

# Efficiency of intracavitary Levobupivacaine infusion for pain management during cystoscopic procedures: A randomized study

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November 19, 2020

## Abstract

**Aim:** This study evaluated the effect of intracavitary levobupivacaine infusion diluted with locally applied isotonic solution for pain control in cystoscopy. **Methods:** Included in this study are 100 patients who had previously undergone transurethral tumor resection for bladder tumor and were followed up by cystoscopy. The patients were randomized into five groups (n = 20). In the first, second, third, and fourth groups, 4, 6, 8, and 10 mL of levobupivacaine HCl (5.0 mg/mL) were mixed with 26, 24, 22, and 20 mL of isotonic solution, respectively. Hence, the total mixture was 30 mL for each group. The fifth group was the control group. In this group, the standard method commonly used in most clinics was utilized. That is, a gel containing Cathejell-2% lidocaine (25 mg lidocaine) was applied. Cystoscopic interventions were performed with a 17.5 Fr rigid cystoscope and 0°, 30°, and 70° lens. During cystoscopy and 30 min later, the pain status of patients was assessed using the Visual Analogue Scale (VAS), and patient satisfaction was questioned. **Results:** The mean VAS score during and after the cystoscopy procedure was significantly lower in the levobupivacaine groups compared to the lidocaine group. In addition, patient satisfaction in the levobupivacaine groups was significantly higher than in the lidocaine group. No drug-related side-effects were observed in all groups. **Conclusion:** Thus, levobupivacaine is a more effective drug than lidocaine alone to control pain during cystoscopy. The use of levobupivacaine is recommended to prevent possible complications of general anesthesia by eliminating the need for the aforementioned as well as its cost-saving advantage.

## 1 INTRODUCTION

Direct visualization of the anterior and posterior urethra, bladder neck, and bladder can be done with cystourethroscopy. Basic indications for cystourethroscopy are hematuria, bladder cancer and suspicion, and lower urinary tract diseases.<sup>1</sup> Cystourethroscopy directly examines the lower urinary tract anatomy, enabling imaging of the macroscopic pathologies and providing an explanation to the clinical picture. The most common indication for cystourethroscopy is the evaluation of macroscopic or microscopic hematuria, and urogenital malignancies are the underlying cause of 10%–26% of cases with microscopic hematuria.<sup>2</sup> Moreover, a bladder tumor is a middle-aged disease that requires close and repeated cystoscopy controls. Cystoscopy and transurethral bladder tumor resection in standard practice operations are done under white light. Before cystourethroscopy, active urinary infection of the patient must be known. Hence, the presence of urinary infection should be detected through urinalysis and, if necessary, with urine culture antibiogram treated before operation.

Cystourethroscopy is performed with rigid or flexible cystoscopes of various sizes. While adult-size rigid cystoscopes range in size from 17 to 25 Fr, flexible cystoscopes range from 16 to 17 Fr. Rigid cystoscope

provides better image quality compared to the flexible cystoscope.<sup>1</sup> While the cystoscopy procedure is mostly performed with flexible cystoscopes in developed countries for the patient's best comfort, rigid cystoscopy is still mostly preferred in developing or underdeveloped countries due to its cost-effectiveness.

Local anesthetics are drugs that reversibly interrupt nerve conduction. Water-soluble lubricating anesthetic is administered as retrograde from the meatus for local anesthesia during cystoscopy in male patients. The urethral clamp is placed and left for 5–10 min. In this way, contact between the urethral mucosal surface and the anesthetic agent is suggested before each urethral instrumentation. As for female patients, the lubricating anesthetic can be directly applied onto the cystourethroscope or administered to the urethra before the procedure.

Lubricating gels, which are conventionally applied repeatedly in cystoscopic procedures containing lidocaine, do not always provide adequate pain control. As a result, general and regional anesthesia, which is used more frequently today, brings additional burden and cost in this patient group, who may have accompanying diseases, and for the patient and the physician not only because of its long preparation requirement but also possible complications. Levobupivacaine is a long-acting aminoamide local anesthetic, which is the pure S enantiomer of bupivacaine hydrochloride. The higher vasoconstrictor effect of levobupivacaine explains the longer duration of the resulting sensory block and lower central nervous system toxicity.<sup>3</sup>

Pain is a sensory, unpleasant emotional sensation and a way of behavior in a certain area of the body whether or not due to strong tissue damage and is related to the subjective, primitive protective experiences of people acquired in the past.<sup>4</sup> Measurement and evaluation of pain is an important step in the diagnosis and treatment of a patient suffering from pain. Pain measurement methods include verbal and visual questioning of pain.<sup>5</sup> Among the visual methods, body diagrams, face scales, as well as the 10-cm straight line known as the Visual Analog Scale is widely used.

