of more than 2 is suggestive of depression.

Study Objectives

The primary objective was to achieve 30% reduction in self-reported pain using the MPQ at 3 months. The secondary objectives were as follows: changes in self-reported pain (MPQ), changes in self-reported disability (ODI), changes in quality of life (EQ-5D and SF-36), and changes in mood (GDS) at 3 and 6 months compared to baseline.

Statistical Analysis

All patient measures of MPQ, ODI, EQ-5D, and SF-36 were reported as medians with the corresponding interquartile range (IQR). The Friedman test was used to compare repeated measures of all scores between baseline and 3 and 6 months post−RDN procedure. The Wilcoxon signed-rank test was used for *post hoc* analysis to compare scores at 3 and 6 months postprocedure to baseline, using a Bonferroni correction. All statistical analyses were performed with SPSS Statistics for Windows, Version 22.0 (SPSS Inc., Chicago, IL).

RESULTS

Twelve patients with LPHS underwent renal denervation procedure and were followed for a total of 6 months. They varied in age between 21 and 62 years. They all had normal albumin excretion rates and estimated glomerular filtration rates (eGFR) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Table 1).

As shown in Table 2, MPQ (median, interquartile range [IQR]) scores at baseline were 38.5 (34.3−63.8), at 3 months 7.5 (0.0−29.5), and at 6 months 2.0 (0.0−18.5) ($P = 0.001$). Similar improvement was observed for mood, as suggested by GDS scores. The scores at baseline, 3 months, and 6 months (median, IQR) were 3 (1.3−5), 1.5 (0.0−3.0), and 1 (1.0−4.5) ($P = 0.002$), respectively. There was a significant improvement in function as suggested by decrease in ODI score (median, IQR). The median and IQR at baseline, 3 months, and 6 months were 43.5% (20.8−59.3%), 13.5% (3.3%−45.3%), and 4.4% (0.0−43.0%) ($P = 0.003$), respectively.

As shown in Table 3, 10 of 12 patients at 3 months and 11 of 12 patients at 6 months had a >30% improvement in the MPQ score compared to baseline, and 8 of 12 patients had a >30% improvement in ODI score.

There was also a significant improvement in the quality-of-life parameters. As compared to baseline median score (32.5 [11.3–78.8]), at 6 months, physical function was 87.5 (37.5–100.0) ($P = 0.042$). Similarly, emotional role had improved, from 33.2 (0.0–91.8) at baseline to 100 (41.7–100) at 6 months ($P = 0.020$). Results of the SF-36 are shown in Table 4.

Table 1. Baseline demographic and clinical data of study patients

Variable	N	Median	IQR
Age (yr)	12	34.0	31.3–46.5
GFR (CKD-EPI)	12	94.0	83.1–109.2
LPHS duration (yr)	12	3.3	1.6–10.8
		%	
Sex (female)	12	91.7%	
Race (Caucasian/white)	12	100.0%	
Proteinuria (urine analysis)	12	Negative 100%	

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; GFR, glomerular filtration rate; IQR, interquartile range; LPHS, loin pain hematuria syndrome.

Table 2. Self-reported pain, disability, and geriatric depression: medians, interquartile ranges, and *P* values at baseline, 3 months, and 6 months

Self-reported measure	Baseline	IQR	3 mo	IQR	6 mo	IQR	*P* value
McGill Pain Questionnaire (maximum: 78)	38.5	34.3–63.8	7.5	0.0–29.5	2.0	0.0–18.5	0.001
Oswestry Disability Index (maximum: 100%)	43.5%	20.8–59.3	13.5%	3.3–45.3	4.4%	0.0–43.0	0.003
Geriatric Depression Scale (maximum: 5)	3	1.3–5	1.5	0.0–3.0	1	1.0–4.5	0.002

On the EQ-5D analysis, there was consistent improvement in all the measured criteria.

The VAS scores improved from 50 (33.8–60.0) at baseline to 65.0 (50.0–75.5) at 3 months and 75.0 (55.0–82.3) at 6 months ($P = 0.022$) (Table 5).

DISCUSSION

To our knowledge this is the first and largest prospective study so far to involve primarily LPHS patients, and indicates that RDN is effective in achieving 6 months of pain control in almost all of these patients. Our study further adds to the published case reports and case series echoing the benefit of RDN in LPHS.[8,9,11] Our findings corroborate that RDN is a safe, effective, and rapid way of attaining pain control in LHPS patients. We also noticed a significant concurrent improvement in mood and quality of life, a reduction in caregiver burden, and a return to productive work.

