UIJ UroToday International Journal®

www.urotodayinternationaljournal.com
Volume 2 - August 2009

Bladder Pain: Clinical Assessment and Treatment

Dagmar Westerling[1,2]
[1]Pain Unit, Department of Anesthesiology, Central Hospital of Kristianstad, Kristianstad, Sweden;
[2]Acute Pain Unit, Department of Anesthesiology, Wake Forest University School of Medicine, Winston Salem NC, USA
Submitted April 23, 2009 - Accepted for Publication May 19, 2009

ABSTRACT

INTRODUCTION: Bladder pain may arise due to infection, inflammation, trauma, cancer, or unknown reasons. Bladder pain may be acute, long term, and/or associated with other symptoms and syndromes. The treatment of bladder pain must consider both the pain and the function of the bladder.

METHODS: The definition, physiology, assessment, pharmacological treatment, and nonpharmacological treatment of bladder pain are reviewed and discussed. Three cases of complex bladder pain are presented.

RESULTS: Bladder pain is a symptom, not a disease. There is no single therapy that is helpful for all patients. Multimodal pain therapy that is tailored to the patient's present situation, genetics, ongoing treatment, and previous treatment(s) may reduce pain and improve quality of life.

CONCLUSION: Multidisciplinary evaluation and referral to a pain specialist should be considered for patients with complicated bladder pain with or without associated long-term pain problems. Patients with complex bladder pain may benefit from a consultation and second opinion from a pain specialist early in the course of the workup and not as a last measure when everything else has failed. Multidisciplinary pain teams with pain specialists should be part of the network available for clinicians who provide care for patients with complex pain problems.

KEYWORDS: Bladder pain; Assessment of pain; TENS; Pharmacology; Analgesia

CORRESPONDENCE: Dagmar Westerling, M.D. Ph.D., Acute Pain Unit, Department of Anesthesiology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston Salem NC, 27157, USA (dagmar.westerling@med.lu.se).

CITATION: *UroToday Int J* 2009 Aug;2(4). doi:10.3834/uij.1944-5784.2009.08.03.

INTRODUCTION

Bladder pain is treated by physicians with various specialties including family practitioners, gynecologists, or urologists. These physicians use many different principles. Referral to a pain specialist may occur, but it is often done late in the course of a pain syndrome, typically when attempted treatment options have failed for different reasons.

The rationale for treatment of bladder pain, painful bladder syndrome/interstitial cystitis (PBS/IC), or chronic pelvic pain (CPP) should be to adjust analgesic treatment to the suffering patient, taking into account individual genetic, environmental, behavioral, pharmacological, and situational differences. Practical information on clinical assessment and treatment of bladder pain are discussed in the present review. Three complex cases of bladder pain in patients referred to the author for evaluation are analyzed. Suggestions for analgesic treatment and the various outcomes of treatments are given.

Definition of Bladder Pain

Pain that arises in the bladder is of visceral origin and has been given many names and definitions. Long-term bladder pain in women may be classified as PBS/IC [1] and in men as chronic prostatitis [2]. Bladder pain is a subgroup of CPP which also includes several somatic pain states. These may present with or without visceral pain from the lower urinary tract or from other viscera (eg, colon, rectum, uterus, ovaries) [3], such as the irritable bowel syndrome (IBS).

Visceral pain is diffuse, difficult to localize, often referred to somatic structures, and sometimes associated with autonomic changes such as increase of heart rate, blood pressure, sweating, and change of color of the skin from very pale to crimson/red [4-7]. The intensity of visceral pain may change in quality and intensity very rapidly [8] from constant, dull and aching to sharp stabbing pain preventing muscular or any other activity. These changes may be irrespective of the causative pathophysiological findings [7]. In comparison with somatic, nociceptive pain, the intensity of visceral pain does not reflect the risk or extent of potential or actual organ damage [8]. Visceral pain is one of the main reasons that patients seek medical care [4,6,8].

Bladder pain is often reported as intermittent pain from the lower abdomen; it can also be felt from the lower back and urethra [9,10]. According to the National Institute of Diabetes, Digestive and Kidney Diseases, the definition of IC requires not only suprapubic pain, frequency, and urgency, but also morphological changes in the bladder [11]. The definition of PBS was later amended as: "Pain related to bladder filling accompanied by other symptoms such as increased daytime and night-time frequency in the absence of proven urinary infection or other obvious pathology" [12]. New nomenclature and a new definition have been proposed: *bladder pain syndrome/ interstitial cystitis* (BPS/IC) consists of bladder pain and at least one other urinary symptom, with further classification according to morphological findings in biopsies and findings at cystoscopy [13].

All bladder pain is not PBS/IC and bladder pain is often not the only type of pain in patients suffering from PBS/IC. Several long-term pain syndromes have been associated with BPS/IC [14] such as fibromyalgia syndrome (FMS), migraine, and IBS, where deficient central modulation of pain has been suggested [15] and recently reported [16,17].

