

The use of surgical sympathectomy in the treatment of chronic renal pain

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Objective To assess the efficacy of renal sympathetic denervation in the treatment of chronic renal pain.

Patients and methods In a 10-year period, 21 patients suffering from chronic renal pain underwent 27 renal denervation operations, six of which were bilateral. The cause of pain was the loin pain haematuria syndrome in 18 patients.

Results Four operations resulted in complete pain relief to date (median follow-up 53.5 months). Pain relief after the other 23 operations in 18 patients lasted a median of 6 months. Assuming that recurrent pain was due to neuronal regeneration, nine of the 18 patients with

recurrent pain underwent a total of 10 re-explorations of the renal pedicle, stripping it of all nerve fibres and areolar tissue. Three of these re-explorations produced complete pain relief to date (median follow-up 40 months). The median pain-free interval of the other seven re-explorations in six patients was 19 months.

Conclusion Renal denervation cures severe intractable pain in about 25% of patients. Recurrence of pain could be prevented in more patients if there was a way of preventing re-innervation.

Keywords Loin pain haematuria syndrome, renal denervation, sympathectomy

Introduction

Irrespective of its aetiology, severe chronic renal pain is a debilitating condition and often leads to avoidable episodes of over-investigation and morbidity [1]. The treatment is difficult and often unsatisfactory; long-term regular treatment with opiates provides only partial relief and is not without side-effects. Similarly, infiltration of the sympathetic nerves supplying the kidney with either local anaesthetic or phenol provides only temporary relief. Although nephrectomy may cure the pain, it cannot be recommended where there is bilateral impairment of renal function or the possibility that the pain may become bilateral.

In an attempt to alleviate severe debilitating chronic renal pain and preserve renal function, we surgically denervated the affected kidney. In this report, we assess the outcome of this operation and briefly review the loin pain haematuria syndrome (LPHS) and regeneration of renal autonomic nerves.

Patients and methods

In a 10-year period (1981–1991) 21 patients (16 women and five men, mean age 45.2 years, range 21–72) underwent surgical renal denervation for the treatment of chronic renal pain. All were assessed at regular clinic interviews to determine the outcome of their operation. The mean period of follow-up was almost

8 years (94 months, range 28–140). Two patients had stopped attending the renal clinic at the time of the review but in each case clinical notes gave sufficient detail for the study to be completed.

Eighteen patients had been diagnosed as suffering from the LPHS, the pain being bilateral in 11 cases. Three patients had other causes of renal pain, one from each of the following conditions: crossed renal ectopia associated with an adynamic bladder; chronic pyelonephritis; and reflux nephropathy. All 21 patients were regularly taking large doses of opiate analgesia.

The diagnosis of LPHS was made only after extensive nephrological, urological and psychological investigation had failed to discover any other cause for the persistent loin pain and haematuria. Investigations included excretory urography, renal arteriography, cystoscopy and renal biopsy. The renal biopsies were examined by immunofluorescence and electron microscopy.

Before considering surgical intervention, all patients underwent at least one trial of local anaesthetic infiltration of the lumbar sympathetic chain. Patients were only considered for surgical denervation if this procedure resulted in a marked, albeit brief, reduction in the severity of their pain. All patients consented to the operation after detailed discussions about the current poor understanding of the cause of their pain, and in the knowledge that a surgical denervation might not result in long-term relief of their symptoms. All operations were performed by the same surgeon and the results assessed independently.

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Surgery

The thoracolumbar sympathetic chain and kidney were explored through an oblique thoraco-abdominal incision through the bed of the 9th rib. The parietal pleura overlying the transverse processes was incised vertically and the sympathetic chain and its communicating ramii excised from the level of T7 down to T12. The upper two lumbar ganglia of the sympathetic chain, and the kidney, were then exposed in the retroperitoneal space through a circumferential incision in the diaphragm. The sympathetic chain from T12 to below the second lumbar ganglion was excised in all but two cases (where previous surgery and consequent scarring rendered it inadvisable), the renal vascular pedicle was exposed and the renal artery(s) and vein(s) stripped of all nerve tissue. Thus the renal sympathetic nerves were divided and excised at two levels, in the sympathetic chain and around the renal blood vessels. The renal capsule was not incised along the convex border of the kidney as advocated by Blacklock [2]. None of these operations or re-operations were associated with any local or general complications. Patients left hospital after 6–8 days.

Some patients with severe recurrent loin pain following surgical renal denervation were offered a re-exploration of the affected kidney with the aim of dividing any pain fibres which may have regenerated. This was performed through an abdominal incision and a transperitoneal approach, so that the first few centimetres of the renal vessels and the adjacent abdominal aorta could be stripped of all connective tissue and nerve fibres. One patient who had had both of these operations performed on both kidneys had her coeliac plexus and all pre-aortic sympathetic nerves covering the upper 8 cm of her upper abdominal aorta excised transperitoneally.