Surgical attempts to interrupt the nerve pathways (transcutaneous electrical nerve stimulation,[12] dorsal rhizotomy,[12] capsaicin instillation into the renal pelvis,[13,14] renal capsulectomy,[15] and thoracolumbar sympathectomy[16]) to achieve pain control have been associated with variable outcomes. Kadi *et al*. showed that 4 of 9 patients (44%) were pain free (median follow-up, 70.5 months) after laparoscopic renal denervation. A further 22% had decreased analgesic requirement.[17] Sheil *et al*. showed that 8 of 22 patients (36%) who underwent radical neurectomy were pain free (mean follow-up, 8.0 years),[18] in contrast to 29 of 35 patients (86%) who underwent renal autotransplantation, who were pain free and narcotic free (mean follow-up, 8.4 years).[18]

The search for a unifying pathogenetic cause for hematuria and loin pain has so far been elusive. Hematuria is typically characterized by dysmorphic red cells and primarily acanthocytes, implying glomerular injury as the source of hematuria.[19,20] Although multiple studies have reported biopsy findings,[19,21,22] we did not subject our patients to a kidney biopsy, as they all had normal GFR, lacked microalbuminuria, and were normotensive. It was not our intention to identify the pathophysiology of the disease, and we found it difficult to justify a biopsy on the basis of isolated hematuria. In addition, a minority of patients will not display hematuria but will have loin pain, which has led investigators to conclude that the sources of pain and hematuria might not be related.[22]

It is conceivable that LPHS represents a diverse group of conditions[19] that clinically present as loin pain and/or hematuria, akin to the histological diagnosis of focal sclerosis in patients with focal segmental glomerulosclerosis. Intractable persistent pain distorts family dynamics,[23] leads to caregiver burnout,[23] and results in increased absenteeism,[24] and is also reported to be associated with higher rates of depression and suicide.[23] We noticed that some patients felt ashamed of the unenthusiastic reception by emergency department staff as a result of multiple trips, wary of meeting emergency department doctors unappreciative of the disease etiology and of being labeled as "frequent fliers" or "drug seekers."

A recently published Dutch study involving patients with polycystic kidney disease (n = 5) and LPHS (n = 6) showed a largely positive but a variable response to pain following RDN.[10] The study involved delivery of radiofrequency energy using first-generation, single-electrode (monopolar catheter) in a circumferential manner. In an elegant study evaluating periarterial renal nerves in bilateral renal arteries with attached abdominal aorta and kidneys from 25 autopsy subjects,[25] a high variability in renal nerve density (proximal vs. distal, ventral vs. dorsal, inferior vs. superior) was identified. There is growing evidence of predominance of efferent nerve fibers, with decreasing prevalence of afferent nerves from proximal to distal peri-arterial renal parenchyma.[25,26] As success of the ablation depended on good electrode–tissue contact, power delivery, electrode–tissue interface temperature, target tissue impedance, and the size of the catheter's active electrode,[27] we elected to use a second-generation balloon-mounted bipolar probe

Table 3. Number of participants who had clinically significant (≥30%) improvement from baseline

Self-reported measure	Number of patients (of 12) with change of ≥30% from baseline to 3 months	Number of patients (of 12) with change of ≥30% from baseline to 6 months
McGill Pain Questionnaire (maximum: 78)	10	11
Oswestry Disability Index (maximum: 100%)	8	8

Table 4. 36-Item Short Form Health Survey (SF-36) medians, interquartile ranges, and *P* values at baseline, 3 months, and 6 months

Self-reported measure	Baseline	IQR	3 mo	IQR	6 mo	IQR	*P* value
Vitality	20	6.3–25.0	27.5	11.3–81.3	57.5	17.5–68.8	0.039
Physical function	32.5	11.3–78.8	70.0	30.0–97.5	87.5	37.5–100.0	0.042
General health perception	23.5	12.5–47.0	45.0	12.5–64.5	41.0	16.3–69.5	0.080
Social role	37.8	15.6–72.0	81.3	50.0–97.0	75.0	37.5–100.0	0.010
Bodily pain	16.0	0.0–32.0	51.0	8.1–86.9	53.0	24.3–86.9	0.030
Physical role	0.0	0.0–0.0	37.5	0.0–50.0	50.0	0.0–100.0	0.011
Emotional role	33.2	0.0–91.8	100.0	54.2–100.0	100.0	41.7–100.0	0.020
Mental health	54.0	22.0–68.0	86.0	70.0–96.0	86.0	65.0–96.0	< 0.001

IQR, interquartile range.

