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Effect of Lumbar Epidural Administration of Neostigmine on Lower Urinary Tract Function

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Background: Neostigmine is cholinomimetic and is used for postoperative analgesia. Its urodynamics effects on voiding function have not been elucidated. **Materials and Methods:** Adult patients without bothersome voiding symptoms planned for rigid cystoscopy under local anesthesia were enrolled. They underwent multichannel urodynamics (filling cystometry and pressure-flow study) before and 30 min after lumbar epidural administration of Neostigmine (2 μg/kg). **Results:** Indications for cystoscopy were check examination for follow up of carcinoma urinary bladder (n = 3), staging for carcinoma cervix (5), and removal of ureteral stent (4). Patients' mean age was 51.9 ± 11.7 years and international Prostatic symptom score 2.34 ± 3.41. A trend of decreased maximum cystometric capacity (MCC) was observed after Neostigmine (413.50 ± 142.45 ml vs. 357.00 ± 145.62 ml; $P = 0.056$) without any change in end-filling pressure. Five patients developed detrusor overactivity (DO) and one had increase in its amplitude ($P = 0.031$). Four patients developed rhythmic rectal contractions and one had increase in its amplitude ($P = 0.219$). There was no difference in any of the voiding parameters. Mean Visual Analog Pain Score (VAS scale 0–10) during cystoscopy for this group was significantly lower than that in a similar group of patients who did not receive Neostigmine prior to rigid cystoscopy (1.16 ± 0.94 vs. 4.57 ± 1.45; $P = 0.0001$). The drug was well tolerated in majority of the patients. **Conclusion:** Epidural Neostigmine is effective in providing analgesia during diagnostic rigid cystoscopy. It leads to development of DO and decrease in bladder capacity without any effect on voiding function. These findings may help clinicians to use it for transurethral procedure-related pain relief without apprehension of voiding difficulty. *Neurourol. Urodynam. 29:443–448, 2010.* © 2009 Wiley-Liss, Inc.

Key words: Neostigmine; overactive detrusor; urodynamics

INTRODUCTION

Intrathecal injection of muscarinic receptor agonists produces anti-nociception in rats, which is reversed by intrathecal atropine.[1] After preclinical toxicity screening, the polar cholinesterase inhibitor, Neostigmine was introduced into clinical trials in 1995 for intrathecal injection[2] and has been found effective in chronic as well as postoperative pain.[3–7]

Nausea and sedation are significant side effects of intrathecal administration of this drug which are uncommonly observed with epidural administration.[2,5–8] Cholinergic side effects, for example, sweating, salivation, and abdominal cramping are exceedingly rare.[8] Genitourinary events have been scarcely reported with intrathecal Neostigmine; these include urinary retention, urinary incontinence, vaginal contractions and ejaculation, etc.[2] There have been reports of increase in urethral resistance associated with the use of cholinomimetic agents.[9,10] Conversely, parenteral Neostigmine has been reported useful in reversing postoperative non-obstructive urinary retention[11] and morphine induced retention.[12] No clinical study is available to elucidate the urodynamic effects of this drug. Therefore, in view of conflicting reports of urological effects of Neostigmine and absence of urodynamic correlates, this study was planned.

MATERIALS AND METHODS

Patients without any bothersome lower urinary tract symptoms undergoing rigid cystoscopy under local anesthesia (using 2% xylocaine jelly for lubrication) were enrolled in the study. To minimize abnormal urodynamic findings at baseline, patients with IPSS score[13] of >7 (of 35) with IPSS global quality of life score[13] >2 (of 6) were excluded from the study. Study protocol was approved by the institutional ethics committee and written informed consent was taken from each patient prior to inclusion.

Neostigmine is available for parenteral use on physician's prescription; the preparation does not contain any preservative. The procedures to evaluate the effect of epidural administration of pharmacological agent (urodynamics and epidural puncture) have been described earlier.[14] Briefly, after ensuring a sterile urine culture, a baseline urodynamic study (UDS) was performed. Neostigmine was then injected in lumbar epidural space using Tuohy graduated epidural needle 18 G 3.5 in. (Portex Ltd, London, UK), in dose of 2 μg/kg body weight and a repeat UDS was performed after 30 min of the injection. Four milligrams of Ondansetron was injected intravenously prior to Neostigmine injection. Following the repeat UDS, the patient was shifted to endoscopy suite for the cystoscopy. Prior to baseline UDS, a test run (filling at physiological rate and voiding into the uroflowmeter) was