Incidence of Bladder Pain

Long-term pain from any part of the body with an intensity greater than 5 on a 10-point numerical rating scale (NRS) occurred in 18% of an adult European population [18]. Long-term pain in older individuals has a much higher incidence, ranging between 45% and 80% [19]. Bladder pain for any reason in both men and women of all ages may be underreported. This may be due to its location and reluctance of patients to seek treatment or to hesitancy of healthcare staff to put medical attention on this area of the body [20]. The prevalence of acute and long-term bladder pain is unknown or variable, respectively. The prevalence of CPP in British women has been reported to be 3.8% [20], which is similar to reported incidence of other long-term pain conditions like low back pain and migraine. In a recent review [21], the prevalence of IC was given as 1 in 1000 women, increasing to more than 5 out of 1000 adult women (depending on diagnostic criteria, time frame, and geographic area). However, other reports [22,23] have suggested that the incidence of IC in adult women is much higher, at 20%-30%. Male IC, previously thought to be very rare, may be more common than was suggested [2].

Physiology of Bladder Pain

Pain from the bladder is normally not present unless the bladder wall is stretched beyond normal intravesical pressures [24], which generally are less than 25 cm H_2O during filling. However, painful stimuli caused by trauma, infection, distension, inflammation, obstruction, irradiation, carcinoma of the bladder, and by other yet unknown reasons activate pain receptors (ie, nociceptors) which consist of free nerve endings [8]. As nociceptors are activated, their threshold for activation decreases, leading to peripheral sensitization [25]. The bladder nociceptors are activated by chemical stimuli as well as by high and low intensity mechanical distension [5,8]. There are also mechanically insensitive receptors (*silent nociceptors*), which are only activated during noxious conditions [5,8]. Apart from signaling of pain through the bladder free nerve endings, the urothelial cells that outline the urinary bladder have transduction properties and may release adenosine triphosphate (ATP) and express transient receptor potential vanilloid type 1 ($TRPV_1$) [8]. The expression of $TRPV_1$ and release of ATP are both important for normal micturition, but may also induce peripheral sensitization of bladder nociceptors. Peripheral sensitization may lead to long-term bladder pain, because extracellular ATP reduces the threshold for stimulation of $TRPV_1$ which normally responds to elevated temperatures and acid [8].

Primary afferent pain signals from the bladder are transmitted through the hypogastric, lumbar splanchnic, and pelvic nerves which reach the dorsal horn at the thoracolumbar and sacral levels [5]. Somatic afferent signals are also projecting to the spinothalamic tract at the same spinal level (L4 -S2) as the urinary bladder, which is the basis for the concept of referred pain [5,6]. The spinothalamic tract relays the nociceptive signal to the pain matrix of the central nervous system (primary and secondary somatosensory, insular, anterior cingulated, and prefrontal cortices; thalamus). The nociceptive input is then processed and modified according to the present situation, genetics, mood, and previous experiences [26]. Long-term pain does not have to involve any known, present peripheral pathology. Central sensitization and lack of central modulation of painful stimuli are the mechanisms by which pain is prolonged beyond the healing of the primary peripheral damage [26,27].

Visceral hyperalgesia and hypersensitivity caused by central sensitization is of importance in functional gastrointestinal disorders [27,28] and may be a contributing factor in long-term bladder pain. Acute pain is a warning sign of upcoming danger, whereas long-term persistent pain has lost this meaning and therefore may be seen as a maladaptive consequence of central and peripheral plasticity [25].

Analysis of Bladder Pain

Pain analysis should answer the questions: where, when and how much does it hurt?

When does it hurt? Does the pain change over time, with activity and treatment? Is the pain constant? Are there sudden increases in pain? A sudden increase in pain occurring when ongoing analgesic treatment is otherwise efficient is referred to as *breakthrough pain* that requires special consideration in cancer patients [29] and in patients with complex pain syndromes caused by nonmalignant disorders. What causes the constant pain and what causes the breakthrough pain? What measures improve the pain and what actions make it worse? These questions are asked during the patient interview and are complemented by a thorough body examination, laboratory tests, and other investigations.

Where does it hurt? A drawing of the body is helpful to mark which areas hurt. The drawing may be used at the first and subsequent follow-up visits. When bladder pain is analyzed the body drawing needs to be specific with anterior, posterior, and perineal views of the pelvic region [9,30].

How much does it hurt? The intensity of the pain should be assessed by appropriate methods. Testing sensitivity for touch, temperature, and pin-pricks can be done by simple, qualitative bedside methods [31] or by quantitative sensory testing (QST) [32]. Either method for assessment of sensitivity and pain threshold should be used in combination with a neurological examination and a thorough patient interview. These methods will help to diagnose neuropathic pain.

The interview and pain analysis may take some time. Some patients have a long story to tell and it may be tempting to interrupt. However, interrupting the patient may actually prolong the interview thus delaying the time to diagnosis and treatment.

Assessment of Bladder Pain

Valid and reliable pain scales and questionnaires (eg, Short Form-36® [SF-36] health survey; Brief Pain Inventory© [BPI]) are used to assess pain and the impact of pain on quality of life. Some clinicians never use pain scales and claim that they can *see* if a patient has pain. It is difficult to *see* either improvement or deterioration and impossible to standardize treatment effects and outcome if pain scales are not used. Visual analog scales (VAS) or numeric rating scales (NRS) are often used for pain intensity, but may be more appropriate for acute than long-term pain. Older patients tend to have difficulty with the VAS concept. If the patient has cognitive difficulties there are also observational rating scales available (eg, Pain Assessment Scale for Seniors with Limited Ability to Communicate© [PACSLAC]; Face, Legs, Activity, Consolability, Cry Scale© [FLACC]; Mobilization-Observation-Behavior-Intensity-Dementia-Pain Scale [MOBID]; Doloplus-2©). These scales have been validated in various age groups [see 33,34, for examples]. Specific questionnaires for assessment of BPS/IC include the O'Leary-Sant Interstitial Symptom and Problem Index [35] and the Pelvic Pain and Urgency/Frequency Patient Symptom Scale© [36].

