

Short communication

Intravesical analgesia for ambulatory urologic procedures: a histopathological study

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Abstract

Background and objective: Local anesthetics and morphine have been reported to be useful for painful diagnostic procedures in the bladder. Tramadol has the potential for use as an intravesical analgesic. However, intravesical use of tramadol has not been described widely. **Methods:** This study was approved by the Animal Ethical Committee of Akdeniz University and performed with standard guidelines for care and use of laboratory animals. In this study we tested the histopathological effects of intravesical tramadol versus saline in 20 adult rats. The control group received intravesically 1 ml saline. Tramadol 50 mg (1 ml) was administered intravesically in the other group. Two hours later, all animals were sacrificed and their bladders were excised. Tissue samples were evaluated macroscopically and microscopically. The data were analyzed with χ^2 and Fisher's χ^2 tests. **Results:** In all the specimens in the control group epithelial edema was seen. This finding may be explained by insertion of intravesical catheter and tissue trauma. Haemorrhagic necrosis of epithelium was observed in four cases only in the tramadol group. This finding demonstrated severe epithelial destruction. However, there was no statistically significant difference when compared with the control group. **Conclusion:** The technique of topical tramadol anesthesia may be very simple, useful and safe for bladder biopsies and cautery in many cases. However, the number of cases examined in this preliminary study after bladder instillation of tramadol was small. For this reason, the results obtained in this study regarding the histopathological effects of tramadol on the bladder, should be further investigated.

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1. Introduction

The past few years mark an ever increasing interest in intravesical analgesia in urological practice. The topical anesthesia of bladder may be an alternative to traditional methods of spinal, epidural or general anesthesia [1].

Tramadol is a safe and effective analgesic in patients of all ages who suffer from moderate to moderately severe chronic pain. Given intravenously, the most common adverse effects with tramadol are dizziness, nausea and constipation but these occur at rates similar to or usually less than other opioid analgesics. In addition, tramadol-treated patients experience

less dyspepsia, physical dependence, withdrawal, tolerance and abuse [2].

In this study, we evaluated the histopathological effects of intravesical tramadol versus saline.

2. Methods

This study was approved by the Animal Ethical Committee of Akdeniz University and performed with standard guidelines for care and use of laboratory animals. In the current study 20 adult female Albino rats, weighing 230–250 g were used. At the beginning of study rats were randomly divided into two groups. In all animals an intravesical catheter was inserted (Balton 3F-181009) and 1 ml saline or study drug were administered intravesically. The first group (control group, $n = 10$) received only saline. Tramadol

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2 mg (Contramal) was administered intravesically in Group 2 ($n = 10$). All animals were sacrificed 2 h later, corresponding to the expected clinical duration of intravesical drug exposure. The bladders were excised.

The vesical mucosal injury was evaluated macroscopically. For light microscopy, tissue samples were fixed in 10% formaldehyde, embedded in paraffin and cut at a thickness of 4 μm . The sections were stained with haematoxylin-eosin, periodic acid-Schiff reagent (PAS) and unna stain for mast cells. Microscopically in each group, epithelial desquamation, epithelial and subepithelial edema, congestion, lenfoid folliculi, vascular proliferation, eosynophyl and mast cell infiltration, squamous metaplasia, inflammatory infiltrations and haemorrhagic necrosis of epithelium was observed and evaluated.

The data were analyzed with χ^2 and Fisher's χ^2 tests. A P value less then 0.05 was considered to be statistically significant.

3. Results

The cystectomy specimens were macroscopically evaluated. No morphological changes were observed in the bladder mucosa. Microscopic findings of all specimens are presented in Table 1.

3.1. Control group (Group 1)

Mast cell infiltration, lenfoid folliculi, and eosynophyl infiltration were seen each in one specimen and, inflammatory infiltration in three specimens. However, epithelial desquamation, epithelial and subepithelial edema, squamous metaplasia, congestion, vascular proliferation and haemorrhagic necrosis of epithelium were seen in the control group.

3.2. Tramadol group (Group 2)

Epithelial desquamation in six specimens, epithelial edema in four and subepithelial edema in eight, congestion