Conflicts of interest: none.
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performed whose results were not recorded. Each UDS consisted of filling cystometry followed by pressure-flow analysis in sitting position using "Solar Silver" digital urodynamic machine (Medical Measurement System, Enschede, The Netherlands). Sterile normal saline (0.9%, w/v) was used as the filling medium and infused at physiological filling rate (one-fourth of body weight). Urodynamic parameters were recorded in filling and voiding phase in accordance with the Good Urodynamic Practice Guidelines of the International Continence Society.[15] Filling was stopped after sensation of "strong desire" when the patient felt he/she could no longer delay micturition (marked as MCC). Filling detrusor compliance (DC) was calculated using the formula DC = MCC/end filling P_{det}. Detrusor overactivity (DO) was measured in accordance with the ICS guidelines.[16] To avoid inclusion of artifacts as DO, proper leveling of P_{ves} and P_{abd} was ensured throughout the filling phase by checking cough response periodically and tracings were manually checked in magnified view after the investigation for configuration of each marked DO. End filling P_{det} was taken at the end of filling phase (in patients without terminal DO) or immediately before the start of terminal DO, whichever applicable.[16] The Abrams–Griffiths (AG) number was defined as $P_{det}Q_{max} - (2 \times Q_{max})$ in men. Urine production during UDS was calculated both before and after the injection of Neostigmine as follows:

$$\text{Urine production} = (\text{voided volume} + \text{PVR}) - \text{volume filled}$$

Actual maximum cystometric capacity (MCC) was calculated as follows:

$$\text{Actual MCC} = \text{observed MCC} + \text{urine production}$$

Actual MCC was used for statistical analysis in preference to observed MCC.

Bladder outlet obstruction (BOO) was defined as an AG number >40 in men, and presence of two or more of the following in females $P_{det}Q_{max} > 50$ cmH_2O, $Q_{max} < 12$ ml/sec, urethral resistance $(P_{det}Q_{max}/Q^2_{max}) > 0.2$, and significant PVR in presence of high pressure or resistance.[17]

Rigid cystoscopy was performed using 21 Fr size cystoscope sheath after lubrication with 2% Xylocaine jelly. The analgesic effect of Neostigmine was evaluated by patient-administered Visual Analog Scale (0–10) for measuring degree of pain during cystoscopy. The pain was also measured similarly in 12 age-, sex-, and indication-matched patients undergoing rigid cystoscopy under local anesthesia using 2% Xylocaine Jelly without administration of Neostigmine. All patients were observed for 6 hr after the injection.

STATISTICAL ANALYSIS

All data were fed into Microsoft-excel worksheet and analyzed using SPSS-16 statistical software for Windows. Normalcy of data was tested and confirmed using one-sample Kolmogorov–Smirnov test. All the variables are presented as mean ± standard deviation (SD). Effect of epidural Neostigmine on various urodynamic parameters was analyzed using "paired *t*-test" for continuous variables and "McNemar test" for categorical variables. *P*-values ≤ 0.05 were considered statistically significant.

RESULTS

Totally 12 patients were enrolled and all completed the study protocol. The indications of rigid cystoscopies were staging for carcinoma cervix (3), check cystoscopy for follow up bladder cancer (5), and stent removal (4). The mean age of the patients was 51.9 ± 11.7 years (range, 39–70) and the American Urological Association symptom score 2.34 ± 3.41 (range, 0–10). Two patients (one man and one woman) with urodynamically proven BOO were included, since they did not have bothersome LUTS based on IPSS. The man had $P_{det}Q_{max}$ 53 cmH_2O, Q_{max} 4 ml/sec, PVR 310 ml with AG no. 45, and woman had $P_{det}Q_{max}$ 28 cmH_2O, Q_{max} 9 ml/sec, PVR of 290 ml, and urethral resistance 0.35 $cmH_2O/(ml/sec)^2$. Their respective urodynamic parameters after Neostigmine injection were $P_{det}Q_{max}$ 37 cmH_2O, Q_{max} 6 ml/sec, PVR 3 ml, and AG 25 for the man, and $P_{det}Q_{max}$ 24 cmH_2O, Q_{max} 10 ml/sec, PVR of 126 ml, and urethral resistance 0.24 $cmH_2O/(ml/sec)^2$ for the woman.

All the patients tolerated the drug without any side effect. Urodynamic parameters before and after epidural Neostigmine administration are shown in Table I.

