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CLINICAL INVESTIGATION **Metastasis**

PREVENTION OF URINARY TRACT INFECTIONS IN PALLIATIVE RADIATION FOR VERTEBRAL METASTASIS AND SPINAL COMPRESSION: A PILOT STUDY IN 71 PATIENTS

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Purpose: To assess the impact of bladder instillations of hyaluronic acid (HA) on the prevalence of urinary tract infection (UTI) in patients receiving emergency radiotherapy for metastatic spinal cord compression.

Methods and Materials: Patients were recruited consecutively at one center and assigned to usual care (UC) (n = 34, mean age 62.2 years) or UC with once-weekly HA instillation (UC + HA) (Cystistat: 40 mg in 50 mL phosphate-buffered saline) (n = 37; mean age, 63.1 years). All patients had an indwelling catheter and received radiotherapy. UTI status was assessed at baseline and during hospitalization.

Results: At baseline, patient groups were comparable, except for the prevalence of UTI at baseline, which was 11.8% and 0% in the UC and UC + HA patients, respectively (p = 0.0477). During hospitalization, 76.5% (vs. 11.8% at baseline, $p < 0.0001$) of the UC patients had a UTI compared with 13.5% (vs. 0% at baseline, p = 0.0541) of the UC + HA patients ($p < 0.0001$). Both groups were hospitalized for similar periods (19.8 days [UC] vs. 18.5 days, p = 0.4769) and received equivalent radiotherapy sessions (4.6 [UC] vs. 5.8 sessions, p = 0.2368).

Conclusions: Patients receiving UC + HA had a 5.7-fold decrease in UTI prevalence over the hospitalization period compared to UC patients, suggesting that bladder instillations of HA effectively prevent UTI in patients with indwelling catheters receiving radiotherapy for nerve compression.

Vertebral metastasis, Urinary tract infection, Hyaluronic acid, Palliative care, Indwelling catheter.

INTRODUCTION

Urinary tract infections (UTIs) are one of the more common bacterial infections, affecting women at a much higher frequency than men (1, 2). When the infection occurs in a genitourinary tract with structural or functional abnormalities, including the presence of an indwelling catheter, the condition is a "complicated" infection that can have serious long-term consequences (1, 2). Catheter-associated UTI is the most common nosocomial infection, and it has been estimated that 5% to 10% of residents in long-term care facilities are managed with chronic indwelling catheters and that such individuals are always bacteriuric (1, 3, 4). Complicated UTIs are particularly common in patients with spinal cord injuries (SCIs) with an overall infection rate of about 2.5 episodes per patient per year (5, 6). UTIs in patients with SCIs are associated with high rates of morbidity and mortality, and urinary tract morbidity is the fourth leading cause of death in this patient population (1, 5, 7).

The most prevalent risk indicator for UTIs in SCI patients is the presence of an indwelling catheter (8); compared with patients with other methods of urinary drainage, such patients have high rates of bacteriuria and a high frequency of recurring UTIs (5, 6, 8). Although the treatment of asymptomatic infection in these patients is controversial, symptomatic infections are treated with a range of antibiotic therapies, a therapeutic approach that must consider also the presence of—or development of—resistant pathogens and the side effects of antibiotic treatment, as well as the cost (5). Procedures designed to prevent the recurrence of infections include intermittent catheterization (9), alternate urinary drainage methods (6), improved catheter construction (5, 10), and the use of prophylactic antibiotics (11). How-

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Preliminary results were presented in 2003 in poster form at the 41st Annual Meeting of Infectious Diseases of America, October 9–12, San Diego, CA; European Cancer Conference #12 (ECCO 12), Copenhagen, Denmark, September 21–25, 2003; 55th Annual Meeting Northeastern Section of the American Urological Association; and at the 16th International Symposium Multinational Association of Supportive Care in Cancer/International Society for Oral Oncology (MASCC/ISOO), June 24–27, 2004, Miami, FL.

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ever, these procedures have met with only limited success: UTIs, and their recurrence, remain a serious problem in patients with SCIs.

An alternative approach to the prevention of UTIs is offered by studies on the mechanisms involved in the interaction of the bacterium with the epithelial cells lining the bladder wall (12, 13). The bladder glycosaminoglycan (GAG) layer normally protects the epithelial cells from urine components, including bacteria, and it has been suggested that recurrent UTIs may be linked to a damaged GAG layer, where bacteria have access to the underlying cells and can establish an infection (14–17). On this basis, repair of the GAG layer using epithelial coating techniques such as heparin (18), oral pentosanpolysulfate (19), or hyaluronic acid (HA) (15) should then have a positive impact on the rate of recurrence of infection (20). This approach has had clinical success in the treatment of interstitial cystitis, a bladder condition that has also been linked to a damaged bladder GAG layer (20). In addition, Delgado *et al.* (21) have recently demonstrated a protective effect of weekly instillations of hyaluronic acid in patients receiving pelvic radiotherapy. It is also of interest to note, with respect to spinal cord injuries, that Salvaggio *et al.* (22) have demonstrated increased GAG excretion in older spina bifida patients and have suggested that this may be an early indicator of bladder damage, directly linking GAG in SCI patients to long-term bladder dysfunction.

