Novel treatment protocol for ameliorating refractory, chronic pain in patients with autosomal dominant polycystic kidney disease

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Autosomal dominant polycystic kidney disease (ADPKD) patients can suffer from chronic pain that can be refractory to conventional treatment, resulting in a wish for nephrectomy. This study aimed to evaluate the effect of a multidisciplinary treatment protocol with sequential nerve blocks on pain relief in ADPKD patients with refractory chronic pain. As a first step a diagnostic, temporary celiac plexus block with local anesthetics was performed. If substantial pain relief was obtained, the assumption was that pain was relayed via the celiac plexus and major splanchnic nerves. When pain recurred, patients were then scheduled for a major splanchnic nerve block with radiofrequency ablation. In cases with no pain relief, it was assumed that pain was relayed via the aortico-renal plexus, and catheter-based renal denervation was performed. Sixty patients were referred, of which 44 were eligible. In 36 patients the diagnostic celiac plexus block resulted in substantial pain relief with a change in the median visual analogue scale (VAS) score pre-post intervention of 50/100. Of these patients, 23 received a major splanchnic nerve block because pain recurred, with a change in median VAS pre-post block of 53/100. In 8 patients without pain relief after the diagnostic block, renal denervation was performed in 5, with a borderline significant change in the median VAS pre-post intervention of 20/100. After a median follow-up of 12 months, 81.8% of the patients experienced a sustained improvement in pain intensity, indicating that our treatment protocol is effective in obtaining pain relief in ADPKD patients with refractory chronic pain.

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary renal disorder, with a prevalence of 4.4 per 10.000.[1] In affected patients numerous cysts are formed in both kidneys and often also in the liver, leading to organ enlargement that can be massive. Renal function decline is the main clinical problem, leading to end-stage renal disease between the fourth and seventh decade of life in most patients.[2] Chronic pain is another debilitating complication, with an estimated prevalence of 60%.[3,4] In a number of cases it can be severe and have a large impact on physical and social activity.[3,4] In case of pain caused by pressure of the enlarged organs on adjacent tissues or by distension of the hepatic capsule, pain stimuli are considered to be relayed via the celiac plexus and major splanchnic nerves, whereas in pain caused by distension of the renal capsule, the predominant pathway is via the aorticorenal plexus and minor and least splanchnic nerves[5] (Figure 1). Chronic pain can be difficult to manage, and may lead to a need for major analgesic therapy and surgical procedures, such as cyst aspiration, cyst fenestration, or even nephrectomy.[6,7] In the literature it has been suggested that nerve blocks can be used for pain management before such invasive therapies are explored.[6–9] However, no study has been performed to investigate the effect of nerve blocks on pain relief in ADPKD patients.

We recently proposed a novel approach for treatment of refractory chronic pain in ADPKD that applies sequential nerve blocks.[8] When after a multidisciplinary assessment non-ADPKD–related causes are ruled out, a diagnostic, temporary celiac plexus block with a local anesthetic agent is performed. In cases in which substantial pain relief is obtained, it is assumed that pain was caused by pressure on adjacent tissues or distension of the hepatic capsule. Consequently, when pain recurs, a long-term block of the major