End filling P_{det}, $P_{det}Q_{max}$, and PVR correlated positively ($P = 0.013$, 0.096, and 0.001, respectively) and Q_{max} and Q_{ave} negatively ($P = 0.014$ and 0.038, respectively) with IPSS. There was no significant difference in urine production before and after Neostigmine injection (Table I). Typical pressure-flow studies before and after Neostigmine injection (of one patient) are shown in Figures 1 and 2, respectively. MCC showed a borderline trend of fall from baseline (Table I; $P = 0.056$). Only one of 12 patients had DO at baseline. Five patients developed DO and one patient had increase in the degree of DO

TABLE I. Urodynamic Parameters Before and After Epidural Neostigmine Administration

No.	Parameter	Value before Neostigmine	Value after Neostigmine	*P*-value
1	First desire	173.58 ± 82.74	148.66 ± 69.67	0.175
2	Normal desire	271.83 ± 94.50	221.00 ± 109.54	0.177
3	Strong desire	331.54 ± 101.75	271.09 ± 106.20	0.120
4	Maximum cystometric capacity	413.50 ± 142.45	357.00 ± 145.62	0.056
5	End filling P_{det}	13.58 ± 9.09	13.00 ± 10.32	0.774
6	Urine production	12.41 ± 20.58	32.08 ± 56.70	0.099
7	Detrusor compliance	40.54 ± 25.33	38.87 ± 20.36	0.825
8	$P_{det\ max}$	42.25 ± 12.71	48.25 ± 18.41	0.158
9	P_{det} at Q_{max}	29.41 ± 12.91	29.58 ± 13.36	0.952
10	Voided volume	342.25 ± 124.57	303.58 ± 170.99	0.182
11	Q_{max}	11.50 ± 4.37	11.58 ± 6.25	0.944
12	Q_{ave}	6.70 ± 2.83	5.67 ± 2.87	0.191
13	Postvoid residue	73.63 ± 123.01	63.36 ± 142.98	0.821
14	Urethral resistance	0.16 ± 0.09	0.16 ± 0.11	0.991
15	AG no.	16.33 ± 18.46	17.83 ± 21.40	0.866

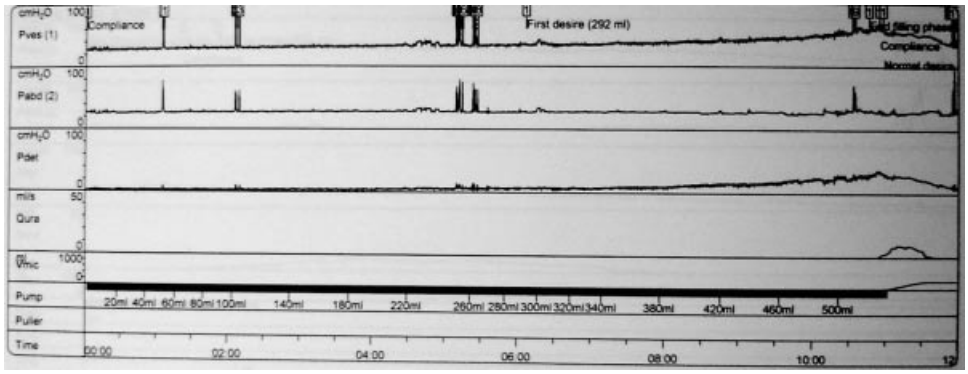

Fig. 1. Urodynamic study in one of the participant women before injection of Neostigmine. No rectal contraction or detrusor overactivity. MCC = 530 ml, compliance = 16.5 ml/cmH_2O.

($P = 0.031$); two had terminal overactivity and four during filling before end filling. None of these patients experienced any incontinence associated with DO. Differences were noted in the baseline and post-Neostigmine-injection urodynamic parameters between the two groups, that is, patients who did not develop (group 1; n = 6) versus who developed or had an increase in the pre-existing DO (group 2; n = 6) (Table II); only one of these was woman ($P = 0.04$; Fisher's exact test). Both the patients with BOO and the only patient with DO at baseline were all in group 2. There was a trend of difference in IPSS between the two groups ($P = 0.09$). Four patients developed rhythmic rectal contractions and one had increase in the degree of rectal contractions ($P = 0.219$) after Neostigmine injection. There was no significant change in the voiding parameters; the two patients with BOO did not report any increase in difficulty in voiding.

