

# Intraurethral Instillation of Ketamine and Lidocaine versus Lidocaine for Male Rigid Cystoscopy: A Prospective Randomized Controlled Trial

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## ABSTRACT

### Background

Male rigid cystoscopy is one of the most common outpatient procedures in urology because of its lower cost, better optical area and better orientation compared with flexible devices. However, performing rigid cystoscopy is not only painful but equally apprehensive in awake male patients.

### Objective

The study was conducted to evaluate the efficacy of lidocaine gel and ketamine solution together compared with lidocaine gel alone during male rigid cystoscopy.

### Method

A total of 76 male patients who visited the hospital for rigid cystoscopy were randomized into two groups before undergoing cystoscopy. The experimental group received 15 ml lidocaine with 2 ml (100 mg) Ketamine solution while the control group received 15 ml lidocaine gel with 2 ml Normal saline. Patient's heart rate and mean arterial pressure were recorded in five minutes interval till twenty minutes after completion of the procedure. The level of pain perception of all the patients was measured with Visual analogue scale (VAS) score, at the beginning, during and after cystoscopy. Independent sample t-test was used to compare outcome measures and p value of < 0.05 was considered statistically significant.

### Result

Out of the total 70 patients analyzed at the end of study with 35 patients in each group, the VAS score in each stage were lower in lidocaine plus ketamine group compared to lidocaine gel alone. The difference was significant at the commencement and middle of the procedure ( $p < 0.05$ ).

### Conclusion

Intraurethral instillation of ketamine and lidocaine is more effective in reducing mean pain score during cystoscopy as compared to lidocaine alone.

## KEY WORDS

*Cystoscopy, Ketamine, Lidocaine, Visual analogue scale score*

## INTRODUCTION

Cystoscopy is usually performed to evaluate the lower urinary tract in cases of hematuria, voiding symptoms, or bladder obstruction.<sup>1</sup> Cystoscopy can be performed with both rigid and flexible endoscopes. Rigid cystoscopes have larger lumen diameter which helps in better visualization, greater irrigation flow and passage of number of working instruments. Flexible cystoscopy in the other hand can be performed in supine position so it is more comfortable to the patients and it helps in visualization of difficult areas.<sup>1</sup> Conventionally lidocaine jelly is commonly used per urethra as local anesthetic to reduce discomfort of patient.<sup>2</sup> The rigid cystoscope is still commonly used because of its lower cost, better optical area and better orientation compared with flexible devices. However, the stiffness of the rigid cystoscope sheath causes discomfort and even pain due to the friction between the wall of the urethra or bladder mucosa and the sheath. This might result in termination of procedure before completion, misdiagnosis of disease and missed diagnosis.<sup>3,4</sup>

Lidocaine 2% jelly is a local anesthetic which acts by alternating signal conduction in neuron by blocking the fast voltage-gated sodium channels in the neuronal cell membrane responsible for action potential propagation.<sup>5</sup>

Topical ketamine, an N-methyl-D-aspartic acid (NMDA) receptor antagonist, has been used in several medical conditions.<sup>6</sup> It crosses most tissue membranes, so it is easily absorbed and has early onset and a short duration of action. It has peripheral action at both opioid and voltage dependent ion channels, such as sodium and L-type calcium channels, which led to its use as a topical gel in several medical conditions.<sup>7</sup>

So, a better option for analgesia during cystoscopy was the aim of this study where we aimed to evaluate the efficacy of lidocaine gel and ketamine compared with lidocaine gel alone in outpatient rigid cystoscopy.

## METHODS

This was a prospective interventional study conducted at the Department of Urology, Tribhuvan University Teaching Hospital (TUTH), Kathmandu over a period of one year (from August 2018 to July 2019). Ethical approval was taken from Institutional Review Board of Institute of Medicine. All male patients undergoing rigid cystoscopy and meeting the inclusion criteria were enrolled. Informed consent was taken from all the participants and they were allocated in experimental group (lidocaine plus ketamine) and control group (lidocaine alone) using computer-based random number generator after which they were subjected to cystoscopy. All data were collected and recorded in a pre-designed proforma.