Results

Initial surgical renal denervation

Twenty-seven renal denervations were performed on the 21 patients. The operation was performed bilaterally in six, all of whom suffered from the LPHS, at an interval ranging from 4 to 40 months. Four of these operations resulted in the permanent relief of pain at a median follow-up of 53.5 months (range 28–111). The median pain-free interval following the other 23 operations was 6 months (range 0.5–60) (Fig. 1). There was no difference in the results of renal denervation between the 18 patients with LPHS and the three with chronic renal pain from other causes. The patient suffering from reflux nephropathy was cured by renal denervation (pain-free period to date, 56 months). The patient suffering from pain caused by crossed renal ectopia had a pain-free

interval of 2 months after denervation. The patient who suffered from chronic pyelonephritis had a pain-free interval of 2 months, but subsequently the pain returned and was treated by nephrectomy.

Re-exploration of the renal pedicle

Nine of 18 patients who did not derive long-term benefit from the initial renal denervation consented to a total of 10 re-explorations of the renal vascular pedicle. This procedure resulted in a further three patients being pain-free to date, at a median follow-up of 40 months (range 24–60), their pain-free interval after their first operation having ranged from 3 to 18 months. The median pain-free period of the six patients who did not gain long-lasting relief after the re-exploration was 19 months (range 3–30) (Fig. 1).

Patients not cured by renal denervation or re-exploration

Fifteen patients (six of whom underwent both a renal denervation and subsequent re-exploration) gained no long-term relief of pain from their operation(s), the median pain-free interval being 7.5 months (range 0.5–60; combining the pain-free interval from both the initial operation and the re-exploration when performed).

The outcome of these patients was: (i) two patients opted for a nephrectomy (one suffered from chronic pyelonephritis, the other from LPHS); (ii) two patients having already undergone a re-exploration underwent a third denervation — in one the renal pedicle was stripped for a third time resulting in 12 months freedom from pain, the other had an operative denervation of the coeliac plexus and is pain-free to date (36 months); (iii) three patients had autotransplantations of the kidney performed by the transplant unit — one of these patients is pain-free to date (24 months), in the other two cases the transplanted kidney became ischaemic in the early post-operative period, resulting in graft nephrectomy; (iv) eight patients continue to suffer from renal pain, in six the pain has been reduced by surgery so that opiate analgesia is no longer required, but in two the pain has returned to its original intensity.

Thus, in summary, seven patients have been cured (to date) of their renal pain by renal denervation, although this required two operations in three and three operations in one, and six patients have had their pain reduced to a degree that does not require opiate analgesia. Six patients have undergone alternative procedures resulting in the loss of four kidneys, and two continue to take large doses of opiates.

The duration of pain relief is not a certain indicator of cure. Whereas most recurrences developed within 12–18 months, two did not occur until 36 and 60

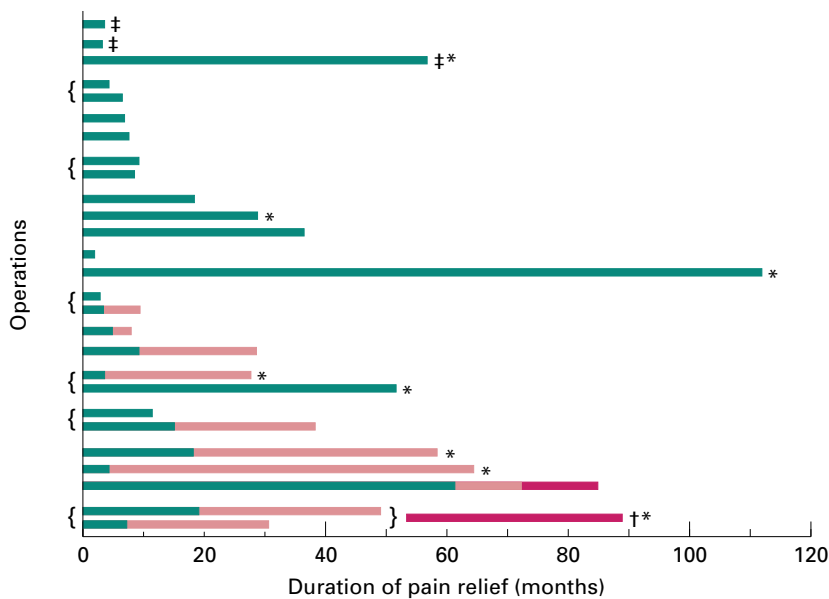


Fig. 1. The duration of pain relief after renal denervation. Each bar represents the results of surgery on a painful kidney, bars bracketed together indicate that the patient underwent bilateral operations for renal pain. The length of the green section of the bar indicates the duration of pain relief (months) achieved by the initial renal denervation and the length of the light red section, the duration of pain relief achieved by re-exploration of the renal pedicle. The length of the dark red bar indicates the duration of pain relief achieved by a third operation. Patients remaining pain-free to date ('cured') are indicated by an asterisk. †One patient was cured of bilateral, recurrent loin pain by a surgical coeliac plexus block. ‡, Not LPHS.

