NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of laparoscopic renal denervation for loin pain haematuria syndrome

Loin Pain Haematuria Syndrome (LPHS) causes pain near the kidney on one or both sides of the body (loin pain) and blood in the urine (haematuria). In this procedure, nerves are stripped from the kidney (renal denervation) using keyhole (laparoscopic) surgery. The ends of the nerves are clipped or heated to stop them growing back. The aim is to relieve pain.

Contents

Abbreviations

Word or phrase	Abbreviation
LPHS	Loin pain haematuria syndrome
MPQ	McGill Pain Questionnaire
PIQ-6	Pain Impact Questionnaire

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in February 2021.

Procedure name

- Loin pain haematuria syndrome

Professional societies

- British Association of Urological Surgeons
- The Renal Association.

Description of the procedure

Indications and current treatment

Loin pain haematuria syndrome (LPHS) causes severe, recurrent flank pain and haematuria (either macroscopic or microscopic). The cause of LPHS is unknown and diagnosis is only made after excluding all other possible renal causes of flank pain and haematuria. Initial treatment of LPHS involves prescription of analgesics, up to and including opioids. If these are unsuccessful, surgical

intervention can be tried, including renal denervation, nephrectomy, and renal autotransplantation.

What the procedure involves

Laparoscopic renal denervation is a minimally invasive procedure to interrupt the sensorial and sympathetic innervation of the kidney to control the pain. The procedure is done under general anaesthesia, using a retroperitoneal approach. Lymphatic and nervous tissue are stripped off the renal artery and vein with subsequent division of all perihilar nervous tissue, with or without mobilisation of the kidney. The laparoscopic technique aims to reduce the anaesthetic time and produce a quicker recovery time than open surgical techniques.

Efficacy summary

Curative/pain free success of intervention

The reported success rate of the intervention, as defined by patients being pain free, and no longer needing regular analgesia was report in 2 case series as 28% (7/25) [1] and 44% (4/9) [2], with median follow up periods of 39.5 months and 28 months respectively.

In the third case study, [3] this was not a specified outcome, but using self-reported pain, 50% (2/4) of patients were pain free at 6 months.

Reduced need for analgesia

Reduced need for analgesia was reported in 100% of patients in a 4 person cases series. [3] In the larger series 30% [1] and 22% [2] of patients reported reduced analgesia use where the procedure had not been completely successful in curing their pain.

Quality of life

In 1 case series [2] the mean score for patients that answered the Pain and Impact on Quality of Life questionnaire (PIQ-6) showed a post-procedure reduction in all domains, with a reduction of 1.4 to 3.3 points, all statistically significant at the $p<0.05$ level. The proportion of patients who noted improved quality of life was not reported.

The 4-person case series used multiple tools to assess physical health, mental health and quality of life. All 4 patients showed improvements in each of these areas, except 1 who showed a decrease in quality of life as measured with the EQ-5D, from 60 to 50. No statistical tests were conducted.

Safety summary

No issues with safety, and no perioperative or intraoperative complications were reported in any of the case series.

Anecdotal and theoretical adverse events

One study [1] discussed the possible risk that the scar tissue created by denervation might increase the difficulty and failure rate of subsequent renal autotransplantation or other surgical interventions used for LPHS.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to laparoscopic renal denervation for loin pain haematuria syndrome. The following databases were searched, covering the period from their start to 27 October 2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with loin pain haematuria syndrome.
Intervention/test	Laparoscopic renal denervation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 37 patients from 3 case series.[1–3]

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on Laparoscopic renal denervation

Study 1 Greenwell (2004)

Study details

Study type	Case series
Country	UK
Recruitment period	Not stated
Study population and number	n=24; 33 laparoscopic renal denervations Patients with loin pain haematuria syndrome
Age and sex	Median age 43 years, 54% (13/24) female
Patient selection criteria	Unclear – appear to have reviewed the notes of all patients that underwent renal denervation (over an unspecified time), where no other cause after urine tests, blood tests, and renal ultrasound, CT or isotope renography, and therefor had received a diagnosis of loin pain haematuria syndrome. In total 32 patients were found, 8 were excluded for missing (5/8) or incomplete notes (3/8).
Technique	All surgeries carried out by one surgeon. No perioperative complications.
Follow-up	Median 39.5 months
Conflict of interest/source of funding	None declared, and funding not reported.

