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INVITED REVIEW

Operational Andrology

# Pain management strategies in penile implantation

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The opioid epidemic continues to be a serious public health concern. Many have pointed to prescription drug misuse as a nidus for patients to become addicted to opioids and as such, urologists and other surgical subspecialists must critically define optimal pain management for the various procedures performed within their respective disciplines. Controlling pain following penile prosthesis implantation remains a unique challenge for urologists, given the increased pain patients commonly experience in the postoperative setting. Although most of the existing urological literature focuses on interventions performed in the operating room, there are many studies that examine the role of preoperative adjunctive pain medicine in diminishing postoperative narcotic requirements. There are relatively few studies looking at postoperative strategies for managing pain in prosthetic surgery with follow-up past the immediate hospitalization. This review assess the various strategies employed for managing pain following penile implantation through the lens of the current state of the opioid crisis, thus examining how urologists can responsibly treat pain without contributing to the growing threat of opioid addiction.

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## INTRODUCTION

In 2019, the opioid epidemic remains the United States' top public health concern. Physicians, especially those in specialties that regularly prescribe opioids, bear great responsibility in counseling patients regarding the risks of opioid addiction as well as providing alternative pain control strategies. Pain management for prosthetic surgery recipients has historically been challenging due to the sensitivity of the male external genitalia to any surgical manipulation. Nevertheless, the onus remains on the urologist to effectively control postoperative discomfort adequately while not relying too heavily on narcotic pain control.

This review addresses pain management as it pertains to penile prosthetic surgery in urology in the climate of the opioid crisis. In addition, we examine the full spectrum of historical pain management following penile implantation, looking at preoperative and intraoperative techniques in urology as well as other surgical fields for minimizing the burden of pain patients may experience postoperatively. Finally, we review limitations of many of the contemporary investigations with regard to postoperative pain reduction and further delineate our own institutional experience employing a comprehensive multimodal analgesia protocol for penile implant recipients.

## BACKGROUND

Prescription opioid abuse was responsible for approximately 15 000 drug overdose deaths with up to 2 million American adults suffering from an opioid use disorder involving prescription opioids in 2015 alone.<sup>1</sup> In addition, roughly 11.5 million Americans reported misusing opioids over the course of 2015.<sup>2</sup> As regular prescribers of opioid narcotics, surgeons and surgical specialists are on the front lines of

prescription opioid abuse. While surgeons and other subspecialists might not prescribe the most opioids, their ratio of opioid prescriptions to total prescriptions was the 2<sup>nd</sup> highest of any field in medicine, second to only pain medicine.<sup>3</sup> Alam and colleagues found that patients who received an opioid prescription within 7 days of a same-day surgery procedure were 44% more likely to become long-term opioid users within 1 year compared to patients who did not receive a prescription.<sup>4</sup> In addition to patients receiving multiple narcotic refills, excess opioid prescribing continues to fuel illicit patient use. A recent investigation determined that an overwhelming majority of patients undergoing urologic surgery keep any prescribed excess opioid narcotics as opposed to appropriately disposing of any unused medications.<sup>5</sup> Opioid diversion for illicit use remains the major concern associated with opioid keeping. The responsibility of the prescriber to understand causes of postoperative pain and appropriately tailor a management strategy remains paramount.

Inflatable penile prosthesis (IPP) surgery is the gold standard for men with erectile dysfunction (ED) refractory to medical therapy. Surgery is now considered an equal line option to the management of ED to other conventional treatments such as inadequate response or intolerance of phosphodiesterase-5 inhibitors, vacuum-assisted devices, intracavernosal injection therapy, or intraurethral suppository therapy.<sup>6</sup> Nevertheless, many patients remain apprehensive on choosing surgery for the management of ED given concerns over pain management. Levels of postoperative pain following IPP implantation are variable; however, patients often struggle obtaining adequate postoperative pain control in the immediate recovery process.<sup>7</sup> Given the elective nature of IPP surgery and the growing concerns with the opioid crisis, urologists have a responsibility to reimagine pain control regimens

and configure management in the preoperative, intraoperative, and postoperative spaces.