months after operation. It is therefore probable a patient cannot be claimed to be permanently cured of this pain.

Discussion

The term loin pain haematuria syndrome was first proposed by Little *et al.* [3] in 1967 who described three young female patients who complained of severe attacks of loin pain, either unilateral or bilateral, which had recurred over many years, and had been associated with episodes of macroscopic haematuria. Renal function, IVP, retrograde pyelography and cystoscopy were all normal. However, renal arteriography revealed abnormalities of the peripheral renal arteries and areas of avascular renal parenchyma. Renal biopsies supported these findings by detecting intimal hyperplasia of the renal arterioles and fibrosis of the renal parenchyma. That no inflammation was present in the specimens and that the fibrosis seen was more akin to the 'ischaemic' type of fibrosis seen in hypertensive patients who do not suffer from either loin pain or haematuria, led the authors to conclude that this syndrome was a separate and previously unrecognized clinical entity caused by repeated episodes of acute arterial constriction or occlusion. They reported that one of these patients underwent a renal denervation by division of the sympathetic nerves around the vascular pedicle, resulting in complete remission of pain for 6 months.

Burden *et al.* [4] investigated 19 patients with recurrent painless haematuria, loin pain, or both loin pain and haematuria in whom urinary infection, calculi and anatomical abnormalities of the urinary tract had been excluded. Of these patients, 12 were women who suffered with both loin pain and haematuria. Their renal

arteriograms showed evidence of cortical scarring, and their renal biopsies showed minimal mesangial and epithelial proliferation associated with pericapsular fibrosis. It was claimed that this group could be distinguished arteriographically from a second group of seven patients, predominantly male, who suffered from painless haematuria and had normal renal arteriograms but similar renal histology. They suggested that the pain in LPHS was caused by repeated intra-renal thrombosis and noted an improvement in some patients on cessation of the oral contraceptive pill, or on commencement of anticoagulation with warfarin. One patient who underwent renal denervation had a 6-month period of pain relief. Although LPHS is more common in females, it can occur in males. Habte *et al.* [5] reported seven cases of the syndrome of which three were male, and Aber and Higgins [6] reported that three of their 51 patients were male. Importantly, in the series by Burden *et al.* and Aber and Higgins, the renal biopsies performed were not all examined by immunofluorescence and electron microscopy. Without these examinations mesangial IgA nephropathy and thin-membrane nephropathy (respectively) cannot be excluded. The diagnosis of LPHS in some of the patients described in these reports is therefore questionable.

Deposition of complement and immunoglobulins in renal arterioles, although present in a wide variety of renal conditions, has been reported in the LPHS. Naish *et al.* [7] reported the deposition of C3, and Burden *et al.* [8] the deposition of complement components C3, C4 and C1q and IgM within the arteriolar walls. Increased amounts of lipofuscin within the glomerular hilum and mesangium of patients suffering from LPHS has also been reported [8].

Support for intravascular thrombosis as an aetiological

factor in LPHS is suggested by reports of a reduction in the heparin-thrombin clotting time [8] and a reduction in platelet life-span with an increase in platelet factor 3 levels [9], although both these reports await confirmation. Similar angiographic findings to those seen in LPHS have been found in patients recovering from renal failure following intravascular coagulation complicating acute cholecystitis [10] and the ingestion of oral contraceptives with oestrogen-containing compounds [11]. However, similar arteriographic findings can be produced as artefacts by defective procedures [12]. A few patients with LPHS who were taking the oral contraceptive pill became pain-free after stopping this therapy, whilst other patients have responded to treatment with warfarin [4,6]. Nevertheless, the frequency with which this syndrome occurs in men excludes oral contraceptive therapy as a prime cause. The association of LPHS with a deficiency of Hageman factor XII (a condition which predisposes to thrombo-embolic disease) has been recognized in a case report by Smellie *et al.* [13] and the presence of circulating platelet aggregates and high levels of fibrinopeptide A (a cleavage product of fibrin) have also been reported in a case of LPHS [14]; these findings await further confirmation.