Analysis

Follow-up issues: All patients were followed up actively. Follow up range was very large (1-168 months), and unclear why.

Study design issues: Unclear over what timeframe and what criteria were used to recruit patients to the case series. No blinding, or control or comparator treatment. Primary outcome was success of procedure, defined by cure of pain as self-reported and not needing further analgesia or further surgical intervention on that side.

Data is presented on analgesia before and after procedure in those that denervation failed. There was no mention of which patients were selected and no mention of an outcome measurement. It appears data was only presented from the 7 patients where their analgesia reduced.

Other issues: There was little methodological detail in the paper.

Key efficacy findings

Number of patients analysed: 24 (32 denervations)

Procedure success (defined as self-reported pain free, not needing analgesia or further surgical intervention

	Successful	Failure
Ipsilateral	28% (7/25)	72% (17/25)
Contralateral	29% (2/7)	71% (5/7)
Repeat ipslateral	0%(0/1)	100% (1/1)

The introduction of the papers states that there were 24 ipsilateral, 8 bilateral and 1 repeat, in contrast to the data that is presented above. The discrepancy appears to be due to a patient that received an ipsilateral denervation, a repeat denervation and then a contralateral denervation being misattributed. However, the overall number of successful cases is consistent,

The paper also states that the procedure was more effective in men (55%) than women (15%), although the data was not presented.

Reduced analgesia in patients where denervation failed fully cure pain:

There was no specific definition of reduced analgesia, but the following data were presented.

	Analgesia	Before	After
1	Dihydrocodeine	8/day	-
2	Dihydrocodeine	8/day	8/day
	Diclofenac	50mg x 3	-
3	Pethidine	250mg 4h	150mg 4h
4	Pethidine	50mg 3h	-
5	MST	8/day	8/day
	Methadone	-	20mgx4
	Coproxamol	-	8/day
6	Tramadol	50mg prn	-
	Ibuprofen	200mg	200mg
7	MST	240mg x2	60x2
	Pethidine	100mg 2-4h	-

The paper concludes that one third of patients where denervation failed to result in complete pain relief had reduced analgesic requirements.

Key safety findings

No peri-operative complications.

1 patient had a further renal denervation on the same side.

6 patients where the procedure failed to be curative, went on to have nephrectomies.

The paper mentions that dense scarring after denervation affected the quality and quantity of vessels available for subsequent auto transplantation.

Study 2 Kadi (2013)

Study details

Study type	Case series
Country	Scotland
Recruitment period	2000 to 2010
Study population and number	n=9; 11 laparoscopic denervations Patients with loin pain haematuria syndrome
Age	Median age 37 years, 100% (9/9) female
Patient selection criteria	Patients were selected from case notes, surgical logs, and electronic systems to find those that underwent laparoscopic denervation for the indication of loin pain haematuria syndrome All patients included had previous renal investigations to rule out other pathology including: Mid-stream urine Biochemical and haematological blood sample parameters Renal tract ultrasound Renal CT scan Isotope renography
Technique	All surgeries were successfully completed as laparoscopic procedures. Median operation time was 150 minutes. Two patients underwent bilateral denervation. The patients were discharged home on the first or send day and there were no intra or peri-operative complications.
Follow-up	Median 28 months
Conflict of interest/source of funding	None noted, and funding not reported.

Analysis

Follow-up issues: All patients were to be followed up actively. 8 patients were successfully followed up, one was lost as they had migrated outside the UK. There was substantial range to length of follow up, from 12 months to 93 months and it is not clear why this was the case.