## METHODS

This comprehensive review was conducted by searching PubMed and EBSCO Host for preexisting studies addressing pain management in IPP surgery, as well as preoperative tactics in other surgical fields for analgesia. We queried each search engine using “penile,” “prosthesis,” “preoperative,” “intraoperative,” “postoperative,” “pain management,” and “surgery” in combination with one another. We excluded case series and trials that were published prior to 2000.

### Preoperative analgesia

Following robust recommendations made by our anesthesiology colleagues, we have previously demonstrated that optimal postoperative pain control begins in the preoperative holding area with desensitization of the pain receptors throughout the central and peripheral nervous system.<sup>7,8</sup> Prior investigations assessing preoperative acetaminophen, and nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 (NSAIDs/COX-2) inhibitors, and gabapentin/pregabalin have shown that these drugs play an important role in decreasing postoperative narcotic usage both in urologic and nonurologic surgeries.<sup>7,8</sup> Acetaminophen, a weak inhibitor of prostaglandin synthesis, has a centrally acting analgesic effect through an unknown mechanism.<sup>9</sup> On the other hand, NSAIDs work by decreasing prostaglandin synthesis, with COX-2 inhibitors being more selective. Such COX-2 agents are also less frequently associated with side effects of other general NSAIDs such as bleeding, renal injury, and gastric ulceration.<sup>10</sup> Several analyses have shown that there is no difference in postoperative pain when treated with a nonselective NSAID, such as ibuprofen, and selective COX-2 inhibitor, such as meloxicam.<sup>11–15</sup> However, the less frequent dosing due to longer duration of action and their improved gastrointestinal side effect profile make selective COX-2 inhibitors preferred by some surgeons.<sup>11–15</sup> Although not performed in urology, a recent comparative analysis in dental medicine between meloxicam and ibuprofen demonstrated better overall pain control, improved sustainability of pain relief, and a dose-dependent reduction in pain to those patients receiving meloxicam.<sup>16</sup> Gabapentin and pregabalin, on the other hand, have no effect on prostaglandin synthesis and instead are centrally acting antiepileptic medications. They work by binding to the  $\alpha_2\delta$  subunit of voltage-dependent calcium channels, which in turn decreases the function of the calcium channel and leads to a decrease in the amount of neuronal hyperexcitability. This effect can be used to treat neuropathic pain in addition to seizures.<sup>17</sup> Pregabalin is preferred by some over gabapentin as it has faster absorption and greater bioavailability; however, it also has additional cost.<sup>8</sup>

While urology data examining the effects of preoperative analgesics on postoperative pain are lacking, there is a bevy of literature across different surgical fields looking at the effects of single drugs as well as drug combinations given prior to surgery on postoperative narcotic usage and pain. Parsa and colleagues examined the effect of administering gabapentin 1200 mg and celecoxib 400 mg versus only celecoxib in patients undergoing bilateral subpectoral breast augmentation.<sup>18</sup> The investigators reported 95.8% of the patients taking combination therapy required no opioid narcotics versus 19.9% of patients taking only celecoxib.<sup>18</sup> El Kenany and El Tahan looked at the effect of preoperative pregabalin at varying dosages on women undergoing elective cesarean delivery. These investigators discovered that patients' high-dose pregabalin required far smaller amounts of postoperative morphine (mean: 6 mg) than patients taking placebo