This study aimed to investigate the effectiveness of locally applied intracavitary levobupivacaine diluted with isotonic solution for reducing the patient's pain. Consequently, comfort and satisfaction is increased by providing deeper and longer mucosal anesthesia with instillation.

## 2 MATERIALS AND METHODS

The study included 100 male patients with previous transurethral resection operation for a bladder tumor and who were followed up with cystoscopy. Patients who were female, who would undergo cystoscopy under local anesthesia for the first time, known to have a urethral stricture, a history of allergy to local anesthesia, uncontrolled hypertension, uncontrolled cardiac disease, and uncontrolled chronic obstructive with lung disease were not included in the study. Necessary explanations about the study were made to all patients, and their detailed consents were obtained. Ethics committee approval was obtained from the local clinical research ethics committee for the study.

Residual urine amount was checked with ultrasound before cystoscopy, and bladder drainage was performed to those with postvoiding residual urine by using a 12F feeding tube lubricated with sterile vaseline. The patients were randomized into five groups. In the first, second, third, and fourth groups, 4, 6, 8, and 10 mL of levobupivacaine HCl were mixed with 26, 24, 22, and 20 mL of isotonic solution, respectively. Hence, the total mixture was 30 mL for each group. The fifth group was the control group. In this group, the standard method commonly used in most clinics was utilized. That is, a gel containing Cathejell-2% lidocaine was applied 20 min before cystoscopy. Meanwhile, levobupivacaine instillation was used 30 min before cystoscopy in the experimental groups.

Cystoscopy procedures were performed by a single surgeon with a 17.5 Fr rigid cystoscope and applied with 0°, 30°, and 70° lens. Patients were enabled to watch the procedure from the video endoscopy system. For the control group, the gel containing only 2% lidocaine preparation was instilled 30 min before the procedure. The VAS was presented to the patients with a diagram to describe "0" and "10" on a 10-cm straight line. Pain was evaluated with VAS during cystoscopy and 30 min after the procedure. Patient satisfaction was assessed after the procedure.

## 2.1 Statistical analysis

The Statistical Package for the Social Sciences for Windows 20 was used to compare the data. Comparisons were made using chi-square, paired  $t$ -test, Kruskal–Wallis, and analysis of variance, and Tukey’s honest significant difference tests.  $P < 0.05$  was considered significant.

## 3 RESULTS

The average age of all the 100 male patients evaluated was 62.37 years . All of the patients evaluated had undergone TUR operation due to a bladder tumor in the clinic of the current study. Any statistical difference in age between the groups was not indicated .

The mean number of cystoscopies performed for control purposes was 8, 7.4, 8.6, 6.45, 7.05 and in the 25-mg lidocaine, 4-mL levobupivacaine, 6-mL levobupivacaine, 8-mL levobupivacaine, and 10-mL levobupivacaine groups, respectively. The number of cystoscopies in the 6-mL levobupivacaine group was found to be significant compared with the 8-mL levobupivacaine group . No significant difference exists in the number of cystoscopies among other groups .

On the one hand, the lowest VAS score during the cystoscopy procedure was 1 , the highest was 5, and the average was 3.6. In the 6-mL levobupivacaine group, 2, 4, and 2.75 were the lowest, highest, and average, respectively. Moreover, in the 8-mL levobupivacaine group, 2, 3, and 2.4 were the lowest, highest, and average, respectively. In the 10-mL levobupivacaine group, 1, 3, and 2.00 were the lowest, highest, and mean, respectively. On the other hand, in the 25-mg lidocaine group, the lowest, highest, and average VAS scores were 4, 8, and 5.55, respectively. The VAS score of the 25-mg lidocaine group during the procedure was significantly higher . Moreover, the VAS scores decreased as the dose increased when the levobupivacaine groups were evaluated by titration. The score of the 4-mL levobupivacaine group during the procedure was significantly higher than the other levobupivacaine groups . No significant difference exists between the other groups in the score during the procedure .