These patients experienced significantly less pain compared to a similar group of patients matched for age, sex, and indication (of cystoscopy) undergoing rigid cystoscopy under local anesthesia using 2% Xylocaine jelly without Neostigmine (1.16 ± 0.94 vs. 4.57 ± 1.45; $P = 0.0001$).

The drug was well tolerated in all the patients. One patient experienced pain at the site of epidural injection for 24 hr which subsided with diclofenac potassium (total 100 mg).

DISCUSSION

Analgesic Efficacy of Neostigmine

Muscarinic receptors are present in the dorsal horn of spinal cord of humans and rats.[18] Intrathecal injection of muscarinic receptor agonists produces anti-nociception in rats, which is reversed by intrathecal atropine.[1] Over 13 years of its clinical existence as intrathecal analgesic, Neostigmine has stood the test of time and has proven dose-dependent efficacy and good tolerability for both acute as well as chronic pain in dosage of 100–750 μg; most commonly used dosage for pain relief is 1–4 μg/kg body weight.[3,4,11] In our series, we used its 2 μg/kg body weight dose by epidural route and we found that Neostigmine provided good analgesic effect during rigid cystoscopy; median VAS pain score of 1 (range 0–3) compared to median 4 (range 3–7) in age-matched controls ($P = 0.0001$). It has also been studied as adjunctive analgesic (dose of Neostigmine mentioned in parentheses) to various neuroaxially administered drugs, for example, lidocaine (1–4 μg/kg[19]), intrathecal Bupivacaine (25–75 μg)[20], epidural Ropivacaine (2–4 μg/kg),[21] and morphine (60 μg),[5] etc., and found to be useful in reducing drug dose, increasing analgesia duration, and decreasing opioid requirement. There is discrepancy among studies regarding dose efficacy of Neostigmine, which can partly be explained by the level of surgical intervention, that is, after knee arthroplasty, it produces 8-hr analgesia at doses <100 μg[6], whereas, after abdominal hysterectomy 480 μg produces analgesia for <4 hr.[7]

Adverse Effects of Neostigmine

Nausea and sedation are significant side effects of intrathecal administration of this drug and are uncommonly observed with epidural administration.[2,5–8] This effect has been found to be related to cephalad distribution of the drug

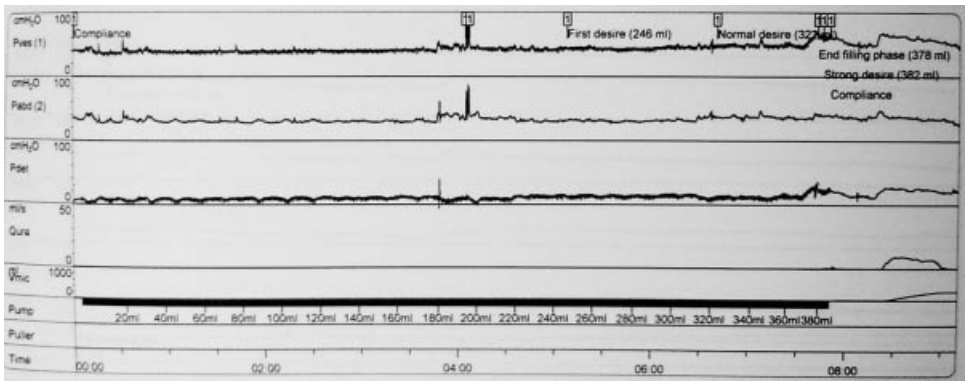

Fig. 2. Urodynamic study in the same woman 30 min after injection of Neostigmine. Low amplitude rhythmic rectal contraction and terminal detrusor overactivity have appeared. MCC = 392 ml, compliance = 11.5 ml/cmH_2O.

TABLE II. Comparison of Baseline and Post-Neostigmine-Injection Urodynamic Parameters Between the Two Groups, That Is, Patients Who Did Not Develop (Group 1; n = 6) Versus Who Developed or Had an Increase in the Pre-Existing DO (Group 2; n = 6)