(mean: 12.9 mg) or low-dose pregabalin (mean: 11.9 mg).<sup>19</sup> Mao and colleagues conducted a meta-analysis of randomized controlled trials to evaluate the levels of pain control achieved by preoperative gabapentin and pregabalin in patients undergoing total hip arthroplasty. The meta-analysis concluded that although the mean pain levels quantified by the visual analog scale (VAS) did not differ significantly (standardized mean difference: 0.46, 95% CI: -0.17–0.48,  $P = 0.36$  at 24 h; standardized mean difference: 1.15, 95% CI: -0.58–2.89,  $P = 0.193$  at 48 h), patients taking either gabapentin or pregabalin decreased the postoperative morphine requirement at 24 h (mean difference: -7.82, 95% CI: -0.95–-0.52,  $P < 0.001$ ) and 48 h (mean difference: -6.9, 95% CI: -0.95–-0.57,  $P = 0.118$ ) substantially although the latter finding was not found to be statistically significant at 48 h.<sup>20</sup> Similarly, in an OB-GYN-conducted randomized controlled trial, investigators gave 1000 mg of intravenous acetaminophen versus placebo to women undergoing scheduled cesarean delivery. The researchers found that women had similar levels of pain postoperatively; however, patients receiving IV acetaminophen required less narcotics (47 mg oxycodone) than the patients receiving placebo (64 mg oxycodone).<sup>21</sup> These studies conducted outside of urology highlight the far lessened requirement of postoperative opioids by giving adjunctive pain medication preoperatively.

### Intraoperative analgesia

Intraoperative analgesia can be subdivided into pain prevention via intraoperative local anesthesia with variations in surgical technique to reduce pain. Penile pain in particular is very hard to control due to the increased number of free nerve endings and corpuscular receptors in the penile tissues.<sup>22</sup> These nerve fibers converge to form the dorsal penile nerve, whose afferent signal then travels along the pudendal nerve into the spinal cord at the S2–S4 level, through the central gray region of the spinal cord to the thalamus and ultimately the sensory cortex. Anywhere along this path can be targeted for anesthesia and pain control, particularly at the dorsal nerve, pudendal nerve, and/or S2–S4 nerve roots.<sup>22</sup>

There have been numerous studies assessing various nerve blockades during IPP surgery, which can be referenced in **Table 1**. All make use of amide-based local anesthetics, such as short-acting lidocaine and long-acting bupivacaine in either a single- or in a multiagent approach.<sup>7,22–28</sup> Amide anesthetics are lipophilic agents that have increasing lipophilicity with increasing potency. Similarly, smaller, more lipophilic molecules correlate with faster onset of action.<sup>29</sup> When acting on neurons, those that are smaller and more myelinated are more susceptible to the depolarizing effects of amide anesthetics. Type C and A $\delta$  nerve fibers are the ones that are responsible for the majority of pain, temperature, and touch sensation, and as such are the clinical targets for local anesthetics.<sup>29</sup>

Numerous urologic IPP investigations have looked at local nerve blocks pre- and intraoperatively to determine whether or not there was an effect on postoperative pain control. Raynor and associates conducted a prospective, randomized controlled trial comparing a dorsal penile nerve block with 10 ml of equal parts 1% lidocaine and 0.5% bupivacaine without epinephrine to a saline control.<sup>23</sup> In their study, they did not perform a concurrent penile ring block.<sup>23</sup> They found that of 15 patients randomized to each group, there was decreased pain in the dorsal nerve block group immediately and 4 h postoperatively. At 23 h postoperatively, there was a decrease in pain, but it was not found to be statistically significant. Importantly, however, both groups had similar narcotic usage despite the decrease in perceived pain in the nerve block group. The authors concluded that nerve blocks should

**Table 1: Selected series assessing pain management strategies in penile implantation**

| Study                                   | Number of patients | Intervention  | VAS score reporting | Pain control assessment >1 day | Narcotic assessment >7 days |
|---|--------------------|---|---------------------|--------------------------------|-----------------------------|
| Man <i>et al.</i> 2018 <sup>7</sup>     | 57                 | Multimodal analgesia protocol                             | Yes                 | No                             | Yes                         |
| Raynor <i>et al.</i> 2012 <sup>23</sup> | 30                 | Dorsal penile nerve block                                 | Yes                 | No                             | No                          |
| Cotta <i>et al.</i> 2016 <sup>24</sup>  | 37                 | Extended release liposomal bupivacaine                    | No                  | No                             | No                          |
| Hsu <i>et al.</i> 2013 <sup>26</sup>    | 128                | Acupuncture plus local penile block                       | Yes                 | No                             | No                          |
| Hsu <i>et al.</i> 2004 <sup>27</sup>    | 137                | Crural block versus pudendal block                        | Yes                 | No                             | No                          |
| Xie <i>et al.</i> 2018 <sup>28</sup>    | 131                | Dorsal penile nerve block and penile ring block           | Yes                 | Yes                            | No                          |
| Hsu <i>et al.</i> 2007 <sup>40</sup>    | 165                | Dorsal penile nerve block, crural block, peripenile block | Yes                 | No                             | No                          |
| Nagao <i>et al.</i> 2000 <sup>42</sup>  | 25                 | Penile block  | No                  | No                             | No                          |
| Ghanem and Fouad 2000 <sup>45</sup>     | 159                | Infrapubic penile block                                   | No                  | No                             | No                          |