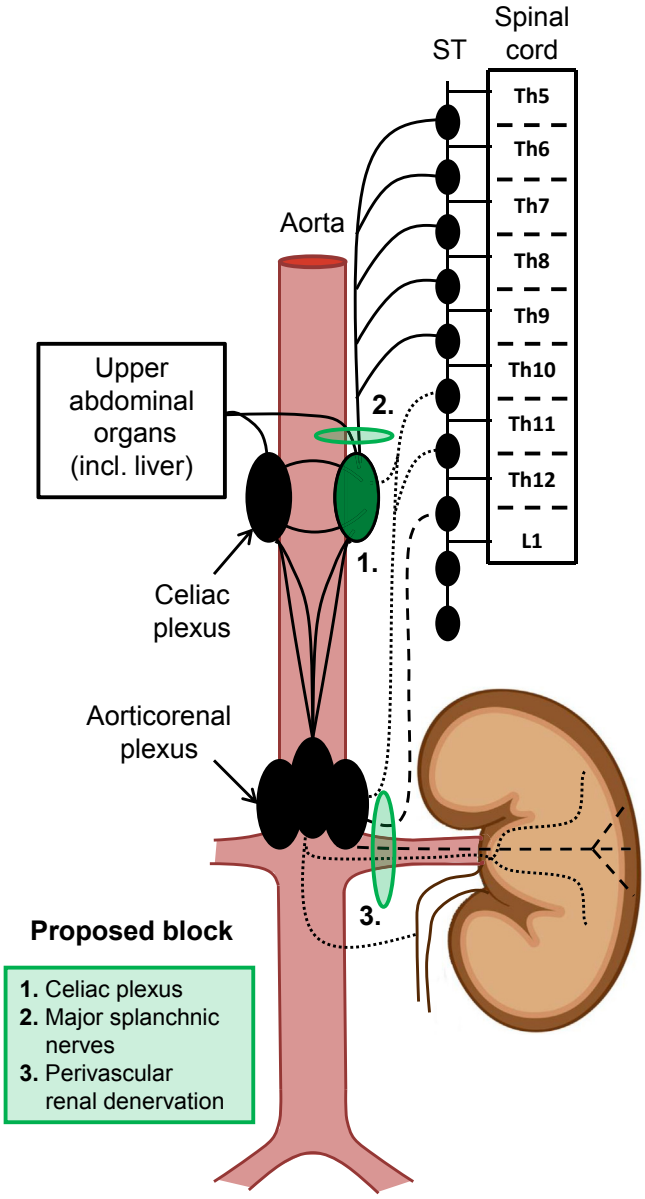

Figure 1 | Schematic representation of the sensory nerve supply of the kidneys and upper abdominal organs. Solid line: major splanchnic nerve providing sensory innervation of the upper abdominal organs, including the liver via the celiac plexus. Dotted line: lesser splanchnic nerve providing sensory innervation of the renal parenchyma and ureter. Dashed line: least splanchnic nerve providing sensory innervation of the renal capsule. The perivascular nerve plexus around the renal artery forms the final common pathway to and from the kidney. ST, sympathetic trunk. Adapted with permission from Bajwa ZH, Gupta S, Warfield CA, et al. Pain management in polycystic kidney disease. *Kidney Int.* 2001;60: 1631–1644.[6]

splanchnic nerves by radiofrequency ablation (RF-MSN block) is performed. When there is no response to the diagnostic celiac plexus block, pain stimuli are likely to be relayed via the alternative pathway (i.e., the aorticorenal plexus), in which case renal denervation is the preferred option. This intervention is executed via a catheter-based technique, originally developed as treatment for refractory hypertension, and has recently been suggested as an effective treatment of chronic pain in selected ADPKD patients.[10,11] Here we present the results of our multidisciplinary protocol consisting of sequential nerve blocks in ADPKD patients with refractory chronic pain.

RESULTS

Patient characteristics

A total of 60 patients visited our Expertise Center for Polycystic Kidney Diseases for analysis and treatment of refractory chronic ADPKD-related pain, of which 3 patients were self-referred. After assessment of inclusion and exclusion criteria, 44 patients were deemed eligible to participate in our treatment protocol (Figure 2). Sixteen patients were ineligible because another treatment option was chosen (such as nephrectomy in patients undergoing renal replacement therapy [RRT] or cyst aspiration in case of a limited number of very large cysts], pain was likely non-ADPKD–related, pain could be treated with additional medication, or the patients rejected the treatment protocol. Characteristics of these ineligible patients are given in Supplementary Tables S1 and S2. Mean age of the included patients was 50 ± 9 years, and 77.3% were female (Table 1). Three patients were RRT-dependent, and in the non-RRT–dependent patients ($n = 41$), mean estimated glomerular filtration rate (eGFR) was 57 ± 25 ml/min/1.73m^2. Pain was present for a median period of 7 years (interquartile range [IQR]: 4–18) and was experienced as refractory for 12 months (IQR: 10–24) (Table 2). Nearly all patients (95.5%) used daily opioids, except one who had a contraindication against opioid use, and 18 (40.9%) had previously been treated by invasive therapies such as cyst aspiration ($n = 8$), cyst sclerotherapy ($n = 4$), cyst fenestration ($n = 5$), or contralateral nephrectomy ($n = 5$). Pain had an impact on patient's work, daily activities, and social life, as indicated by low physical component score (PCS) and mental component score (MCS) (34 ± 17 and 50 ± 21, respectively). No associations of total kidney volume, total liver volume, or combined kidney and liver volume with visual analogue scale (VAS) score were found ($P = 0.6$, $P = 0.3$, and $P = 0.5$, respectively).

Sequential blocks

In all 44 patients an ipsilateral, diagnostic, temporary celiac plexus block with 10 ml of bupivacaine 0.5% was performed. Kidney size was no limitation to perform a nerve block. In 36 patients (81.8%), substantial pain relief was obtained (median change in VAS pre-post intervention: 50/100 [IQR: 26–68]; $P < 0.001$) (Figure 2 and Table 3). In 13 patients (36.1%) pain did not recur (i.e., remained below 50/100) after the initial celiac plexus block and no further action was taken (median change in VAS pre-post intervention: 60/100 [IQR: 35–70]; $P < 0.002$) (Table 3). Twelve of these 13 patients were no longer dependent on daily-use opioids, and only 5 used daily acetaminophen.

In the remaining 23 patients (63.9%), pain recurred after a median follow-up of 6 (IQR: 3–11] weeks, for which reason