Prior to the procedure, complete history was taken and physical examination was done. During the process of

cystoscopy, patient was examined in lithotomy position and urethral meatus and surrounding parts were sterilized with povidone iodine.

Then, 15 ml of 2% w/v (300mg) lidocaine gel (Lox Jelly 2%, Neon Laboratories Limited) was used in both study groups. While 2 ml (100 mg) ketamine clear solution (Kmine, National Healthcare, Nepal) was mixed with lidocaine gel for intra urethral instillation in experimental group, 2 ml normal saline was mixed with lidocaine gel and instilled in control group. Penile clamp was used for 15 minutes to prevent ejection and to facilitate dwell time for lubricant penetration and absorption into the tissue. After 15 minutes of instillation of assigned lubricant gel patients were subjected for cystoscopy using a Karl Storz 19 Fr cystoscope. Sterile saline irrigation was used during the process.

The mean arterial blood pressure, heart rate, oxygen saturation of all the patients, before cystoscopy, during cystoscopy, and after removal of the cystoscope was recorded.

Similarly, intensity of pain was measured by a 10 cm Visual Analogue Scale (VAS) three times, first during the entrance of the cystoscope, then during cystoscopy, and finally fifteen minutes after removal of the cystoscope. A drop in mean VAS score by 2 was considered efficacious during the study.

All patients were examined for nausea, vomiting, and hallucination and were kept in observation at recovery room till one hour after the procedure.

Data were collected in preformed proforma and analyzed using the statistical package for social sciences, SPSS version 20. Independent sample t-test was used to compare outcome measures and p value <0.05 was considered statistically significant.

## RESULTS

The age of the male patient undergoing rigid cystoscopy ranged from 16 to 88 years. Maximum number of patients was in the category of 56-65 as shown in table 1. Majority of the patients didn't have any significant comorbidity. Twenty-nine patients underwent cystoscopy for LUTS followed by DJ removal.

The mean age of patients in lidocaine plus ketamine group was 47.431 while in lidocaine only group was 42.60 which was comparable (Table 2). Also, there was no statistically significant difference in the baseline mean arterial pressure and heart rate among the patients in two groups, showing that patients were evenly distributed in two groups (Table 2).

The mean arterial pressure (MAP) was recorded at every five minutes interval after instillation of assigned lubricant. Patients were subjected to cystoscopy at 15 minutes. MAP

**Table 1. Comorbidities and Indications of cystoscopy**

Characteristics	Categories	Frequency (n)	Percentage (%)
Age in categories	16-25	12	17.1
	26-35	12	17.1
	36-45	13	18.6
	46-55	10	14.3
	56-65	14	20.0
	> 65	9	12.9
Co- morbidities	None	51	72.9
	HTN	9	12.9
	DM+HTN	4	5.7
	Others	4	5.7
	DM	2	2.9
	Indications of Cystoscopy	LUTS	29
DJ removal		26	37.1
Surveillance of bladder tumor		7	10.0
Hematuria		5	7.1
Others		3	4.3

**Table 2. Characteristics of patients**

Characteristics	Lidocaine only group	Lidocaine gel plus ketamine group	p-value
Age	42.60±16.50	47.431±17.95	0.245 <sup>a</sup>
MAP	92.37±12.97	92.31±7.29	0.982 <sup>a</sup>
HR	76.97±8.76	80.49±9.09	0.104 <sup>a</sup>

<sup>a</sup>Independent sample t-test, MAP= Mean Arterial Pressure, HR= Heart Rate, p-value significant at < 0.05

among the patients in two groups were comparable before and during cystoscopy.

The VAS score at the commencement of the procedure, middle of the procedure, and 15 minutes after removal of the cystoscope in both groups were measured. Mean pain scores in all stages were found to be lower in the patients who received lidocaine and ketamine. However, the difference was significant at the commencement and middle of the procedure only (p value < 0.05) as shown in Table 3.