VAS: visual analog scale

always be given unless there is an allergy or other contraindication; however, their investigation did not conclude whether the nerve block should be performed prior to incision or at the conclusion of the case. In fact, there are no studies looking specifically at urologic surgery to answer this question. Although this has been investigated by general surgeons who have concluded there to be no analgesic difference in preincisional versus postincisional wound infiltration, we contend that doing a postoperative block following prosthesis surgery may carry a higher risk of inadvertently sticking one of the implant components.<sup>30,31</sup>

A later study by Xie and colleagues looked at the efficacy of combination penile dorsal nerve and ring block with either bupivacaine, ropivacaine, or control (no injection) in 131 men undergoing IPP implantation in 2013.<sup>28</sup> They chose to perform both a ring and dorsal nerve block based on a 2005 study of pediatric circumcision patients, which showed superior analgesia with a combination block than any individual component.<sup>32</sup> Xie's group reported both bupivacaine and ropivacaine blocks had significantly less pain immediately postoperatively and on postoperative day 1 (no difference between experimental groups), but that there was no difference between experimental and control groups on postoperative days 2–7. Due to the increased expense and cardiotoxicity of bupivacaine, the authors recommended the use of ropivacaine.<sup>28</sup>

Modifications to long-acting bupivacaine, such as incorporating it into a liposomal suspension, can provide prolonged local anesthetic for up to 96 h to help decrease need for postoperative narcotics.<sup>22</sup> Research in the breast reconstruction literature has shown that patients who receive liposomal bupivacaine have less postoperative pain and have a shorter length of hospitalization (1.5 days vs 2 days) compared to controls.<sup>33</sup> Similarly, in the IPP literature, when liposomal bupivacaine was compared to a control group who received standard bupivacaine or no local anesthetic, the controls required 3.2 times the amount of postoperative narcotics.<sup>24</sup> However, despite an increased narcotic usage, there has been no identified difference in postoperative pain between groups. In addition, the cost of liposomal bupivacaine severely limits its use, costing approximately \$285 compared to \$5 in controls.<sup>24</sup> Many of these studies are importantly limited by short-term follow-up and only critically investigate the immediate postoperative period, but not the patient's entire recovery.<sup>24,33–39</sup>

Other groups have looked at alternative nerve blocks, such as crural and pudendal blocks, as well as postoperative augments to these blocks. In cases not involving general anesthesia, Hsu and associates initially used a pudendal block in combination with a dorsal nerve block for outpatient IPP implantation, but eventually transitioned to using crural blocks in addition to dorsal nerve blocks.<sup>27</sup> In addition, the investigators reported that all 137 men who underwent IPP

implantation had satisfactory anesthesia with no men experiencing postoperative perineal aching, a finding seen previously with pudendal blocks.<sup>27</sup> However, the researchers also noted that using local anesthesia for such cases was considerably more difficult when a three-component IPP was used, and thus the staggering majority of the implants used in this study were two-component IPPs.<sup>27</sup> Finally, Hsu and colleagues also looked at the effects of acupuncture as an augment to further potentiate the anesthesia from the local block and found that 87% of men were willing to undergo this anesthetic technique again for outpatient IPP implantation.<sup>26</sup> A major limitation to this analysis was the lack of controls when reporting the observed findings. Citing an overall reduction in health-care cost of 35%, these researchers routinely perform implantation under pure local anesthesia, with very few patients requiring additional sedative medications.<sup>40</sup>