Study design issues: As a case series there was no blinding or control group, and no comparator intervention. It is not clear whether the recruitment process included all patients that fulfilled the criteria or if any patients were excluded for any reason. Outcome measures were pain relief, primarily defined as no further need for analgesia. The paper also gives results for patients with reduced analgesic requirements, but this is not defined. A table of medication before and at follow up is included, but these are not always directly comparable, and do not include dosing information.

The secondary measure was the PIQ-6 questionnaire, which is a validated tool to assess pain severity, and impact on functional health. A lower score is better, indicating less impact and pain. The mean difference in score is assessed pre-procedure and at follow up, but those do not mention the statistical test used to compare these means. In additional all patient scores were combined, so it was not possible to calculate the number of patients that reported improved quality of life.

The outcomes were assessed at 6 weeks, 6 months, and at least 1 year after surgery, although only the results from the latest follow up are included. Follow up was undertaken by a member of the team that had not been involved in the surgery.

Study population issues: Only 9 cases included, all female and relatively young (20-51) years. 6 of the patients had previous renal surgical procedures (ureteric stenting or ureteropyleography)

Key efficacy findings

Number of patients analysed: 9

Need for analgesia

- 4/9 patients no longer needed analgesia after a median follow up of 70.5 months.
- 2/9 of patients had reduced analgesia requirements. .

Paper reports a 66% success rate in the procedure based on primary outcomes. (44% if only including those no longer requiring analgesia).

Pain and impact on quality of life

Data for 8 patients using the PIQ-6 before surgery and at follow up, scored from 1 to 6. A lower score is better, indicating less pain or impact of quality of life.

Question	Pre-procedure score mean	Post-procedure score mean	p value
1	6	2.7	0.002
2	4	2.1	0.001
3	4	2.5	0.007
4	4	2.5	0.007
5	4	2.6	0.013
6	4	2.3	0.004

Key safety findings

No reported intra or peri-operatively complications. No mention of any post-surgical complications. One patient that did not achieve pain relief after this procedure went on to have a nephrectomy.

Study 3 Prasad (2016)

Study details

Study type	Case series
Country	Canada
Recruitment period	Not reported
Study population and number	n=4 Patients with loin pain haematuria syndrome
Age	Ages: 28, 30, 30, 62 year old. 4/4 female.
Patient selection criteria	Selection criteria unclear. Patients had undergone haematological and biochemical testing, and CT scanning to rule out other causes.
Technique	All 4 were bilateral
Follow-up	6 months
Conflict of interest/source of funding	Conflicts of interest not reported. No relevant financial interests.

Analysis

Follow-up issues: All patients actively follow up, and none were lost to follow up.

Study design issues: Unclear recruitment method. Appears to be all cases undertaken at the centre, (Southern Saskatchewan, Canada), but unclear on the recruitment period. No comparator or control group, and no blinding. No statistical tests were used.

Primary outcomes were:

- Reduction in use of pain medications, both amount and frequency
- Changes in self-reported pain, as measured by the McGill Pain Questionnaire (MPQ). Score 0-78, lower is better.
- Quality of life, as measured by the EuroQol 5 Dimensions visual analogue scale (EQ-5d VAS score 0-100, higher is better), and the Short Form Health Survey (SF-36, scored on vitality, physical function, general health perception and social role, scored 0-100, higher is better)
- Mood, as measured by the Geriatric Depression Score, scored 0-5 lower is better.
- Disability as measured by the Oswestry Disability Index. Scored 0-100% lower is better.

Study population issues: Small numbers, large range in ages, and all were female.