Comorbidity in Bladder Pain

Bladder pain is a symptom, not a disease. Bladder function, including the presence or absence of bladder pain, needs to be assessed in every medical workup of patients with pain and/or analgesic treatment. Frequency of micturition, urgency, urinary incontinence, and other problems with voiding should be addressed in addition to problems with sexual function.

Pain from the bladder can be caused by a simple lower urinary tract infection in an otherwise healthy individual. Alternatively, the bladder pain can be a very pressing symptom with or without obvious causes in a patient with multiple health problems, organ dysfunction, or poor compliance. These patients may have several medications that predispose for drug interactions and side effects.

Psychiatric disease (eg, depression and panic disorder) have been reported to be associated with PBS/IC [12]. Other psychosocial problems may further complicate the evaluation and care of a patient with bladder pain.

TREATMENT OF BLADDER PAIN

Pharmacological Treatment: Systemic

According to the analgesic ladder [37], acute nociceptive pain is treated with acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and weak or strong opioids if the intensity of pain is high.

There are several contraindications for treatment with NSAIDs. These include cardiovascular disease, allergy, gastrointestinal morbidity, coagulopathies, concomitant treatment with

doi:10.3834/uij.1944-5784.2009.08.03
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

anticoagulants, old age, and renal dysfunction. Long-term treatment with NSAIDs or cyclooxygenase II inhibitor (COX II) selective drugs may cause serious side effects that can offset the positive effects of the treatment. Long-term analgesic treatment with acetaminophen has weak scientific support and should be reevaluated at every visit and with every new prescription.

Weak or strong opioids are excellent for acute, nociceptive pain but have abundant side effects, the most troublesome of which are tolerance and the risk of dependence and addiction [38]. Opioids should be tapered and stopped as acute pain subsides. Opioids should not be considered for long-term nonmalignant pain until other treatment has been tried and found insufficient. All pain cannot be managed with opioids -- not even cancer pain. Visceral pain from the bladder may be sensitive to opioids, but so is the micturition reflex [39]. Treatment with opioids may lead to urinary retention and difficulty initiating micturition.

Tolerance to opioids may be treated with an increase in dosage, but this may also produce changes in pain sensitivity with the risk of opioid-induced hyperalgesia [40]. Long-term treatment with opioids in nonmalignant pain requires close monitoring and may not be successful in spite of monitoring [41]. Injections of opioids should never be given for long-term nonmalignant pain because the risk of addiction and infection increases with this route of administration.

Many patients (up to 50 % or more) given opioids for long-term pain stop the treatment due to insufficient analgesia and/or side effects, mainly constipation, sedation, and nausea [42, 43]. Other patients appear to do well for long periods of time on low, constant opioid doses [38]. Follow-up of opioid treatment including compliance, analgesic effect, and side effects is therefore necessary.

Neuropathic pain and/or conditions with poor central modulation are different from strict nociceptive pain and require other pharmacological treatment principles [44]. Amitriptyline, a tricyclic antidepressant, is the first-line treatment of neuropathic pain. It is given in low dose 2-3 hours before bed. Newer antidepressants like venlafaxine and duloxetine may be better tolerated in higher dosage compared to amitriptyline, due to its anticholinergic side effects. The side effects may be intolerable in older patients [45] in whom the risk of causing urinary retention should be considered. Common anticholinergic effects are dry mouth, sweating, cardiac arrhythmias, confusion, and urinary retention. Weight gain is a common side effect of most antidepressants and also of the antiepileptics gabapentin and pregabalin, which are the main alternatives to antidepressants in neuropathic pain [44]. Amitriptyline, gabapentin, and lately pregabalin and duloxetine are oral drugs that may be indicated and used in FMS [46,47] and in IBS [48]. These drugs have the ability to reduce central hyperexcitability and thus pain, an indication that may also be of interest in the treatment of long-term bladder pain.

Dosage of drugs should be kept as low as possible and titration should be slow in long-term pain. It is preferable to wait some time for any positive effect of pharmacological treatment than to have a patient stop drug treatment because of severe side effects caused by rapid titration.

Systemic anti-inflammatory/immunosuppressive/modulatory treatment has been tried or suggested for treatment of bladder pain [49], apart from NSAIDs and COX II selective drugs. The intention is to modify an inflammatory contribution to pain in PBS/IC. The use of corticosteroids, cyclosporine, methotrexate, tumor necrosis factor receptor inhibitors (etanercept and infliximab), interleukin 10, and bacillus Calmette Guerin (BCG) which is instilled in the bladder (see below) has been described [49]. Large randomized studies are not available and side effects of most of the treatments may limit usefulness in large patient populations.

Allergies are related to PBS/IC and therefore antiallergic treatments have been suggested. Hydroxizine or several other drugs [49] may be useful in some patients but have sedative and anticholinergic side effects. These side effects limit dosage, especially in elderly patients who may become drowsy and confused.