(6 electrodes) to achieve better contact with the arterial wall. We also decided to use multiple ablations in each artery 20 (± 4) to augment our chances of denervating the entire arterial tree, as the renal nerves reside closer distally than proximally. Both sides received RDN, as the pain invariably occurs on the contralateral side.[19] To reduce the procedural variability resulting from the involvement of multiple professionals, we made a conscious attempt to restrict these to a single proceduralist (K.G.).

Compared to published case studies,[10,28] our patients underwent 3 to 4 times the previously attempted ablations with RDN, which no doubt contributed to superior pain relief. Of the patients, 50% were completely off pain medications 6 months after the procedure. There was near unanimity among recipients about a major improvement in their quality of life. Our group believed that the return of patients back to work justified this relatively expensive procedure, as our institutional costs to the taxpayer were $14,500 (Canadian dollars) per procedure.

We noticed an altered pain threshold in the majority of our patients. Institution guidelines mandated that the procedure be performed under local anesthesia with the assistance of generous conscious sedation (based on our experience in patients with hypertension). Midway through our study, we had to amend the procedure to be performed under brief general anesthesia due to patients' vivid recollection of the procedure and difficulty lying still on the table. This increased the institutional resources, as we had to seek the assistance of an anesthetist for induction of general anesthesia. Also, later, patients had to recover in a postoperative recovery unit for 4 additional hours rather than in a conventional step-down bed. We observed that patients complained about the use of a vascular closure device, which was used to achieve early hemostasis: all subjects complained of intense pain at the site and of poor mobility as a consequence for the following 48 to 72 hours. These observations were unique to patients with LPHS, as we did not observe similar pain in patients undergoing RDN for hypertension or after renal artery stent insertion.

We were aware of the association of addiction and factitious pain,[29,30] but postprocedure 6 of 12 patients spontaneously weaned themselves off of narcotics. Of the remaining 6 patients, 4 patients decreased the dose and frequency of the medications and had to continue taking narcotics, whereas 2 patients believed that the loin pain had improved and continued to take a reduced dose but at the same frequency due to concurrent regional pain syndromes. The majority of our patients on follow-up had recurrence of pain, indicating nerve regeneration, by 9 months (although not to preprocedural levels), and one-half of the patients underwent a second procedure between 9 and 15 months after the first procedure. One patient underwent the procedure a third time and, at the time of writing, remains pain free. Although patients in our study did not show any evidence of postprocedural complications, there is certainly the possibility of complications in the form of femoral artery pseudoaneurysm at the site of the arterial puncture, and the potential for endothelial damage due to the

Table 5. EQ-5D and VAS quality-of-life medians, interquartile ranges, and *P* values at baseline, 3 months, and 6 months

Self-reported measure	Baseline	IQR	3 mo	IQR	6 mo	IQR	*P* value
Mobility	2.0	1.3–2.0	1.0	1.0–1.8	1.0	1.0–2.0	0.012
Self-care	2.0	1.0–2.0	1.0	1.0–1.0	1.0	1.0–1.0	0.006
Pain discomfort	3.0	2.0–3.0	2.0	1.0–2.0	1.5	1.0–2.0	< 0.001
Usual activities	2.0	2.0–2.0	1.0	1.0–2.0	1.0	1.0–2.0	0.001
Anxiety, depression	2.0	1.3–2.0	1.0	1.0–2.0	1.0	1.0–1.8	0.021
VAS	50.0	33.8–60.0	65.0	50.0–75.0	75.0	55.0–82.3	0.022

IQR, interquartile range; VAS, visual analog scale.

circumferential delivery of thermal energy. All patients underwent postprocedure renal angiography, and we did not identify any evidence of vascular injury.

Results of this study will no doubt have to be followed up with a randomized controlled trial involving a sham arm. Nevertheless, the initial improvement in pain observed in these patients opens up the possibility of conducting further clinical studies of LPHS with RDN as the treatment modality. Also, long-term clinical studies are needed to fully evaluate the beneficial effects of RDN. The negative results associated with RDN in blood pressure trials,[31] venoplasty in multiple sclerosis,[32] vertebroplasty for wedge compression fractures,[33] use of percutaneous laser myocardial revascularization,[34] cardio-inhibitory syncope with implantation of a pacemaker,[35] and intra-articular injection of anti-inflammatory medications[36] should temper our enthusiasm regarding the apparently positive results to be proved only to have a sham impact. Nevertheless, our initial findings suggest that the impact of percutaneous intravascular delivery of thermal energy via a bipolar device with multiple energy delivery sites is positive.

DISCLOSURE

All the authors declared no competing interests.

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