



Exploring the role of perioperative pregabalin in ureteroscopy enhanced recovery after surgery (ERAS) protocols

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Ureteroscopy is one of the most frequently performed urologic procedures. Post-ureteroscopy pain is common, with 6% of opioid-naïve patients having persistent opioid use afterwards (1). Additionally, 10% of patients visit the Emergency Department postoperatively, with flank pain being one of the most common presentations (2). The development of enhanced recovery after surgery (ERAS) protocols, initially developed for open abdominal surgeries, have found applications in endourology including after ureteroscopy. The goal is to optimize postoperative pain and patient recovery, while minimizing narcotic use. This has become an important topic amidst the growing opioid epidemic.

Ureteroscopy-ERAS protocols have been designed to target different aspects of pre- to post-procedural care (3-5). In particular, postoperative protocols have focused on early tube removal, mobilization, and non-opioid analgesia. Opioids are reserved only for breakthrough pain and in the lowest dose needed. Nonsteroidal anti-inflammatory drugs (NSAIDs) have been shown to offer excellent pain control in patients with renal colic, helping to decrease inflammation and ureteral contractions (6). The Study of Ketorolac vs. Opioid for Pain after Endoscopy (SKOPE) was the first double-blind randomized trial to show non-inferiority of NSAIDs compared to opioids post-ureteroscopy (7).

Recently, there has been increased interest in the role of gabapentinoids in acute postoperative pain. Traditional analgesics are anti-nociceptive, reducing sensory input at the site of tissue injury. Although the exact mechanisms are unclear, gabapentinoids decrease the excitability of dorsal horn neurons, blocking hyperalgesia and central sensitization (8). Compared to gabapentin, pregabalin has a more favourable pharmacokinetic profile. It has higher bioavailability, faster absorption, and dose-independent absorption (9). Several meta-analyses have been done focusing on pregabalin in the postoperative setting (8,10,11). Pregabalin has been shown to significantly decrease pain scores at 2 hours and total daily opioid consumption, while decreasing opioid-related side effects (11). Pregabalin is normally taken two to three times a day for neuropathic pain. However, no differences have been seen between 100–300 mg and single versus repeat dosing perioperatively (10). These meta-analyses attempted to further stratify by procedure, however ureteroscopy was not included.

To address this unknown in the literature, Rosen and colleagues evaluated the utility of a single 300 mg preoperative dose of pregabalin for post-ureteroscopy pain (12). The authors should be commended on this well designed, blinded, randomized, real-world pragmatic study. Although pregabalin was well tolerated with minimal side effects, no significant difference was found in post-operative

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pain scores. Despite this, it may be too early to dismiss the role of pregabalin for ureteroscopy completely.

As the authors acknowledged, limitations of their study included the discrepancy in patient characteristics despite randomization. The pregabalin group was younger (44 *vs.* 57 years) and more were pre-stented (23% *vs.* 15%). Older age has been associated with lower pain intensity in patients with ureteric stents post-ureteroscopy (13), but conversely pre-stenting may offer pain advantages.

The largest limitation is that the study time points may not have been optimal. The primary outcome was based on pain scores after 1 hour in the recovery unit, which may be confounded by lingering anesthetic affects. It may have been helpful to have further scores within the first 24 hours. Additionally, pregabalin has a half-life of 6.3 hours. Later time points within the first month would be unlikely affected by a single pre-operative dose. Future studies may consider either different timepoints for pain assessment, or a longer duration of prescription.

About half of patients in each group were stented at the end of ureteroscopy. Ureteric stents can be quite symptomatic and a source of postoperative pain. Further analysis of pain in patients with and without stents with pregabalin would also be of interest.

Consistent with previous studies, post-ureteroscopy pain had a high burden on unexpected healthcare visits in this study. Between both pregabalin and placebo groups, 15–17% required emergency room visits or admission within the first 30 days, with majority being for pain. Excluding emergency visits, 14–27% had further unplanned interaction with the urology team, and 18 patients had clinic interactions. A better understanding and management of post-ureteroscopy pain could help reduce unplanned interactions, conserve resources, and improve perioperative quality of life for patients.

The ideal ERAS protocol likely involves appropriate preoperative patient counselling on expected postoperative pain, coordination and collaboration with the anesthesia team, and a post-operative combination of predominantly non-opioid medications. This may include NSAIDs, alpha blockers, anticholinergics, acetaminophen, pyridium, and/or pregabalin. This study showed that pregabalin is well tolerated in the perioperative setting, however, the effect of a single preoperative dose does not appear to have a large effect on postoperative pain in the immediate recovery period. Further studies will be needed to clarify the role of longer prescriptions of pregabalin, and also to assess the role of other individual components of ERAS protocols.

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