Pharmacological Treatment: Local

The rationale for local treatment of bladder pain is to keep high drug concentrations in the painful bladder in order to avoid systemic side effects. The cells in the urothelium act as a barrier, but they are also active in sensory signaling and transduction of nociceptive stimuli [8]. Therefore, it is attractive to apply drugs locally close to the target of the therapy. The major drawback of intravesical drug application is that it requires repeated catheterizations of the bladder, which necessitate medical assistance and may also lead to infections. If pain relief only lasts for short periods of time, local administration of drugs into the bladder is a less attractive therapy for long-term pain.

Intravesical administration has been described for several different drugs in PBS/IC and for bladder pain. Some intravesical therapies are directed toward inhibition of mastcells (heparin in combination with lidocaine 1% and 2%, respectively [49]). Inhibition of TRPV1 with capsaicin or resiniferatoxin hopefully

doi:10.3834/uij.1944-5784.2009.08.03
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

results in desensitization of nociceptive c-fibers [50]. Other intravesical therapies are given in order to substitute for a deficient glycosaminoglycan layer in the bladder (pentosan polysulfate [49]) or for idiopathic (dimethyl sulfoxide [51]) or immunomodulatory reasons (BCG [21]). Inhibition of peripheral opioid receptors (intravesical morphine for postoperative pain in children [52]) has also been attempted, although a subsequent randomized, controlled study was negative [53]. Injections of botulinum toxin have been given in the trigone and into the external sphincter and bladder base mainly to treat incontinence, but this treatment has also been shown to improve urinary frequency and bladder pain in a limited number of patients [54].

Local intravesical treatment with any of the above-mentioned therapies may be successful in selected patients with PBS/IC. However, evidence for the treatment varies, ranging from at least one randomized trial to nonexperimental studies like case reports and comparative studies [21]. According to the European association of Urology (EAU) guidelines, treatment with BCG is not recommended [55].

Nonpharmacological Treatment

Concomitant with all other treatment, the patient with bladder pain should have access to information about pain, treatment options, and possible outcomes. Strategies for everyday life, diet, and exercise are important. Multidisciplinary pain rehabilitation should be attempted early in the course of bladder pain, especially when other long-term pain syndromes are associated with it. Psychological treatment (eg, cognitive behavioral therapy, relaxation, counseling) is used for FMS [56] and IBS [57] and may be helpful in managing long-term bladder pain with or without pain at other locations.

Physiotherapy, relaxation techniques, and transcutaneous electric nerve stimulation (TENS) should be encouraged. TENS has been shown to reduce lower abdominal acute pain following surgery [58,59]. TENS reduced bladder pain in a limited number of patients with long-term voiding dysfunction [60] and has been used in patients with IC [61]. TENS is inexpensive, noninvasive, devoid of serious side effects, and can be applied by the patients in their home.

Invasive Treatment

Debilitating, severe bladder pain may be treated by invasive analgesic treatment, especially if the alternative is surgery with removal of the bladder. Spinal catheters may be subcutaneously tunneled to a port and used for continuous infusion of local anaesthetics in combination with opioids such as morphine [62] and/or clonidine (an α_2-adrenoceptor agonist with analgesic properties). Bladder pain caused by cancer or nonmalignant disease may be treated by spinal administration for many months or even years [63]. Side effects include a low risk of infection [64]. Spinal opioids may also have a long-term impact on hormonal status causing erectile dysfunction, hypothyroidism, and immunosuppression [38]. Tolerance of local anesthetics may necessitate dose adjustment over time.

Neurostimulation may be effective for some patients. Spinal cord stimulation is a cost-effective alternative to poor outcomes with expensive pharmacotherapy. It may be useful for neuropathic pain, pain associated with arterial insufficiency, or severe angina pectoris [65]. Positive outcome of percutaneous stimulation of the sacral nerves has been reported in patients with IC [66].

The following case reports illustrate management of three complex patients with bladder pain.

CASE REPORT 1

Case 1 is a married, 45-year-old woman with constant severe pain in the lower abdomen that extends into the vagina and urethra. She has severe bouts of breakthrough pain 5-10 times per day, described as coming from the urethra. The pain started following an operation for obesity more than 5 years ago when the patient pulled a bladder catheter with the cuff still inflated and experienced an acute tear in the urethra. There is nothing pathological to be seen either by external inspection of the vulva, external orifice of the urethra, or during several cystoscopies. Gynecological examination is painful because she has allodynia in the vulva. Sexual intercourse is impossible.

The patient has had several antibiotic treatments due to suspected bacterial cystitis but bacterial cultures have been negative. Due to severe pain during micturition she was given a permanent suprapubic bladder catheter. Initially, this gave her some relief but now it causes both spontaneous pain and pain by movement of the catheter.

The patient is referred to the pain clinic by her urologist, who has advised her not to undergo more surgery. Several surgical treatments have been performed on her urethral sphincter with short-lasting effects (2-3 days of improvement) followed by increased pain.

The woman has been treated for depression for more than 15 years and is seeing her psychiatric team every 2 weeks. She has taken her present antidepressive medication (duloxetine and mirtazapine) for more than 3 years. Social problems are

doi:10.3834/uij.1944-5784.2009.08.03
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

abundant and she is not working. She does not exercise and her eating habits are poor; she is still obese. She has been treated by her family doctor with acetaminophen 4-5 g/day and immediate release oxycodone (5 mg) up to 4 times daily. She is desperate to be cured.

Pain analysis. The patient has severe visceral pain of an intensity ranging between 6 and 10 on a 10-point numeric rating scale (NRS). She may have sensitization and possibly neuropathic pain caused by repeated suprapubic catheterization and surgery. The patient suffers from allodynia, psychosocial problems, depression, and panic disorder with anxiety. Antidepressive treatment may cause urinary retention. The patient may be at risk of developing opioid dependence. She has chronic constipation, possibly related to the use of opioids.