Renal innervation and neuronal regeneration

Pain is conducted from the kidney via sympathetic afferents which accompany the sympathetic innervation, usually derived from spinal segments T10 to T12. Nerves from the kidney reach these segments by travelling along the renal artery to the renal plexus, which is composed of filaments from the coeliac plexus, coeliac ganglion, aorticorenal ganglion, lowest thoracic splanchnic nerve, first lumbar nerve and aortic plexus [15,16]. A surgical procedure that divides these nerves should therefore be a reasonable method of treating intractable renal pain. This can be achieved either by renal denervation or by renal autotransplantation, the former involving less risk to renal function.

Neuronal regeneration of autonomic nerves following autotransplantation of canine kidneys is well documented [17,18]. After an initial period of 8 weeks when there are no adrenergic autonomic nerves distal to the arterial anastomosis, regeneration of these nerves is apparent at 3 and complete by 6 months. Neural degeneration and regeneration in human renal allografts and isografts was also studied by Gazdar and Dammin [19] who concluded that 19 days after renal transplantation most renal axons had degenerated, but that by the 28th day there was demonstrable regeneration of these nerves and that the number of regenerating axons increased as long as the graft survived. They noted no difference in neural regeneration between isografts and

allografts, but were surprised by the degree of neuronal regeneration considering that the transplanted kidney was anastomosed to the internal iliac artery with no attempt at neural realignment.

Treatment of chronic renal pain

Before considering renal denervation, all treatable causes of chronic renal pain, such as renal calculi, must be excluded. If the pain is due to a diseased kidney with little renal function, nephrectomy may be appropriate.

LPHS is diagnosed by excluding identifiable renal disease; most reported series confirm that the patient's life has been made unbearable by the pain and almost all become dependent on maintenance therapy with opiate analgesia. Splanchnic nerve blockade produces only temporary relief of symptoms and the use of transcutaneous electrical nerve stimulation may only reduce symptoms. Patients with unremitting, severe loin pain present a difficult management problem that may be helped by surgery. The selection of patients for surgery requires careful evaluation; they should have severe pain requiring frequent admissions to hospital. A psychiatric evaluation should assess the degree of drug dependency and also the presence of psychological disorder [20]. A renal nerve block should cause a temporary reduction in the severity of their pain. If then indicated, renal denervation can be attempted by either dividing the renal splanchnic nerves directly, or by performing a renal autotransplant.

Neuronal regeneration of renal sympathetic pain fibres could explain why, in the present series, after all the patients had had a pain-free period following renal denervation, the pain returned in most by 10 months, and why the pain-free period after a second operation was usually a little longer. The six patients who were cured were assumed not to have had effective re-innervation. Shiel *et al.* [21,22] have reported successful results of renal autotransplantation for pain caused by LPHS in nine patients, eight of whom remained pain-free after a mean interval of 18 months (range 2–36). Similarly, in a series of nine renal autotransplantations, Chin [23] reported success (freedom of pain or a reduction in analgesic requirement) in eight patients (median follow-up 43 months), but one patient required a graft nephrectomy for recurrent pain in the graft area. Recurrent renal pain one year after renal autotransplantation has also been reported [24,25]. In a series of 12 renal autotransplantations, with a follow-up of 24–56 months, Parnham *et al.* [25] reported complete freedom of pain in only three of 11 patients, a recurrence rate considerably higher than the 10% reported by Chin [24]. The long-term outcome of renal autotransplantation for the treatment of chronic renal pain in many patients has yet to be assessed.

The results of the present three renal autotransplants were disappointing, with two early graft failures related to ischaemia despite adequate perfusion at the time of operation. All three patients had previously undergone a renal denervation (which included stripping of the renal pedicle) and this possibly induced physiological hypersensitivity of the renal arterioles to circulating catecholamine, which may have jeopardized tissue perfusion.

Unfortunately the pain of LPHS is frequently bilateral (11 of 18 patients in the present series) and bilateral renal autotransplantation is a major undertaking for a condition that, apart from the pain it causes, runs a benign course. Despite this, both Sheil *et al.* [22] and Chin [23] report a willingness amongst their patients to undergo a renal autotransplantation in the contralateral kidney if it subsequently causes pain, and have reported a few successful bilateral renal autotransplants. In the present series, 13 of the 21 patients who have undergone one or more attempts at renal denervation have either been cured or experienced a significant reduction of their pain. Efforts directed at preventing regeneration of the splanchnic nerves after their division should make this operation still more effective. Eventually, a greater knowledge of the mechanisms causing the pain may lead to new forms of therapy and encouraging preliminary results in the use of intra-ureteric capsaicin have been reported [26].

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