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Prevalence of Opioid-Related Dysuria in Patients With Advanced Cancer Having Pain

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Abstract

The aim of this study was to assess the prevalence of opioid-induced dysuria in patients with advanced cancer having pain and to evaluate the possible factors associated. A consecutive sample of 308 patients admitted to an acute pain relief and palliative care unit during 8 months was surveyed. The exclusion criteria were an expected survival less than 2 months, cognitive disturbances, bladder catheter in situ, nephrostomy, urether-cutaneostomy, cistostomy, and no pain. At admission and before discharge, the following data were collected: age, gender, primary cancer, previous pelvic radiotherapy, urinary infection, presence of pelvic masses, previous pelvic surgery, dysuria, incontinence, previous episodes requiring bladder catheterization, hematuria, local vesical chemotherapy, recent use of alkaloids, psychiatric disturbances, peripheral neuropathy, use of opioids and their doses and routes of administration, use of symptomatic treatment for dysuria and its efficacy, need for catheterization, and removal of the catheter. A total of 170 patients admitted for pain control were surveyed. Most patients (147, 86.5%) were receiving opioids at admission. The mean age was 65.1 (SD 12.2) and 106 patients were males. Twenty-five patients presented with dysuria at admission (of which 22 were taking opioids, 14.9%). Eleven patients were inserted a bladder catheter at admission for urine monitoring and 18 patients had urinary incontinence. During admission, 31 patients presented dysuria (of which 28 were taking opioids, 19%). The prevalence of dysuria was more frequent in males, in patients presenting pelvic masses or who had pelvic surgery. These correlations were also confirmed in multivariate analysis. Opioid switching during admission was correlated to the occurrence of dysuria. Patients with chronic cancer pain receiving opioid therapy present a prevalence of bladder dysfunction of about 15%, which is influenced by several concomitant factors. Further studies should be performed to explore the presence of dysuria in patients with no pain and not receiving opioids to know the real weight of opioid therapy with respect to other variables.

Keywords

dysuria, bladder dysfunction, cancer pain, opioid therapy

Opioids are the mainstay of cancer pain management. The incidence and severity of adverse effects associated with the administration of opioids can play an important role in the success or failure of pain management in patients with cancer. In recent years, opioid-related adverse effects including drowsiness, nausea and vomiting, constipation, delirium, myoclonus, pruritus, endocrine and immunological changes, and respiratory depression have been evaluated in critical reviews and recommendations based on the existing evidence have been suggested [1-4].

Dysuria has been reported as a bladder dysfunction characterized by disturbances in micturition, incomplete elimination of urine, or full bladder with inability to void.[5] Difficulty with micturition associated with the use of opioids has seldom been reported and is more evident during short-term use of opioids[6] or particularly when opioids are administered spinally.[7,8] An incidence of 18% urinary retention was found in postoperative patients and the use of morphine was a significant risk factor.[9]

It has been reported that the opioid-receptor system is involved in bladder and urethral function, although the exact mechanism by which opioids cause urinary retention is incompletely understood.[10] Animal and human studies suggest that a significant component of the effect is owing to a combined action on the spinal cord and brain, although peripheral effects

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at the bladder may also play a role.[8,11] Mechanisms seem to be mediated through central as well as peripheral opioid receptors situated in the spinal cord and in the bladder, respectively. Opioids decrease the force of detrusor contraction, decrease the sensation of fullness, but probably do not increase sphincter tone. These effects are reversed by both central and peripheral opioid antagonists.[12]

In patients with advanced cancer having chronic cancer pain, different factors may impair bladder function. Opioid-induced dysuria has never been assessed in literature and data regarding their prevalence in patients chronically receiving systemic opioids for management of cancer pain are lacking. The aim of this study was to assess the prevalence of opioid-induced dysuria in a consecutive sample of patients with advanced cancer having pain and to evaluate the possible risk factors associated.

Methods

A consecutive sample of 308 patients with pain admitted to an acute pain relief and palliative care unit during 8 months were surveyed. The exclusion criteria were an expected survival less than 2 months, cognitive disturbances, bladder catheter in situ, nephrostomy, urether-cutaneostomy, cistostomy, and no pain. Informed consent and institutional approval were obtained.