Suggested treatment. Immediate-release oxycodone as needed is replaced by a controlled-release preparation of oxycodone twice daily. The dose is not increased, but rather kept low. Hopefully, it can be tapered if other treatment improves the situation. Subsequently, oral pregabalin is introduced which may improve allodynia, neuropathic pain, and psychiatric status. Anti-inflammatory treatment with NSAIDs may be suggested, but should be omitted if not helpful. Acetaminophen is stopped because it has not improved the condition during long-term therapy with more than full dose. Lidocaine gel (5%) is tried locally to relieve allodynia. Adequate laxatives are prescribed in combination with exercise and improved diet.

Counseling, supportive therapy, physiotherapy with TENS, and relaxation techniques are used concomitantly with pharmacologic therapy, which is slowly introduced and monitored closely for effectiveness and side effects.

Outcome. Pain control is improved. On good days the patient rates her background pain as 4 out of 10 (NRS). The severe breakthrough pain continues but attacks occur less frequently, especially as constipation is relieved. Increase of pregabalin above 200 mg x 2 does not improve pain control but causes drowsiness.

The psychosocial issues have a strong impact on the situation. Long-term supportive therapy is helpful. TENS (high frequency, *burst* stimulation using 4 electrodes placed over the symphysis) is also helpful, but compliance is fairly low. The patient would rather be "fixed" with surgery, although her urologist has told her that surgery will not improve the situation. Tapering of drugs may prove much more difficult than starting new medications and therefore requires considerable effort from both the patient and the treatment team.

CASE REPORT 2

Case 2 is a 65-year-old male. He has had Parkinson's disease (PD) for 10 years that is treated with levodopa. The patient has walking difficulties, intention tremor, speech problems, and an expressionless face. A year before the present admission, the patient was treated with end-to-end gut anastomosis and irradiation due to a small tumor in the rectum. The patient has been given injections of morphine for severe pain. Recurrence of the rectal cancer is investigated and ruled out through coloscopic examination, computerized tomography (CT) scans, scintigraphy, and functional magnetic resonance imaging (fMRi). Cystoscopy is negative and there are no pathological findings in the scrotum or penis.

Pain analysis. The pain is diffuse and dull in the lower abdomen. Ultrasound showed that as the urinary bladder volume increases, the pain over the symphysis increases and radiates to the scrotum and penis. The pain has an intensity range of 7-9 on a 10-point NRS. The pain is visceral, arising in the bladder and/or gut, and has neuropathic components. Low pain thresholds have been associated with PD [67]. It is difficult to use observational rating scales with patients who have PD due to the lack of expression, rigidity of extremities, and poor mobility. The patient cannot void because of pain inhibition and/or morphine side effect. A bladder catheter is inserted, which partially relieves pain but causes irritation in the urethra. The morphine injections do very little to improve pain but increase nausea, constipation, dizziness, and nightmares.

Suggested diagnosis and treatment. This patient suffers from bladder pain that is referred to the genitals. The pain may have neuropathic qualities and may be caused by the patient's previous cancer treatment, leaving a sensitized bladder following irradiation and surgery in the area. In a recent report, 83% of PD patients reported pain [68]. The patient has several side effects of opioids and the injections of morphine are withdrawn and replaced with low-dose controlled-release buprenorphine as a patch. Amitriptylin may cause hypertension in combination with levodopa and therefore is not considered for treatment of neuropathic pain components in this patient. He is slowly titrated on gabapentin to a low dose of 400 mg x 3. TENS, physical activity, laxatives, and ondansetron for nausea are introduced. The patient receives thorough information on the status of his previous cancer diagnosis.

Outcome. Reduction of opioids does not increase pain but decreases nightmares and dizziness. As constipation is treated and gabapentin is initiated, pain relief is improved. The bladder catheter can be removed, although residual bladder volume needs to be monitored when gabapentin is used.

http://www.urotodayinternationaljournal.com
doi:10.3834/uij.1944-5784.2009.08.03
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

TENS, reassurance, and increased physical activity are helpful. The patient still has pain but of lower intensity, rated 4-5 on a 10-point NRS.

CASE REPORT 3

Case 3 is a 40-year-old woman who is married with 3 children. She has carcinoma of the cervix with metastatic spread to the urinary bladder. She describes severe pain in the lower abdomen located over the symphysis that is referred to the groin and to the back. Cystoscopy shows hemorrhagic cystitis, tumor invasion, and coagulated blood. The patient requires cystoscopy and bladder irrigation on several occasions to retrieve large, occluding blood clots.

Pain analysis. The intensity of the pain ranges from 4-10 on a 10-point NRS. The pain is constant, with severe breakthrough pain caused by bladder contractions and by passing of clotted blood. Distension of the bladder increases both pain and voiding frequency. There are no signs of neuropathic pain such as sensory deficits or radiating pain.

