In Focus

Catheter-based renal denervation as a novel treatment for loin pain haematuria syndrome

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Renal denervation using a catheter delivering radiofrequency energy to the renal artery vessel wall has recently emerged as a promising new treatment for difficult-to-treat hypertension. The beneficial effect of this intervention, attributable to sympathetic nerves interruption, has been coherently demonstrated in both an observational study [1, 2] and a controlled trial [3, 4]. Of note, according to the available follow-up studies, the hypotensive effect of renal denervation has been shown to last for up to 2–3 years. The European Society of Hypertension has published a position paper with recommendations for the application of this new technique including the eligibility criteria and issues that need to be addressed in further trials [5]. Several other conditions associated with sympathetic overactivity as diverse as heart failure, atrial fibrillation, insulin resistance [6], sleep apnoea [7] and polycystic ovary syndrome [8] have been described as being responsive to renal denervation and/or are being subjected to further study. Renal denervation has become a hot topic as illustrated by the large number of ongoing and planned trials of the technique [9]. In this issue, Gambaro et al. describe the use of catheter-based renal denervation for yet another indication, namely pain control in loin pain haematuria syndrome (LPHS).

LPHS is a rare condition of uncertain aetiology and definition. Over 100 papers on LPHS have been cited in PubMed (accessed on 18 March 2013) so far, but many nephrologists agree that the actual number of cases is probably far larger. First described in 1967, LPHS is still a poorly understood condition consisting of recurrent flank pain often accompanied by non-visible or visible haematuria. Patients are typically young at onset. The pain is often unilateral, but recurrences on the contralateral side after invasive treatment are the rule rather than the exception. Pain exacerbations may be accompanied by low-grade fever and sometimes urinary symptoms mimicking urinary tract infection [10]. Episodes of (particularly) visible or non-visible haematuria are very often accompanied by exacerbation of loin/flank pain. The duration of such episodes is variable but in some cases symptoms persist for months and cause serious disability. Pain may be severe and associated with nausea and vomiting, mimicking renal colic. Often, opioid analgesics are eventually prescribed in the most severe cases. Kidney function remains normal and development of hypertension is not associated with the syndrome. Although spontaneous disappearance of symptoms can occur after years, many patients remain symptomatic long-term [11]. A diagnosis of LPHS can only be made after a thorough evaluation for, and exclusion of other causes of loin pain and/or haematuria. Interestingly, many patients report a history of nephrolithiasis [12]. A kidney biopsy shows no glomerular abnormalities, but intratubular erythrocytes are seen more often than in healthy controls (7.2 versus 1.6%), suggesting a glomerular origin of haematuria [12]. Disparate structural abnormalities of the glomerular basement membrane, from excessive thickening to excessive thinning, may be the explanation [12]. Several other hypotheses for the cause of LPHS have been proposed including microvascular abnormalities, abnormal platelet function, intra-tubular microcrystal formation and complement activation [10, 13]. The complexity of this disorder is underscored by the fact that many patients meet the criteria for somatoform disorder on the basis of other physical complaints preceding the onset of LPHS [14].
LPHS, although rare, is a condition that challenges the urologists and nephrologists to whom these patients are referred since treatment is difficult. Pain is often severe, necessitating high-dose analgesics including opioids. Clinical experience suggests that ~5 days treatment with an intravenous opioid is usually successful in terminating a painful episode, though patient-controlled analgesia protocols are sometimes needed. Management by multidisciplinary teams including a psychiatrist/psychologist and a pain specialist is advisable, yet results are often disappointing with more than half of the patients experiencing no improvement in pain [14]. Several invasive strategies have therefore been explored in the past for very severe cases. Intra-ureteric capsaicin administration to interrupt nociceptive fibres was reported to produce short-term pain relief, but was abandoned because it was found to be associated with irreversible renal damage [15]. The fact that regional nerve blocks can give temporary relief has led to the application of neuromodulation with implantable electrodes and intrathecal pumps delivering opioids [16, 17]. Permanent denervation of the kidney by either surgical neurectomy (often combined with capsulotomy) or even autotransplantation of a kidney has been performed for LPHS. One report comparing these techniques found renal neurectomy to be less successful than autotransplantation with 33 versus 76% of patients being pain-free in long-term follow-up (mean 8 years) [18]. Comparable success rates for surgical denervation were found in other studies [19, 20]. Chin et al. [21] reported similar long-term success of autotransplantation with 69% of 26 procedures leading to the absence of pain at a mean follow-up of 7 years. However, recurrences in the transplanted kidney and/or in the contralateral kidney are not unusual, and all authors reported graft loss from perioperative complications (due to ischaemia or thrombosis) [18, 21, 22]. Thus, LPHS remains a very challenging clinical condition to treat and as such, it qualifies as a disorder for which it is appropriate to investigate novel, innovative approaches to alleviate the suffering and disability of patients with its most severe forms.