At admission, based on patient's history, clinical examination, and results from recent neuroimaging examinations or laboratory data, the following data were collected: age, gender, primary cancer, previous pelvic radiotherapy, urinary infection, presence of pelvic masses, previous pelvic surgery, dysuria, incontinence, previous episodes requiring bladder catheterization, hematuria, local vescical chemotherapy, recent use of alkaloids, psychiatric disturbances, peripheral neuropathy, use of opioids and their doses, and routes of administration. Before discharging patients home, the following parameters were recorded: use, doses, and route of administration of opioids, dysuria, use of symptomatic treatment for dysuria and its efficacy, need for catheterization, and removal of the catheter

Statistical Analysis

All continuous data are expressed as a mean $\pm$ standard deviation of the mean. The association between parameters and dysuria at admission and during admission was tested by Pearson chi-square test and Fisher exact test for frequency analysis, as appropriate. Furthermore, continuous variables were converted into categorical variables using each cutoff level and the ratio of the patients with converted variable was analyzed. All variables were used for the determination of statistically significant prognostic factors for dysuria. The odds ratio (OR) and the 95% confidence intervals (CI) for the risk factors were also calculated. Parameters found to have a P value of less than .20 in the univariate logistic regression analysis were entered into stepwise multiple logistic regression model for the determination of statistically significant, independent, prognostic factors for dysuria. All P values were 2-sided and P values less than .05 were considered statistically significant. Data were analyzed by the Epi Info software (version 6.0, Center for Disease Control and Prevention, Atlanta, Georgia) and SPSS Software (version 14.0, SPSS Inc, Chicago, Illinois)

Results

Of the 308 patients surveyed, 138 patients were excluded, because they did not have pain, or due to short life-expectancy, nephrostomy, urether-cutaneostomy, cistostomy, and cognitive failure.

The mean age of 170 patients admitted for pain control who were assessed was 65.1 (SD 12.2) and 106 patients were males. Most patients (147, 86.5%) were receiving opioids at admission. Thirty-six male patients had a history of prostatic hypertrophia, 7 and 17 patients had received pelvic radiotherapy or presented pelvic masses, respectively. Twenty-eight patients had a previous pelvic surgery and four patients had urinary infection. No patient had a previous bladder instillation of chemotherapic agents, 6 patients had a previous treatment with vinca-alkaloids, and 8 patients had psychiatric disorders. Finally, 25 patients presented dysuria at admission (of which 22 were taking opioids, 14.9%). Eleven patients were inserted a bladder catheter at admission for urine monitoring and 18 patients had urinary incontinence.

Thirty-one patients presented with dysuria during admission (of which 28 were taking opioids, 19%). Twenty-seven patients (18.3%) did not change the opioid dose during admission, 61 patients (41.5%) increased the dose by 30% to 50%, 20 patients (13.6%) increased the dose by 50% to 100%, 9 patients (6.1%) increased the dose more then 100%, and 44 patients (29.9%) were switched to another opioid. In 6 patients, data were missed. Five patients discontinued opioids for different reasons. During admission, 26 patients required a bladder catheterization and in 3 patients it was possible to remove it before the discharge. Flavossato-propifenazone, used as symptomatic treatment according to local policy and availability, was used in 7 patients and was effective in reducing dysuria in 6 patients.

Data regarding univariate and multivariate logistic regression are shown in Tables 1 and 2, respectively. The prevalence of dysuria was higher in males during admission. Patients presenting pelvic masses were more likely to have dysuria at admission, and patients who had pelvic surgery were more likely to present with dysuria either at admission or during admission. These correlations were also confirmed in multivariate analysis. Opioid switching during admission was associated with the occurrence of dysuria (see Tables 1 and 2).

Discussion

Although the use of opioids for a short period of time, either systematically or spinally, for example in the postoperative period, has been reported in literature,[8,13] data regarding the relationship between the use of opioids and dysuria are lacking in patients with chronic cancer pain. Occasionally, a bladder

Table 1. Univariate Logistic Regression Analysis Regarding Dysuria at Admission and During Admission and Parameters Examined

	Dysuria at Admission			Dysuria During Admission		
Variables	Odds Ratio	95% CI	*P* Value	Odds Ratio	95% CI	*P* Value
Age >75	1.31	0.47-3.61	.599	0.94	0.35-2.53	.905
Male	2.00	0.75-5.35	.163	2.85	1.09-7.43	.032
Prostatic hypertrophia	0.76	0.26-2.23	.630	0.97	0.38-2.51	.965
Pelvic radiotherapy	2.24	0.41-12.26	.351	3.32	0.70-15.68	.129
Pelvic mass	3.53	1.16-10.67	.025	1.31	0.39-4.33	.657
Pelvic surgery	5.40	2.11-13.83	.0004	3.59	1.46-8.79	.005
Urinary infection	5.73	0.76-42.80	.088	4.34	0.58-32.14	.150
Previous treatment with vinca-alcaloids	0.0	0.0-0.0	.984	0.0	0.0-0.0	.982
Hematuria	1.35	0.14-12.64	.790	1.03	0.11-9.58	.977
Peripheral neuropathy	0.75	0.08-6.42	.797	1.40	0.26-7.30	.688
Psychiatric disturbances	1.85	0.35-9.76	.465	0.57	0.06-4.86	.612
Opioids at admission	1.06	0.28-3.94	.924	1.42	0.39-5.22	.588
Opioid switching	1.33	0.52-3.35	.544	2.35	1.03-5.36	.040