In the present study, the impact of HA bladder instillations on the incidence of UTIs was examined in patients with SCI resulting from metastatic spinal cord compression, all of whom were hospitalized for radiotherapy and had an indwelling catheter.

METHODS AND MATERIALS

This was a single-center, prospective observational study designed to assess the impact of HA treatment on the prevalence of UTI in patients hospitalized for medullar compression radiotherapy. Patients (≥18 years of age) coming from home, recruited in a consecutive manner between April 2000 and April 2002 after presentation at the emergency department, had metastatic acute spinal cord compression and were hospitalized as a result of neurologic signs requiring radiation for emergency decompression. All patients were treated at Hospital Universitario Doce de Octubre in Madrid and received radiation therapy for decompression using an identical radiation protocol.

All the patients involved in the study had an indwelling catheter because of acute urinary retention or incontinence using a polytetrafluoroethylene (BARDIA) or silicone (PORGES SA) coated 14 or 16 Foley catheter without any anesthesia.

The first 34 patients recruited represented the usual care group (UC), defined as radiotherapy combined with the standard treatment normally used in patients with this condition, which included complete rest, analgesics (nonsteroidal antiinflammatory drugs), muscle relaxants, opioid analgesics (codeine, tramadol), corticosteroids, bisphosphonates (zoledronic acid) if the compression was caused by bone metastasis, surgical laminectomy (if required), bedsore management, as well as rehabilitation and inpatient psychosocial care.

The next 37 patients recruited represented the usual care plus hyaluronic acid group (UC + HA), defined as UC (as described above) plus weekly instillations of HA (Cystistat, Bioniche Life Sciences Inc., Belleville, Ontario, Canada) at a dose of 40 mg in a volume of 50 mL phosphate-buffered saline (UC + HA). The instillation was carried out under sterile conditions, using the urethral catheter, after the removal of residual urine. After instillation, a clamp was used to close the catheter, and Cystistat was allowed to remain in the bladder for 30 min. For patients with reduced bladder capacity, the instillation was carried out in two series of 25 mL each on the same day. Patients received weekly instillations for as long as they were hospitalized.

UTI status was assessed for all patients at admission (baseline assessment) by urinalysis and standard bacteriologic examination. The same methods were used to confirm the presence of a UTI during hospitalization after the appearance of clinical symptoms in the two groups indicating an infection. Furthermore, the UC + HA patients had a systematic urinalysis and bacteriologic examination before the HA weekly instillations. At the Hospital Universitario Doce de Octubre, a UTI is defined as isolation of a uropathogen in quantities $\geq 10^5$ colony forming units/mL, and this standard criterion was used in the present study. All the patients presenting a UTI (at baseline and during the hospitalization) were treated with i.v. antibiotics. A complete patient medical history and relevant demographic data were recorded by retrospective chart review using a case report form specifically designed for the study. In addition, durations of hospitalization and antibiotic use were recorded for each patient.

In a statistical analysis of the data, the numbers of patients with UTIs in the UC and UC + HA groups were determined and expressed as percentages. The Fisher's exact test for proportions was used to compare the number of infections in both groups and to determine the statistical significance of the impact of HA on the prevalence of infection. The same test was used in comparisons of other categorical clinical variables. Noncategorical variables in both treatment groups (age, time since diagnosis, duration of hospitalization, etc.) were compared using the Wilcoxon rank–sum test. Study data were analyzed using SAS software (Version 8.2) (SAS Institute Inc., Cary, NC).

The purpose of this study was to determine whether HA prophylactic bladder instillation was able to decrease the incidence of UTIs in a population of urinary catheterized medullar compression patients during the hospital stay for emergency radiation therapy.

RESULTS

Demographics and clinical history for study patients on hospital admission (baseline assessment) are shown in Table 1. Although patients in both groups had similar ages, the majority of subjects in the UC group were male, whereas females were the majority in the UC + HA group; however, this difference was not statistically significant ($p = 0.2356$). There were significant differences in the distribution of cancer types within each group ($p = 0.0458$). In the UC + HA group, more patients had breast and prostate cancer, whereas lung cancer was more common in the UC group. In correlation, there were also significant differences in the previous therapy both groups had received; more patients in the UC + HA group had hormone therapy. The treatment