In their case report in this issue, Gambaro et al. describe a patient with a typical LPHS also suffering from hypertension successfully treated for both pain and hypertension with catheter-based renal denervation. At 6 months, the patient has remained pain-free and normotensive without antihypertensive treatment. Since catheter-based renal denervation has been shown to be a safe procedure in the trials reported so far, this treatment could be the long-sought less invasive treatment for LPHS.

However, many questions remain. The first is whether pain fibres can also be interrupted by the denervation procedure. The afferent sensory innervation of the kidney consists of unmyelinated fibres using substance P and calcitonin gene-related peptide as primary neurotransmitters. In contrast to the efferent innervation that is distributed to all segments of the renal vasculature and tubules, the sensory nerve endings are primarily located in the renal pelvic wall. The cell bodies of these nerves are predominantly located in the T12-L3 dorsal root ganglia [23]. Most fibres seem to travel to the spinal cord alongside the renal artery in close proximity to the lumen [24]. The afferent nerves must also be involved in the perception of pain, but the population of fibres involved is unknown [25]. During catheter-based renal denervation, significant pain is evoked [1], thus supporting an effect on pain perception fibres with the procedure. A second issue is the possibility of re-innervation after the procedure. The difference in the success rate of the two surgical procedures (neurectomy versus autotransplantation) has been attributed to more frequent re-innervation with the former or, alternatively, less complete denervation with the neurectomy procedure [18]. Renal allotrafts have been shown to be not completely denervated but to have structurally abnormal innervation in the renal hilum and parenchyma with evidence of regeneration after transplantation [26]. However, nephrolithiasis in grafts does not typically cause pain, suggesting absence of functional nociceptive fibres [27]. In rats, re-innervation with both sensory and efferent fibres has been shown to occur after surgical denervation [28]. However, in the trials of renal denervation for hypertension, a sustained decrease in blood pressure is found, with no evidence of functional re-innervation. This issue will probably become clearer over the coming years. In theory, renal denervation can be repeated in cases with evidence of re-innervation.

Another puzzling point in the case report by Gambaro is the remarkable hypotensive effect of unilateral renal denervation. One would expect the remaining sympathetic innervation to and from the left kidney to keep blood pressure high. A possible explanation is that the right kidney, being smaller and painful, was diseased and generated increased sympathetic drive on its own. In this regard, a recent report by Shetty et al. of a patient whose renal pain secondary to polycystic renal disease disappeared after catheter-based renal denervation for treatment of hypertension is of obvious interest. This patient had immediate resolution of pain but decrease of systolic blood pressure did not occur until 3 months later [29]. This might suggest a different effect of catheter-based renal denervation on afferent sympathetic and nociceptive fibres. Furthermore, these authors suggest that renal denervation for pain management could also have a role in polycystic kidney disease patients, in whom pain can also be a difficult-to-treat problem sometimes necessitating operative measures.

Thus, whereas the observations by Gambaro are hypothesis generating, solid evidence is needed before recommending renal denervation for the treatment of LPHS and other painful renal diseases. In light of the modest results of surgical denervation, the danger of publication bias (with only positive results being reported) and the possibility of a large placebo effect in this poorly understood syndrome, a clinical trial should be performed. We envisage a pan-European, investigator-initiated, industry-independent trial in patients with LPHS and inadequate response to conservative treatment referred to national centres with expertise in renal denervation. These patients could be randomized to catheter-based denervation or a control intervention with pain control as the primary outcome. Well-validated pain scoring methods would be used. Given the rareness of this disorder, participation of centres across Europe would be necessary. With inclusion of one to two patients per centre, enrolling up to 40 patients should be possible. The design could allow crossover after 6 months. Such a trial would also include long-term follow-up and would clarify whether catheter-based renal denervation is
the answer to the unmet need in a category of patients affected by this rare condition.

In conclusion, LPHS remains an enigmatic syndrome that can cause debilitating pain which often responds poorly to conservative care. Instead of the drastic surgical measures taken in the past, a safe, less-invasive, treatment may now be available. Application of catheter-based renal denervation should be subjected to a properly conducted clinical trial in order to provide definitive evidence for its effectiveness, or otherwise, in LPHS.

CONFLICT OF INTEREST STATEMENT

None declared.


REFERENCES