Table 2. Stepwise Multivariate Logistic Regression Analysis Regarding Dysuria at Admission and During Admission and Parameters Examined

	Dysuria at admission				Dysuria during admission			
Variables	Coefficient ± SE	Odds Ratio	95% CI	*P* Value	Coefficient ± SE	Odds Ratio	95%CI	*P* Value
Male	1.66 (0.6)	5.27	1.36-20.38	.016	1.56 (0.5)	4.79	1.51-15.16	.007
Pelvic surgery	1.96 (0.6)	7.13	2.19-23.15	.0011	1.47 (0.6)	4.37	1.29-14.79	.017
Opioid switching					1.16 (0.4)	3.19	1.27-7.98	.013

dysfunction during the use of tramadol has been reported,[14] but no prospective investigation has ever been performed.

In patients with advanced cancer, there also are several factors that may impair bladder function. Micturition occurs in response to afferent signals from the lower urinary tract, and distension of the bladder wall is the primary stimulus. Thus, adequate sensory input is the prerequisite for bladder control, and changes in sensory mechanisms may give rise to disturbances in bladder function. This requires coordination of the smooth muscles of the bladder and urethra and of striated muscles of the outflow region and pelvic floor by a complex neural control system. The volumes at which sensation to void occurs wide in individuals. Peripheral control of voiding is influenced by α-adrenergics for the neck of the bladder and by β-adrenergics for the dome and mainly depends on the sacral parasympathetic system for detrusor.[15] Moreover, it seems that activation of serotonergic system can suppress voiding by enhancing efferent control of urethral outlet and inhibiting the parasympathetic excitatory input to the urinary bladder.[16]

Bladder distension induced by retention may lead to bladder catheterization, which is uncomfortable in a setting of patients with advanced cancer, especially in older men who may have an underlying element of bladder outlet obstruction or in patients who may have borderline detrusor function due to the illness or induced by treatment. Neurological deficits due to a damage from previous treatment, including surgery and radiotherapy, other drugs, or preexisting conditions may reduce bladder ability to void. Most opioids reduce sympathetic tone and enhance parasympathetic tone.[7] Moreover, the pain threshold for the bladder may further contribute to retention.

The prevalence of dysuria in patients taking opioids was 14.9% and slightly increased during admission with increasing doses of opioids without attaining significance. More complex pain situations, requiring multiple opioid regimens such as switching, were more frequently associated with the occurrence of dysuria. Alternately, tolerance to this adverse effect may develop with one opioid, with changes more likely occurring with switching. The results of the present study also show that the risk to develop dysuria is associated with different factors, frequently present in cancer patients. Rather, dysuria seems to be related to gender but not necessarily age or a prostatic hypertrophia history, a previous pelvic surgery, the presence of a pelvic mass, these factors being significant in multivariate analysis. Thus, multiple conditions related to the illness or anticancer treatments may influence the occurrence of micturition disturbances in patients receiving opioids.

This is the first study dealing with the prevalence of dysuria in patients with advanced cancer having chronic pain receiving opioids, so that no comparison with existing data is possible. Most information is gathered from short-period studies. In postoperative care age, gender, volume of intravenous fluids,

preexisting urinary symptoms, and anorectal and lower urinary tract surgeries were risk factors for catheterization.[6,17] Opioids modified cystometric measurements, while anti-inflammatory agents did not induce urodynamic changes. [11]

The treatment of opioid-induced dysuria has never been assessed and only anecdotal suggestions have been provided. The use of flavossato-propifenazone, used as symptomatic treatment according to local policy and availability, was relatively effective, although this finding should be explored in appropriate comparative studies. Moreover, the decision to start this treatment was based on individual considerations and patients' tolerability of the symptom.

In conclusion, patients with chronic cancer pain, receiving opioid therapy, present a prevalence of bladder dysfunction of about 15%, which is influenced by several concomitant factors. Given the complex clinical picture of patients with advanced cancer, further studies should be performed to explore the presence of dysuria in patients with no pain and not receiving opioids or in noncancer patients with chronic pain receiving opioids to know the real weight of opioid therapy with respect to other variables.

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