**Table 3. Comparison of Mean Visual Analogue Scale (VAS) Score**

VAS score	Lidocaine gel (mean±SD)	Lidocaine gel plus ketamine (mean±SD)	p value*	Mean difference
Entrance of cystoscope	3.94±1.392	3.06±1.51	0.013a	0.886
During Cystoscopy	6.66±1.589	5.60±1.81	0.012a	1.057
15 min after end of cystoscopy	3.34±1.781	2.71±1.79	0.146a	0.629

<sup>a</sup>Independent sample t-test, \*p-value significant at < 0.05

The mean cystoscopy time in the lidocaine only group was 7.03 minutes while it was 6.51 minutes in lidocaine plus ketamine group which was comparable as shown by the p value of 0.107 in table 4.

**Table 4. Comparison of Cystoscopy time**

Characteristics	Lidocaine only Group	Lidocaine plus ketamine group	p-value
Cystoscopy time (min)	7.03±1.38	6.51±1.24	0.107 <sup>a</sup>

<sup>a</sup>Independent sample t-test

## DISCUSSION

Cystoscopy still remains an uncomfortable procedure causing discomfort to the patients. The male urethra is longer and narrower compared to female, this is one of the reasons why cystoscopy is generally painful for them. The most painful part of the procedure is when the cystoscope passes through the membranous urethra.

While the search for better analgesic agent for rigid cystoscopy is still ongoing, the standard is far beyond our reach. In our common practice however topical lidocaine gel is the most commonly used agent because of its simultaneous role as a lubricant and local anesthetic. Numerous research groups have questioned the value of the analgesic effect of lidocaine gel as a sole lubricant for cystoscopy. In 2008 two meta-analyses with contradictory results were published on this issue. Study by Aaronson et al. concluded that intraurethral instillation of lidocaine gel provides control of moderate to severe pain and benefit to male patients undergoing cystoscopy while Patel et al. showed no statistically significant difference in pain scores between lidocaine gel and plain gel instillation.<sup>8,9</sup>

In the quest of better analgesic agent for cystoscopy, Zhang et al. and Somoro et al. in their different studies observed a decreased pain level by allowing the patient to view the cystoscopy on a screen.<sup>10,11</sup> In an attempt to reduce pain during cystoscopy, cooling the lidocaine gel installed into the urethra before the male rigid cystoscopy failed to decrease the pain level.<sup>12</sup> Vasudeva et al. in their study examined the optimal dwell time of intraurethral lidocaine gel before insertion of the cystoscope.<sup>13</sup> They concluded that 15 min is more effective than both 5 and 10 min for patient as well as physician assessment of pain intensity.

In the past because of its effects on NMDA and non-NMDA glutamine, monoaminergic, opi-oid, nicotinic, and muscarinic cholinergic receptors, intravenous ketamine has been used effectively for treatment of catheter-related bladder discomfort (CRBD).<sup>14,15</sup> Another study by Farhad Etezadi et al. regarding preemptive effect of intraurethral instillation of ketamine-lidocaine gel on postoperative CRBD after lumbar spine surgery, showed intraurethral instillation of ketamine-lidocaine gel reduced the incidence of CRBD at recovery (p < 0.001) along with reduction in severity of CRBD (p < 0.05) during the first and second visit compared

**Table 5. Comparison of Mean VAS score with other study**

Our Study	Moharari et al.					
	Lidocaine group	Lidocaine + keta-mine group	p- value*	Lidocaine group	Lidocaine + keta-mine group	p-value*
VAS score						
Entrance of cystoscope	3.94± 1.392	3.06±1.51	0.013 <sup>a</sup>	6.5±2.17	4.8±1.96	0.003
During Cys-toscopy	6.66± 1.589	5.60±1.81	0.012 <sup>a</sup>	6.7±2.27	4.7±2.1	0.001
15 min after end of cys-toscopy	3.34± 1.781	2.71±.79	0.146 <sup>a</sup>	5.7±2.26	3.9±1.93	0.002

with control group.<sup>16</sup> The mean pain intensity score and opioid requirement to relieve postsurgical pain were lower in keta-mine group during all the study time points from recovery and after transfer to ward.<sup>16</sup>