The lowest, highest, and average VAS scores after the cystoscopy procedure were 1, 3, and 2.20, in the 4-mL levobupivacaine group, respectively. However, the lowest, highest, and average VAS scores were 1, 3, and 1.80 in the 6-mL levobupivacaine group, respectively. In addition, the lowest, highest, and average VAS scores were 1, 2, and 1.45 in the 8-mL levobupivacaine group, respectively. The lowest, highest, and average VAS scores were 1, 2, and 1.15 in the 10-mL levobupivacaine group, respectively. The lowest, highest, and average post procedure VAS scores in the 25-mg lidocaine group were 2, 5, and 3.35, respectively. In addition, the post procedure VAS scores of the 25-mg lidocaine and 4-mL levobupivacaine groups were significantly higher than the other groups . The post procedure score of the 6-mL levobupivacaine group was significantly higher than the 10-mL levobupivacaine group . Any significant difference was not detected in the postprocedure score among the other groups .

Patient satisfaction in this study was 70% in the 4-, 6-, and 8-mL levobupivacaine groups. However, it was 95% in the 10-mL levobupivacaine group. No significant difference in satisfaction values among other groups was found . Moreover, patient satisfaction was 30% in the 25-mg lidocaine group, which was significantly lower than the other groups .

## 4 DISCUSSION

Rigid cystoscopy is still widely used compared with flexible cystoscopy in outpatient operations or an office setting in most countries due to the low cost. The current prospective randomized study has shown that levobupivacaine is significantly more effective than lidocaine alone as a local anesthetic in rigid cystoscopy. The VAS scores during the procedure in this study were determined to be meaningfully high only in the lidocaine and 4-mL levobupivacaine groups compared with other higher-dose levobupivacaine groups. After the procedure, VAS scores were significantly higher only with the lidocaine, 4-mL levobupivacaine, and 6-mL levobupivacaine groups compared with other higher-dose levobupivacaine groups. The highest patient satisfaction rates were found in the 10-mL levobupivacaine group. Thus, it is believed that this is the first randomized study on the use of levobupivacaine urethrally in local cystoscopy procedures.

The mean age of the subjects in this study was 62.37 years old, and no statistical difference exists among the groups. In a previously reported study, older patients were reported to significantly tolerate cystoscopy better than younger patients.<sup>6</sup> Therefore, the absence of a significant age difference among the groups in this study did not cause this error.

Goldfischer et al., in 1997, compared the use of intraurethral lidocaine gel 20 min before rigid cystoscopy with the lubricant only for local anesthesia in rigid cystoscopy.<sup>7</sup> In that study, although no difference was reported in pain control in female patients, significantly less pain level was documented among men in the group in which the lidocaine gel was used. In another published study, intravesical lidocaine gel application in rigid cystoscopy 5 and 10 min before the operation was reported to not be overall beneficial. It was also reported that reducing anxiety among women on pain sensation was positive while it did not make a difference in men.<sup>8</sup> Thus, this study did not include female patients and studied only male patients. This study is a randomized prospective study similar to both studies. The study of Goldfischer et al. reported that different cystoscopes were used and that no difference between size and pain exist. However, the current study preferred to standardized using a single-size cystoscope.<sup>7</sup>

The detailed information given to the patients by the healthcare team before the procedure reduced anxiety and positively affects the level of pain.<sup>9</sup> The patient group of this study had undergone cystoscopy at least six times before, and they were included in the study as a group who knew what they would encounter during the procedure. Consequently, it did not affect the state of anxiety and anxiety-related pain of the patients because no statistical difference exists between the groups compared to the previous cystoscopy numbers.

Although some studies in the literature preferred the way of measuring pain status at different stages of cystoscopy, this study decided to assess pain both during and 30 min after the procedure because it would be more practical and reliable.<sup>10</sup>

Some studies suggest that the intraurethral administration of lidocaine is ineffective and that its administration does not provide sufficient absorption.<sup>8,11-13</sup> Most of the specified studies were done with a flexible cystoscope, and it is observed that evaluations were made only 5 and 10 min after the procedure in rigid cystoscopy studies.<sup>8</sup> However, some studies have reported that lidocaine has an onset of action from 15 to 60 min.<sup>14,15</sup> In addition, levobupivacaine has a longer effect than lidocaine.<sup>3</sup> Therefore, cystoscopy was started 30 min after the applications in both the lidocaine gel and levobupivacaine groups in this study. A second VAS assessment was made 30 min after the cystoscopy.