Many high-volume implanters have anecdotally reported decreased pain when the penoscrotal approach has been avoided or when touting “minimally invasive”, infrapubic, or subcoronal approaches. With respect to surgical techniques to reduce postoperative pain, other than through the use of local anesthesia, there have been no studies to our knowledge comparing pain reduction strategies of various IPP placement approaches.<sup>22</sup> Moncada and colleagues conducted an important analysis characterizing the effect of intraoperative corporal dilation on increased pain as measured via the VAS at both 1 day and 7 days postoperatively.<sup>41</sup> In their standard procedure, the authors describe dilating the corpus cavernosum spongy tissue using a blunt Hegar dilator and then passing the Furlow inserter once proximally and distally to measure corporal length.<sup>41</sup> The authors do not mention the size of instrument used. They found that patients who underwent dilation reported shorter perceived penile length and poorer erectile function scores at 3 and 6 months postoperatively.<sup>41</sup> The authors concluded that corporal dilation was not a requisite step in primary IPP implantation cases.

## DISCUSSION

Although there remains a paucity of urological literature regarding novel pain management strategies in IPP surgeries, there are some important limitations to the work completed to date. Nagao and associates analyzed twenty patients who received a penile block intraoperatively, and while they followed their cohort for up to 5 years postoperatively, they did not assess pain levels outside of 4 h following surgery and did not mention how pain levels were assessed.<sup>42</sup> Xie and colleagues looked at different medications used for dorsal penile nerve blocks as well as penile ring blocks using the VAS to quantify pain levels and followed patients for only 1 week postoperatively.<sup>28</sup> Raynor and associates randomized patients to receive a dorsal penile

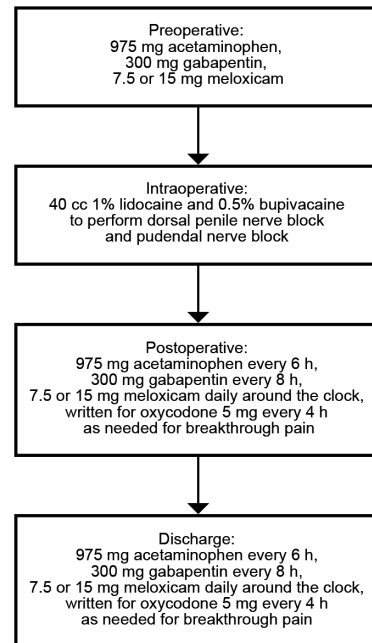
nerve block or placebo and used the VAS to assess pain at only up to 23 h postoperatively.<sup>23</sup> Similarly, the aforementioned Hsu comparative analysis of crural nerve blocks to pudendal nerve blocks utilized the VAS to assess pain at only up to 24 h postoperatively.<sup>27</sup> Finally, in a similar fashion, Cotta and colleagues assessed the effect of liposomal bupivacaine on total morphine equivalents (TME) used postoperatively and patients' self-reported pain scores up to only 23 h postoperatively.<sup>24</sup>

While the duration of action of nonliposomal local anesthetics does not last beyond the immediate perioperative period, much of the long-term postoperative pain control may be affected by the synergistic combination of immediate perioperative and postoperative pain control. Thus, there remains a paucity of data looking at long-term outcomes greater than 1 week. In addition, much of the existing literature looks only at preoperative or intraoperative interventions without much attention to improving postoperative regimens that traverse the entire recovery period. In order to truly effect change, urologists will need to examine pain management strategies in the entirety of the postoperative space.