Key efficacy findings

Number of patients analysed: 4

Medication use

Patient	Baseline	Score at 3 months	Score at 6 months
1	2	0	1
2	2	0	1
3	3	0	1*
4	3	1	1*

*At 75% reduction in dose

Self reported pain, measured using McGill Pain Questionnaire (MPQ). Score 0-78, lower is better

Patient	Baseline	Score at 3 months	Score at 6 months
1	60	0	0
2	57	11	0
3	38	4	6
4	36	14	17

Disability, measured using the Oswestry Disability Index. Score 0 to 100%, lower is better

Patient	Baseline	Score at 3 months	Score at 6 months
1	15%	0%	2%
2	18%	7%	0%
3	29%	20%	16%
4	62%	40%	44%

Depression, using the Geriatric Depression Score. Score 0 to 5, lower is better

Patient	Baseline	Score at 3 months	Score at 6 months
1	1	0	0
2	1	0	0
3	4	1	3
4	5	3	3

Quality of life measured using the EQ-5D. Score 0 to 100, higher is better

Patient	Baseline	Score at 3 months	Score at 6 months
1	20	60	70
2	50	70	80
3	70	70	72
4	60	50	50

Quality of life domains measured by SF-36. Score 0 to 100, higher is better

Vitality

Patient	Baseline	Score at 3 months	Score at 6 months
1	55	65	65
2	25	85	90
3	15	40	35
4	0	15	15

Physical function

Patient	Baseline	Score at 3 months	Score at 6 months
1	95	90	100
2	50	100	100
3	35	70	60
4	0	30	30

General Health perception

Patient	Baseline	Score at 3 months	Score at 6 months
1	67	67	72
2	25	57	62
3	32	52	37
4	5	10	20

Social role

Patient	Baseline	Score at 3 months	Score at 6 months
1	75	88	75
2	63	75	100
3	38	100	90
4	25	88	88

Key safety findings

No peri- or postoperative complications were reported.

Validity and generalisability of the studies

- As all the studies included were case series, they all have the same underlying validity issue; there is no control or comparator treatment group. In addition, none of the studies use masking or blinding when following up the patients, leading to the potential for bias.
- In addition, while all studies looked at reduction in analgesia use as an outcome, only one study [1] provided data on the medication regimes (including doses) before the intervention and at follow up, and none provided any methodology in how reduction in analgesia use was assessed, particularly when comparing different drug classes and doses.
- In all three studies the case selection methodology was lacking, while it appears that in each study, all cases undertaken in that centre are included, this is not directly specified, and for two studies,[1,3] no recruitment period in specified. There is little information on how these cases were found nor information on any additional inclusion and exclusion criteria, other then missing records. Only one study [1] included information on cases that had missing data.
- Assessing the impact of the intervention of patient quality of life is also difficult. Of the two studies that assessed this, one [2] pooled all the patient scores together, and one [3] , while using a comprehensive battery of tools, only contained 4 patients, and only followed them up for 6 months.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

IP overview: Laparoscopic renal denervation for loin pain haematuria syndrome

Percutaneous transluminal radiofrequency sympathetic denervation of the renal artery for resistant hypertension. NICE interventional procedures guidance IPG418 (2012). Available from: https://www.nice.org.uk/guidance/ipg418

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Professional expert questionnaires for Laparoscopic renal denervation for loin pain haematuria syndrome were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Issues for consideration by IPAC

There is one on-going interventional trial due to complete in July 2022 which will randomise patient to either laparoscopic denervation or sham surgery. N=10. ClinicalTrials.gov Identifier: NCT04332731

References

1. Greenwell, T. J., et al. "The outcome of renal denervation for managing loin pain haematuria syndrome." *BJU international* 93.6 (2004): 818-821.
2. Kadi, N., Mains, E., Townell, N., & Nabi, G. (2013). Transperitoneal laparoscopic renal denervation for the management of loin pain haematuria syndrome. Minimally Invasive Therapy & Allied Technologies, 22(6), 346-351.
3. Prasad, Bhanu, et al. "Renal denervation in patients with loin pain hematuria syndrome." American Journal of Kidney Diseases 69.1 (2017): 156-159.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane)	27/10/2020	Issue 10 of 12, October 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane)	27/10/2020	Issue 10 of 12, October 2020
International HTA database (INAHTA)	27/10/2020	n/a
MEDLINE (Ovid)	27/10/2020	1946 to October 26, 2020
MEDLINE In-Process (Ovid)	27/10/2020	1946 to October 26, 2020
MEDLINE Epubs ahead of print (Ovid)	27/10/2020	October 26, 2020