The additional cost of levobupivacaine used in this study currently ranges from 33 to 66 Turkish lira. This does not bring a huge cost in countries with strong social security institutions such as Turkey. A South Korean study for ureteral stenting similarly reported that sedation with propofol brings about a tolerable cost. However, almost twice the cost stands out as the difference in detailed local and sedation applications.<sup>16</sup> The cost of performing rigid cystoscopy is lower in Turkey than the use of flexible cystoscopes.

Many methods have been tried to reduce pain in cystoscopy procedures. Müntener et al. compared the transrectal periprostatic lidocaine blockade with the standard approach but found no significant difference in VAS and concluded that periprostatic blockade for transurethral procedures was ineffective.<sup>17</sup> Al-Hunayan et al. investigated the effect of transperineal urethrosphincteric lidocaine blockade and found that the discomfort/pain rates of the study group were significantly lower than the other control groups. In addition, no significant side-effects were reported.<sup>10</sup> However, in this study, infiltration from the perineum to the prostate apex requires experience and does not seem practical for the patient and the healthcare team. Thus, the practice of the current study is significantly more practical and easier to apply.

In another study, as a different approach, oral zaltoprofen administered with intraurethral lidocaine before cystoscopy was reported to decrease pain compared with only intraurethral lidocaine.<sup>18</sup> Karthikeyan et al. compared 75 mg diclofenac sodium administered orally and intraurethral lidocaine 1 h before cystoscopic ureter stent extraction with only placebo and intraurethral lidocaine.<sup>19</sup> Consequently, the diclofenac group reported significantly less pain levels. In both studies, effective oral nonsteroidal anti-inflammatory drugs were similarly used. During the SARS-CoV-19 pandemic, drugs such as diclofenac were reported to increase

renal involvement in patients infected with SARS-CoV-19, increasing the TMPRSS2 gene expression.<sup>20</sup> The use of such drugs should be avoided as much as possible due to their potential nephrotoxicity, especially with the SARS-CoV-19 pandemic.

Several pieces of the literature have reported that local anesthesia is used especially in the treatment of bladder tumor laser ablation, fulguration, and diathermy in the level that the patients can tolerate.<sup>21-25</sup> However, these studies are case series and have not yet become the standard approach. In addition, Stravodimos et al. have published that local levobupivacaine intravesical infiltration in resection of superficial bladder tumors is an appropriate method for pain control and can be an alternative to general anesthesia.<sup>26</sup> This was a pilot study reporting that levobupivacaine was first administered as intraurethral infiltration. It is one of the most reliable local anesthetics in terms of side-effects because levobupivacaine passes into the systemic circulation on a limited amount.<sup>3</sup> No drug-related side-effects were observed in this study. Therefore, it is suggested that intraurethral instillation of levobupivacaine can be used for local anesthesia for outpatient cystoscopy procedures in light of the results of this study.

This study has some limitations. First, this is a randomized, prospective, but not a double-blinded study. Second, the study involved a relatively small number of patients. In addition, pain levels were measured during and after 30 min, but the cystoscopy stages were not separately considered. Evaluating the individual cystoscopy stages could create inconsistency in the patient group of this study.

## 5 CONCLUSION

This study found that levobupivacaine administration diluted with transurethral instilled isotonic solution in cystoscopy interventions is a more effective method for pain control compared to lidocaine gel alone. Thus, more effective pain control was achieved in the patient group in which instillation with 10 mL of levobupivacaine was applied. At the same time, patient satisfaction was higher in the levobupivacaine groups in comparison with the lidocaine group. Although this method can prevent possible general anesthesia complications by eliminating the need for general anesthesia and is cost-effective, studies with larger series are needed.

## DISCLOSURE

Authors declared no conflicts of interest.

## ETHICAL APPROVAL

This study was approved by local ethical committee of Şişli Etfal Training and Research Hospital.

## PATIENTS' CONSENT

Informed consent was obtained from all patients.

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