Low plasma levels of ketamine can inhibit nociceptive central sensitization and have a preventive analgesic effect; also, the local analgesic effect of ketamine has been explained by neuronal sodium channel block and inhibition of development of secondary hyperalgesia by peripheral action on the NMDA receptor.<sup>17-19</sup> Nejati and colleagues reported that intranasal ketamine is an effective agent in reducing the pain of nasogastric tube insertion.<sup>20</sup> In addition, topically applied ketamine reduces capsaicin evoked mechanical hyperalgesia and was used as an adjuvant for post-operative analgesia prolongation after minor gynecologic procedures.<sup>21</sup>

In a similar study done by Moharari et al. who added ketamine to lidocaine gel and observed significantly lower scores on the visual analogue scale compared to lidocaine alone.<sup>22</sup> In the study they monitored the hemodynamic changes and level of pain perception at the beginning, during, and after cystoscopy.

In the view of limited research on this subject matter our study tried to evaluate the efficacy of Lidocaine in conjugation with ketamine to make male rigid cystoscopy more comfortable to the patients. Since, there have been very few studies with ketamine as intraurethral local anesthetic, we added ketamine to the lidocaine which is being conventionally used as intraurethral anesthetic agent rather than using ketamine alone. As a control 2 ml normal saline was added in place of ketamine in control group. The mean VAS score in the experimental group was lower in comparison to control group. However, the statistically significant difference in the level of pain intensity was observed at the entrance of cystoscope and during cystoscopy only.

In the study by Moharari et al. they found the ketamine in conjugation with lidocaine lowered the VAS score by two points compared with lidocaine alone.<sup>22</sup> This level of difference was not seen in our study. In our study the mean VAS score decreased by one at the entrance of cystoscopy and during cystoscopy. Though the result was statistically significant, we cannot confirm whether adding ketamine solution to the lidocaine gel was actually beneficial to the patient.

During the course of the study we measured the mean arterial pressure and heart rate at 5 minute interval from instillation of assigned lubricant till 20 minutes after completion of the procedure in all the patients included in the study. Though there was no significant difference in the mean arterial pressure in the two groups, the heart rate in the experimental group was consistently higher after cystoscopy which was statistically significant. This might be due to some systemic absorption of Ketamine. Measuring the plasma concentration of ketamine during and after the cystoscopy procedure would have helped for the better understanding of the study process. However we couldn't incorporate this in our study. In the study by Moharari et al. however the mean arterial pressure and heart rate were comparable throughout the study.<sup>22</sup>

Our study tried to incorporate more sample compared to the study by Moharari et al.<sup>22</sup> We had 35 patients in each study group while Moharari et al. included 30 patients in each arm.<sup>22</sup> Similarly 10 ml of the lidocaine gel was used in each group in the study by Moharari et al., however we used 15 ml of the lidocaine gel in the respective groups.<sup>22</sup> The dose of ketamine was same in both the study though. The standard deviation of VAS was 2.2 in the study by Moharari et al. in their pilot study, while no pilot study was conducted before our study.<sup>22</sup> Such study would have certainly helped us in our study to see the general trend of pain tolerance in our study population.

As the cystoscopy was performed by multiple Urologists, there may be chances of observer bias. Assessment of immediate effect of ketamine and lidocaine for 20 minutes only may not have been sufficient enough to advocate for the efficacy of the combination as compared to lidocaine alone. A larger multi-centric study is needed to further validate the findings of our study.

## CONCLUSION

Intraurethral instillation of ketamine and lidocaine resulted in a VAS pain score reduction of approximately one at the time of entrance of cystoscope and during cystoscopy. However more study is needed to verify the efficacy of higher doses of intraurethral instillation of ketamine and its systemic effect.

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