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	kidney diseases/
2	Hematuria/
3	Flank Pain/
4	((kidney* or loin* or flank*) adj4 (discomf* or pain*)).tw.
5	(haematur* or hematur*).tw.

6	LPHS.tw.
7	or/1-6
8	exp Sympathectomy/
9	*sympathetic nervous system/
10	denervation/
11	(denervat* or sympathe* or neurectom* or neurotom*).tw.
12	(RSD or RDN).tw.
13	Urologic Surgical Procedures/
14	or/8-13
15	exp Laparoscopy/
16	Laparoscopes/
17	(laparoscop* or transperiton* or telescop* or peritoneoscop* or celioscop*).tw.
18	(pelvi* adj4 endoscop*).tw.
19	or/15-18
20	7 and 14 and 19
21	animals/ not humans/
22	20 not 21

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Abdalla, O., Phan, Y. C., & Sriprasad, S. (2020). Laparoscopic renal denervation for the management of refractory loin pain. European Urology Open Science, 19, e1075.	Case series. N=17. 15 female. Median follow up 24 months.	8/17 (47%) patients were cured of pain at median follow up of 13.5 months. On a numerical rating scale (NRS of pain) the mean score in patients dropped from 8.4 to 2.5 (p=0.14) No significant perioperative adverse events. 2 patients required repeat surgery.	Conference abstract, insufficient information to assess methods and analysis quality
Grech, A. K. (2016). Loin pain haematuria syndrome-a narrative review of pain management strategies. The Korean Jjournal of Pain, 29(2), 78.	Narrative review. 2 papers relating to laparoscopic denervation.	Improved quality of life of 2/3 of patients in one paper. Reduction of pain of in 25% of patients in one paper.	Narrative review, the only two papers that were related to this procedure were already included in table 2. (Kadi and Greenwell)
Srougi, V., Duarte, R. J., Srougi, M., & Yu, L. (2016). Laparoscopic Kidney Denervation for Refractory Loin Pain: Can We	Case study. N=1 1 year follow up	Denervation successfully completed with complete relief of pain at follow up.	Single case study, larger series included in table 2

Predict Outcomes?. Urology case reports, 8, 31-33.			
Gambaro, Giovanni, et al. "Percutaneous renal sympathetic nerve ablation for loin pain haematuria syndrome." Nephrology Dialysis Transplantation 28.9 (2013): 2393-2395.	Case study. N=1. 6 months.	Denervation successfully completed with complete relief of pain at follow up.	Single case study, larger series included in table 2
Clark, D., Somani, B., Kadi, N., & Townell, N. (2009). Is laparoscopic renal denervation the treatment of choice for loin pain-haematuria syndrome (LPHS): experience from Scotland. Journal of endourology (Vol. 23, pp. A93)	Case series. N=10, 100% female. Median follow up 48 months.	Procedure was curative in 4/10 (40%) of patients at median follow up of 38 months. In 4/6 of the patients where the procedure failed required less analgesia	Abstract only. In addition, one authors (Kadi) has published a case study from a similar time period, from the same location, with similar demographics (100% female) so likely overlap of study.
Andrews, B. T., Jones, N. F., & Browse, N. L. (1997). The use of surgical sympathectomy in the treatment of chronic renal pain. British journal of urology, 80(1), 6-10.	Case series. N=21.	4/21 patient experienced complete pain relief (median follow up 53.5 months).	Procedure was open rather than laparoscopic.