The multimodal analgesia (MMA) protocol proposed by our institution helps counterbalance many of the limitations of prior pain-related investigations at the time of penile implantation. In this carefully planned analysis, we reviewed VAS scores in patients receiving either standard opioid only based narcotic therapy compared to patients receiving MMA. The MMA protocol which is demonstrated in **Figure 1** involved a careful utilization of agents already discussed earlier in this review: preoperative administration of acetaminophen, gabapentin, and meloxicam; both dorsal penile and pudendal nerve block intraoperatively; and continuation postoperatively of the preoperative regimen.<sup>7</sup> The dorsal penile nerve block has been extensively described in other literature.<sup>23</sup> At our institution, we perform the pudendal nerve block in all IPP patients in either the supine or lithotomy position. In the supine position, we inject 10 cc of a 50%/50% mixture of 1% lidocaine and 0.5% bupivacaine into the penile branch of the pudendal nerve approximately 1–2 cm lateral to the corpus spongiosum with the needle oriented posterolaterally and repeat the same injection of the contralateral side of the penis. In the lithotomy position, we palpate Alcock's canal in between the scrotum medially and the ischial tuberosity laterally and inject 10 cc of the aforementioned mixture with the needle oriented posterior-laterally on both sides of the penis. Injection of the pudendal nerve in the lithotomy position achieves blockade for a larger nerve distribution, while supine administration addresses the penile aspect of the blockade (which is admittedly most paramount in implant recipients).

The outcome measures included a comparative analysis of VAS scores at immediately following surgery and on postoperative day 1 as well as a critical assessment of narcotic prescription refills recorded in a mandated statewide registry at least 6 weeks postoperatively. This, to date, remains the only study in the penile implant literature that reports efficacy of a postoperative and discharge pain management protocol that traverses the standard recovery period following penile implantation.

Importantly, as this continues to be a budding area for investigation, there have been several recent abstracts presented assessing novel pain control maneuvers. A recently described novel approach to IPP pain control involves soaking hydrophilic based coated implants in local anesthetic. In the United States, this type of creative design is only possible for Coloplast (Copenhagen, Denmark) designed penile implants given the surgeon tailored coating properties of the Titan and Genesis penile implant devices. In this abstract presented by Chung and colleagues, an *in vitro* analysis of the local analgesic-eluting properties



**Figure 1:** Einstein inflatable penile prosthesis multimodal analgesia protocol.<sup>7</sup>

of the Coloplast Titan Implant was conducted to determine if it dilutes the antimicrobial soak. The authors looked at the minimum inhibitory concentration achieved with the implant soak through 14 days of *in vitro* testing; then, forty patients were randomized to receive the implant with or without the analgesic dip.<sup>43</sup> The researchers reported that not only did the antimicrobial drugs maintain their zone of microbial inhibition through all 14 days, but that patients randomized to receive the implant dipped in local anesthetic had lower VAS scores and less analgesia requirements throughout the study.<sup>43</sup> Important limitations of this abstract include a lack of follow-up throughout the entire recovery process. In addition, as patients experienced neuropathic pain following this (or any) surgery, an implant placed intracorporally might do little to negate nerve-related pain that might arise from the nerve roots that course dorsolateral and external to the penis. In a similar early report presented as an abstract, Brennan and colleagues explored the efficacy of a ropivacaine intraoperative implant soak and compared it to the standard dorsal nerve/penile ring block injection used as a standard.<sup>44</sup> No difference in VAS scores was reported between patients undergoing the ropivacaine soak to standard local injection in the recovery room or at the time of follow-up appointment.<sup>44</sup> Similar to Chung's investigation, limitations that needed further clarification included whether validated pain assessment questionnaires were utilized and whether pain assessments traversed the entire follow-up period. Finally, these studies, while important, are preliminary reports of data in abstract form and we eagerly anticipate manuscript publication where further nuanced details regarding the study protocol and analysis could be presented and discussed.

## CONCLUSION

In summary, given the current weight and widespread impact of the opioid crisis, well-conceived pain management strategies are critical at the time of penile implantation. While there is some literature outlining preoperative and intraoperative interventions, these studies are generally limited in their length of follow-up and might have poor applicability especially as surgeons face increasing pressure to reduce



opioid prescriptions following any operation. Additional investigations assessing the implementation of multimodal analgesia protocols need to be conducted with long-term follow-up and in multi-institutional cohorts in order to adequately assess and validate the promising results of dramatic narcotic reduction following a historically painful operation.

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