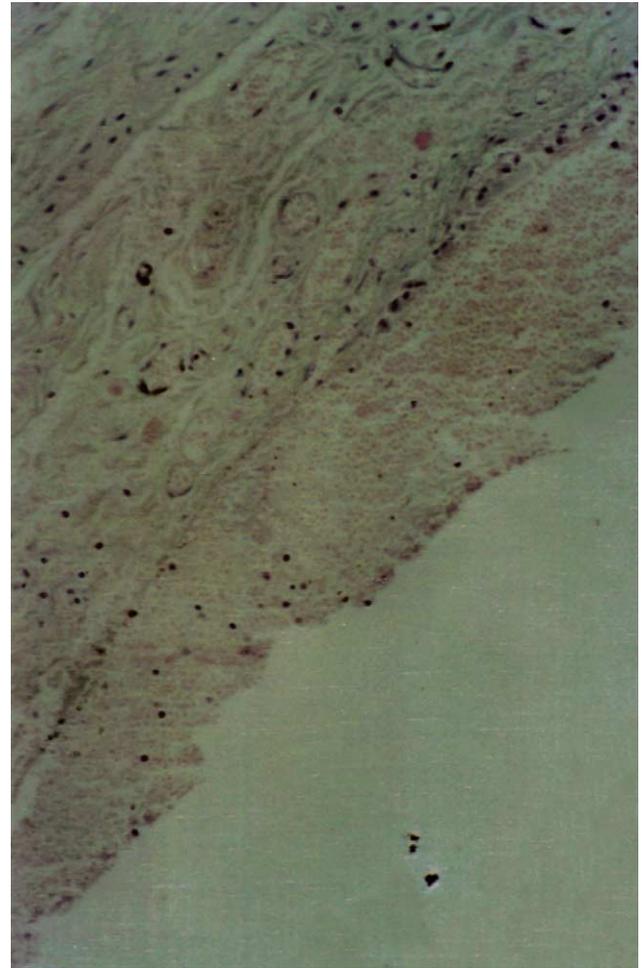


Fig. 1. Microscopic events in the tramadol group.

in seven, vascular proliferation in four, eosynophyl infiltration in five inflammatory and mast cell infiltration in three and lenfoids in two specimens, were seen in animals from Group 2. In addition, haemorrhagic necrosis of epithelium was determined in four of the specimens in the tramadol group (Fig. 1). However, squamous metaplasia was not observed in this group.

3.3. Statistical comparisons of all parameters for the two groups

All histopathologic findings were statistically compared between study groups. There were no statistical significant differences about lenfoid folliculi, vascular proliferation, mast cell infiltration, squamous metaplasia and inflammatory infiltrations between study groups. Squamous metaplasia was not seen in the tramadol group.

The hemorrhagic necrosis of epithelium was observed in four cases (40%) of the tramadol group. This finding demonstrated a severe epithelial destruction, but without statistical significant difference when compared with the control group ($P = 0.87$).

Table 1
The histopathological findings in saline and tramadol groups

Histopathological findings	Saline group ($n = 10$)	Tramadol group ($n = 10$)
Epithelial desquamation	–	6
Epithelial edema	–	4
Subepithelial edema	–	8
Congestion	–	7
Lenfoid folliculi	1	2
Vascular proliferation	–	4
Mast cell infiltration	1	3
Eosynophyl infiltration	1	5
Squamous metaplasia	–	–
Inflammatory infiltration	3	3
Hemorrhagic necrosis of epithelium	–	4*

* $P > 0.05$, $P = 0.87$.

4. Discussion

Intravesical analgesia and anesthesia for minor procedures of the bladder have been described in recent years. The intravesical use of lignocaine and bupivacaine have been evaluated for analgesia, complications, adverse reactions, patient acceptance and costs [1,3–5]. The use of intravesical morphine has been described for analgesia in a few clinical studies [6,7]. Intravesical morphine provided effective analgesia for postoperative pain after bladder surgery and after ureterovesical reimplantation in children. Plasma morphine levels were determined by high pressure liquid chromatography and they were not detectable.

Tramadol is a central analgesic with low affinity for opioid receptors and therefore presumably another mechanism of analgesic action. Neurotransmitter release and uptake experiments were used to characterize the effects of tramadol on the central noradrenergic and dopaminergic systems [8]. Tramadol analgesia was only partially mediated by a μ opioid agonist effect. Tramadol analgesia thus results from an action on opioid receptors other the μ subtype and/or from nonopioid effects [9].

It has been suggested that opioid receptors may be present on bladder nociceptive afferents and may be activated for production of peripheral analgesia [6,7]. Intravesical instillation of tramadol may be a useful, safe, effective and affordable anaesthesia for the ambulatory care of patients requiring transurethral bladder biopsy, resection or fulguration with a potential for cost savings. However, the use of intravesical tramadol has not been described. In our experimental study, we compared the histopathological effects of tramadol versus saline on the bladder of 20 female rats. The histopathological changes observed in the tramadol group were different from the findings seen in the specimens of the control group. Particularly, the severe epithelial destruction demonstrated by haemorrhagic necrosis of epithelium was observed only in the tramadol group, in four specimens (40%). In this histopathological study, we evaluated especially hemorrhagic necrosis, because hemorrhagic necrosis demonstrates severe epithelial destruction and it is an irre-

versible change. Other pathologic findings were also more common in the tramadol group. However, the other findings are slight and reversible changes, and may be clinically unimportant. The occurrence of other pathologic findings was not statistically different from the control group; the lack of statistical difference may be the result of too few subjects.

The technique of topical tramadol anaesthesia may be very simple, useful and safe for bladder biopsies and cautery in many cases. The number of cases examined in this study after bladder instillation of tramadol was small. For this reason, the results obtained in this preliminary study regarding the histopathological effects of tramadol on the bladder, should be further investigated.

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