Suggested treatment and outcome. Acetaminophen and NSAIDs are combined with several subsequent strong opioids (morphine, fentanyl, and hydromorphone) given by different routes of administration (oral controlled release, transdermal patch supplemented by oral immediate release tablets, and later injections). Initially, the analgesic effect is acceptable. However, breakthrough pain becomes frequent, intense, and sudden, so patient-controlled analgesia using a portable pump is started. The route of administration is changed from subcutaneous to a tunneled spinal (intrathecal) indwelling catheter with a subcutaneous port. Spinal administration of a low, continuous infusion of local anesthetics with morphine is initiated. A bladder catheter is necessary because the spinal treatment affects bladder emptying. Walking ability is preserved and systemic opioids are tapered and stopped. This improves the patient's mood, fatigue, constipation, and nausea. Larger doses of local anesthetics can be administered through the spinal port, inducing spinal anesthesia for surgical interventions like bladder irrigation to treat large occluding blood clots. The treatment is continued successfully for 4 months until the death of the patient in her home.

PREVENTION OF LONG-TERM PAIN

Long-term pain is common and difficult to treat. In order to prevent long-term pain, assessment and treatment of acute pain should be as efficient as possible. Untreated perioperative pain may contribute to long-term nonmalignant postsurgical pain [69]. Patients with deficient central modulation of pain [70], which has been reported in several long-term pain syndromes such as FMS, IBS, temporomandibular disorder, and migraine [15,16,17], need special attention for effective treatment of postoperative pain. Unresolved, severe bladder pain in patients with long-term opioid therapy, drug addiction, or long-term pain from body parts other than the bladder should be evaluated by a pain specialist.

CONCLUSION

Bladder pain is a visceral pain symptom that may occur in acute or long-term pain conditions. Acute bladder pain usually subsides once the underlying cause is treated. In long-term bladder pain there may be no peripheral pathology to treat, so the pain is not only the symptom but also a disease of its own. Peripheral and central sensitization increases sensitivity to pain. Combined with deficient central modulation, the pain threshold decreases. Long-term bladder pain such as that associated with BPS/IC causes low-threshold mechanoreceptors in the bladder to signal pain at low, normally innocuous bladder pressures. The pain is relieved by bladder emptying and patients may need to void very frequently. Thus the normal function of the urinary bladder as storage organ is disrupted.

In order to diagnose and treat patients with long-term bladder pain, a thorough interview and clinical examination are necessary. Both elderly patients and younger individuals may have several comorbidities and impressive lists of medications. The comorbidities and the medications must be addressed in order to obtain realistic and hopefully achievable treatment goals. Pharmacological and nonpharmacological treatment should be introduced following assessment and diagnosis. Follow-up and analysis of compliance, benefits, and side effects of treatment are mandatory.

Ineffective and/or potentially harmful therapy should be tapered and discontinued. If no peripheral pathology can be found, local treatment of bladder pain may have poor chances of success and therapeutic efforts should target central sensitization and modulation of pain.

Referral of patients to a pain specialist needs to be considered when therapeutic measures provide disappointing results or as soon as the patient has been diagnosed with one or more concomitant pain problems and syndromes. The right time to refer a patient to a pain specialist differs from case to case. However, patients with complex bladder pain may benefit from a consultation and second opinion from a pain specialist early in the course of the workup and not as a last measure when everything else has failed. Multidisciplinary pain teams with pain specialists should be part of the network available for clinicians who provide care for patients with complex pain problems.

doi:10.3834/uij.1944-5784.2009.08.03
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

REFERENCES

[1] Hanno P, Nordling J, van Ophoven A. What is new in bladder pain syndrome/interstitial cystitis? *Curr Opin Urol.* 2008;18(4):353-358.

[2] Forrest JB, Schmidt S. Interstitial cystitis, chronic nonbacterial prostatitis and chronic pelvic pain syndrome in men: a common and frequently identical clinical entity. *J Urol*. 2004;172(6 Pt 2):2561-2562.

[3] Malykhina AP. Neural mechanisms of pelvic organ cross-sensitization. *Neuroscience*. 2007;149(3):660-672.

[4] Ness TJ, Gebhart GF. Visceral pain: a review of experimental studies. *Pain*. 1990;41(2):167-234.

[5] McMahon SB, Dmitrieva N, Koltzenburg M. Visceral pain. *Br J Anaesth*. 1995;75(2):132-144.

[6] Giamberardino MA. Recent and forgotten aspects of visceral pain. *Eur J Pain*. 1999;3(2):77-92.

[7] Al-Chaer ED, Traub RJ. Biological basis of visceral pain: recent developments. *Pain*. 2002;96(3):221-225.

[8] Cervero F, Laird JMA. Understanding the signaling and transmission of visceral nociceptive events. *J Neurobiol.* 2004;61(1):45-54.

[9] Fitzgerald MP, Brensinger C, Brubaker L, Propert K, ICDB Study Group. What is the pain of interstitial cystitis like? *Int Urogynecol J Pelvic Floor Dysfunct*. 2006;17(1):69-72.

[10] Fitzgerald MP, Koch D, Senka J. Visceral and cutaneous sensory testing in patients with painful bladder syndrome *Neurourol Urodyn* 2005;24(7):627-632.

[11] Hanno PM, Landis JR, Matthews-Cook Y, Kusek J, Nyberg L Jr. The diagnosis of interstitial cystitis revisited: lessons learned from the National Institutes of Health Interstitial Cystitis Database study. *J Urol*. 1999;161(2):553-557.

[12] Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn*. 2002;21(2):167-178.

[13] van de Merwe JP, Nordling J, Bouchelouche P, et al. Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. *Eur Urol*. 2008;53(1):60-67.

[14] Warren JW, Howard FM, Cross RK, et al. Antecedent nonbladder syndromes in case-control study of interstitial cystitis/painful bladder syndrome. *Urology*. 2009;73(1):52-57.

[15] Kosek E, Hansson P. Modulatory influence on somatosensory perception from vibration and heterotopic noxious conditioning stimulation (HNCS) in fibromyalgia patients and healthy subjects. *Pain*. 1997;70(1):41-51.

[16] Sandrini G, Rossi P, Milanov I, Serrao M, Cecchini AP, Nappi G. Abnormal modulatory influence of diffuse inhibitory controls in migraine and chronic tension-type headache patients. *Cephalalgia*. 2006;26(7):782-789.

[17] King CD, Wong F, Currie T, et al. Deficiency in endogenous modulation of prolonged heat pain in patients with irritable bowel syndrome and temporomandibular disorder. *Pain*. 2009;143(3):172-178.

[18] Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10(4):287-333.

[19] Maxwell CJ, Dalby DM, Slater M, et al. The prevalence of current daily pain among older home care clients. *Pain*. 2008;138(1):208-216.

[20] Dalpiaz O, Kerschbaumer A, Mitterberger M, Pinggera G, Bartsch G, Strasser H. Chronic pelvic pain in women: still a challenge. *BJU Int*. 2008;102(9):1061-1065.

[21] Fall M, Oberpenning F, Peeker R. Treatment of bladder pain syndrome/interstitial cystitis 2008: Can we make evidence-based decisions? *Eur Urol*. 2008;54(1):65-75.

[22] Burkman RT. Chronic pelvic pain of bladder origin: epidemiology, pathogenesis and quality of life. *J Reprod Med*. 2004;49(suppl 3):225-229.

[23] Parsons CL, Tatsis V. Prevalence of interstitial cystitis in young women. *Urology*. 2004;64(5):866-870.

[24] Ness TJ, Richter HE, Varner RE, Fillingim RB. A psychophysical study of discomfort produced by repeated filling of the urinary bladder. *Pain*. 1998;76(1-2):61-69.

[25] Woolf CJ, Ma Q. Nociceptors-noxious stimulus detectors. *Neuron*. 2007;55(3):353-364.

[26] Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron*. 2007;55(3):377-391.

[27] Moshiree B, Zhou Q, Price DD, Verne GN. Central sensitisation in visceral pain disorders. *Gut*. 2006;55(7):905-908.

[28] Knowles CH, Aziz Q. Basic and clinical aspects of gastrointestinal pain. *Pain*. 2009;141(3):191-209.

doi:10.3834/uij.1944-5784.2009.08.03
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

[29] Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G. The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. *Eur J Pain*. 2009;13(4):331-338.

[30] Warren JW, Brown J, Tracy JK, Langenberg P, Wesselmann U, Greenberg P. Evidence-based criteria for pain of interstitial cystitis/painful bladder syndrome in women. *Urology*. 2008;71(3):444-448.

[31] Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. *Pain*. 2007;129(3):256-259.

[32] Rolke R, Magerl W, Campbell KA, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *Eur J Pain*. 2006;10(1):77-88.

[33] Husebo BS, Strand LI, Moe-Nilsson R, Husebo SB, Snow AL, Ljunggren AE. Mobilization-Observation-Behavior-Intensity-Dementia Pain scale (MOBID): development and validation of a nurse-administered pain assessment tool for use in dementia. *J Pain Symptom Manage*. 2007;34(1):67-80.

[34] Zwakhalen SM, Hamers JP, Abu-Saad HH, Berger MP. Pain in elderly people with severe dementia: a systematic review of behavioural pain assessment tools. *BMC Geriatr.* 2006;6:3.

[35] O'Leary MP, Sant GR, Fowler FJ Jr, Husebo SB, Snow AL, Ljunggren AE. The interstitial cystitis symptom index and problem index. *Urology*. 1997;49(Suppl. 5A):58-63.

[36] Parsons CL, Dell J, Stanford EJ, et al. Increased prevalence of interstitial cystitis: previously unrecognized urologic and gynaecologic cases identified using a new symptom questionnaire and intravesical potassium sensitivity. *Urology*. 2002;60(4):573-578.

[37] World Health Organization. *Cancer Pain Relief*. Albany, NY: WHO Publications Center;1986.

[38] Ballantyne JC. Opioid analgesia: perspectives on right use and utility. *Pain Physician*. 2007;10(3):479-491.

[39] Igawa Y, Westerling D, Mattiasson A, Andersson KE. Effects of morphine metabolites on micturition in normal, unanaesthetized rats. *Br J Pharmacol*. 1993;110(1):257-262.

[40] Chu LF, Angst MS, Clark D. Opioid-induced hyperalgesia in humans: molecular mechanisms and clinical considerations. *Clin J Pain*. 2008;24(6):479-496.

[41] Eriksen J, Sjogren P, Bruera E, Elkholm O, Rasmussen NK. Critical issues on opioids in chronic non-cancer pain: an epidemiological study. *Pain.* 2006;125(1-2):172-179.

[42] Kalso E, Edwards J, Moore R, McQuay H. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. *Pain*. 2004;112(3):372-380.

[43] Noble M, Tregear SJ, Treadwell JR, Schoelles K. Long-term opioid therapy for chronic noncancer pain: a systematic review and meta-analysis of efficacy and safety. *J Pain Symptom Manage* 2008;35(2):214-228.

[44] Attal N, Cruccu G, Haanpaa M, et al. EFNS guidelines on pharmacological treatment of neuropathic pain. *Eur J Neurol*. 2006;13(11):1153-1169.

[45] Hanlon JT, Schmader KE, Kornkowski MJ, et al. Adverse drug effects in high risk older outpatients. *J Am Geriatr Soc.* 1997;45(8):945-948.

[46] Crofford LJ, Mease PJ, Simpson SL, et al. Fibromyalgia relapse evaluation and efficacy for durability of meaningful relief (FREEDOM): a 6-month, double-blind, placebo-controlled trial with pregabalin. *Pain*. 2008;136(3):419-431.

[47] Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain*. 2008;136(3):432-444.

[48] Bradesi S, Herman J, Mayer EA. Visceral analgesics: drugs with a great potential in functional disorders? *Curr Opin Pharmacol*. 2008;8(6):697-703.

[49] Theoharides TC. Treatment approaches for painful bladder syndrome/interstitial cystitis. *Drugs*. 2007;67(2):215-235.

[50] Cruz F, Dinis P. Resiniferatoxin and botulinum toxin type A for treatment of lower urinary tract symptoms. *Neurol Urodynam* 2007;26(suppl 6):920-927.

[51] Rossberger J, Fall M, Peeker R. Critical appraisal of dimethyl sulfoxide treatment for interstitial cystitis: discomfort, side effects and treatment outcome. *Scand J Urol Nephrol*. 2005;39(1):73-77.

[52] Duckett JW, Cangiano T, Cubina M, Howe C, Cohen D. Intravesical morphine analgesia after bladder surgery. *J Urol*. 1997;157(4):1407-1409.

doi:10.3834/uij.1944-5784.2009.08.03
ISSN 1944-5792 (print), ISSN 1944-5784 (online)

[53] El-Ghoneimi A, Deffarges C, Hankard R, Jean-Eudes F, Aigrain Y, Jacqz-Aigrain E. Intravesical morphine analgesia is not effective after bladder surgery in children: results of a randomized double-blind study. *J Urol*. 2002;168(2):694-697.

[54] Giannantoni A, Porena M, Costanini E, Zucchi A, Mearini L, Mearini E. Botulinum A toxin intravesical injection in patients with painful bladder syndrome: 1-year follow up. *J Urol*. 2008;179(3):1031-1034.

[55] Guidelines EAU 2009. European Association of Urology (EAU) Website. http://www.uroweb.org/professional-resources/guidelines/?0. Accessed June 15, 2009.

[56] Carville SF, Arendt-Nielsen S, Bliddal H, et al. EULAR evidence-based recommendations for the management of fibromyalgia syndrome. *Ann Rheum Dis*. 2008;67(4):536-541.

[57] Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut*. 2009;58(3):367-378.

[58] Chen L, Tang J, White PF, et al. The effect of location of transcutaneous electrical nerve stimulation on postoperative opioid analgesic requirement: acupoint versus nonacupoint stimulation. *Anesth Analg*. 1998;87(5):1129-1134.

[59] Hamza MA, White PF, Ahmed HE, Ghoname EA. Effect of the frequency of transcutaneous electrical nerve stimulation on the postoperative opioid analgesic requirement and recovery profile. *Anesthesiology*. 1999;91(5):1232-1238.

[60] Walsh IK, Johnston RS, Keane PF. Transcutaneous sacral neurostimulation for irritative voiding dysfunction. *Eur Urol*. 1999;35(3):192-196.

[61] Peeker R, Fall M. Treatment guidelines for classic and non-ulcer interstitial cystitis. *Int Urogynecol J Pelvic Floor Dysfunct*. 2000;11(1):23-32.

[62] Sjoberg M, Appelgren L, Einarsson S, et al. Long-term intrathecal morphine and bupivacaine in "refractory" cancer pain. I. Results from the first series of 52 patients. *Acta Anaesthesiol Scand*. 1991;35(1):30-43.

[63] Sjoberg M, Nitescu P, Appelgren L, Curelaru I. Long-term intrathecal morphine and bupivacaine in patients with refractory cancer pain. Results from a morphine:bupivacaine dose regimen of 0.5:4.75 mg/ml. *Anesthesiology*. 1994;80(2):284-297.

[64] Nitescu P, Sjoberg M, Appelgren L, Curelaru I. Complications of intrathecal opioids and bupivacaine in the treatment of "refractory" cancer pain. *Clin J Pain*. 1995;11(1):45-62.

[65] Borjesson M, Andrell P, Lundberg D, Mannheimer C. Spinal cord stimulation in severe angina pectoris- a systematic review based on the Swedish Council on Technology assessment in health care report on long-standing pain. *Pain*. 2008;140(3):501-508.

[66] Maher CF, Carey MP, Dwyer PL, Schluter PL. Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. *J Urol*. 2001;165(3):884-886.

[67] Brefel-Courbon C, Payoux P, Thalamas C, et al. Effect of levodopa on pain threshold in Parkinson's disease: a clinical and positron emission tomography study. *Mov Disord*. 2005;20(12):1557-1563.

[68] Beiske AG, Loge JH, Ronningen A, Svensson E. Pain in Parkinson's disease: prevalence and characteristics. *Pain*. 2009;141(1-2):173-177.

[69] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618-1625.

[70] Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: Pre-operative DNIC testing identifies patients at risk. *Pain*. 2008;138(1):22-28.