Parameters	Group 1 (n = 6)	Group 2 (n = 6)	*P*-value
MCC[a]	331.2 ± 113.1	495.8 ± 123.6	0.055
MCC[b]	266.8 ± 106.8	447.2 ± 126.0	0.016
End fill P_{det}[a]	8.2 ± 2.7	19.0 ± 10.2	0.054
End fill P_{det}[b]	7.7 ± 4.8	18.3 ± 11.9	0.023
Compliance[a]	41.6 ± 9.2	39.5 ± 36.4	0.262
Compliance[b]	45.9 ± 23.2	31.7 ± 15.9	0.262
Voided volume[a]	325.0 ± 113.1	359.5 ± 143.7	0.522
Voided volume[b]	253.6 ± 103.3	353.5 ± 218.3	0.200
$P_{det}Max$[a]	32.66 ± 8.54	51.83 ± 7.88	0.009
$P_{det\ max}$[b]	38.5 ± 7.34	58.00 ± 21.53	0.132
$P_{det}Q_{max}$[a]	19.2 ± 4.7	39.7 ± 9.6	0.005
$P_{det}Q_{max}$[b]	19.2 ± 5.4	40.0 ± 10.2	0.006
PVR[a]	6.5 ± 15.9	154.2 ± 150.5	0.091
PVR[b]	15.3 ± 30.8	121.0 ± 205.7	0.320

[a]Before injection of Neostigmine.
[b]After the injection.

after intrathecal administration. Therefore, strategies to reduce this toxicity include head-up position of patient, catheter infusion rather than high volume bolus injection, use of hyperbaric solution, use of anti-emetic and epidural administration.[2] We used Ondansetron 4 mg prophylactically for antiemesis; none of our patients complained of any nausea or vomiting.

Urological Effects of Neostigmine

We did not find any incidence of urinary retention after Neostigmine injection even in presence of BOO. Voiding difficulty has been reported with other medications used for pain relief through spinal route. COMET study group reported 62–79% incidence of clean intermittent catheterization following various regimens of Bupivacaine used for labor analgesia.[22] Bromage et al.[23] reported 90% incidence of voiding difficulty following epidural morphine. Genitourinary events have been reported earlier with intrathecal Neostigmine. Hood et al.[2] conducted a Phase I safety assessment trial of intrathecal administration of Neostigmine and observed several genitourinary effects, including transient urinary retention, urinary urgency, urinary incontinence, vaginal contractions and ejaculation, etc. particularly at doses ≥500 μg, which was significantly higher than that used in our study (at 2 μg/kg body weight). Conversely, Tang et al.[12] studied the effects of preoperative phenoxybenzamine on preventing epidural-morphine-induced urinary retention and effect of intramuscular Neostigmine on releasing the retention. Phenoxybenzamine was not effective in preventing the retention when used alone. Neostigmine could significantly release the retention only when phenoxybenzamine was administrated preoperatively.

However, till date no clinical data on urodynamic assessment are available for these effects. Preclinical studies suggest that cholinesterase inhibitors decrease PVR in BOO animal models both with and without concomitant α-adrenergic antagonist.[24,25] In fact, parenteral Neostigmine has been used in reversing postoperative non-obstructive urinary retention[11] and morphine-induced retention.[12] Therefore, clinical report of urinary retention associated with use of spinal Neostigmine is intriguing; it may partly be explained by cephalad diffusion of the intrathecally injected Neostigmine to the cerebral cortex and partly by increase in the urethral resistance associated with cholinomimetic drugs, as discussed below.

Cerebral Effects of Cholinergic Neurotransmission

Connections between the frontal cortex and the septal-preoptic region of the hypothalamus as well as between the paracentral lobule and the brainstem are thought to be responsible for inhibitory control of micturition reflex.[26] Several of these connections are cholinergic (Muscarinic) and cholinergic loss in these areas as seen in Alzheimer's disease and middle cerebral artery infarct is associated with DO and incontinence.[27] Nakai et al.[28] induced DO by occluding middle cerebral artery occlusion in female Sprague–Dawley rats and found that bladder capacity was increased by injection of low dose of centrally acting cholinesterase inhibitor (donepezil hydrochloride). However, they did not find any impairment in detrusor contractility during voiding phase. Therefore, the "retention" observed by Hood et al.[2] may have been actually a delay in initiation of micturition reflex due to increase in MCC (central action).

Cholinomimetic Agents and Urethral Resistance

There is controversy about effect of cholinomimetic drugs on urethral resistance with more data in favor of increase in urethral resistance[9] thereby decreasing their potential efficacy in detrusor underactivity (DUA) especially without concomitant use of alpha blocker.[10]

The mechanisms are as follows: cholinergic receptors are found not only in the detrusor, but also in the smooth muscles of the bladder base and the urethra. Longitudinal smooth muscles of the urethra are continuous with the longitudinal layer of the detrusor, implicating a role in the opening of the bladder neck and shortening of the urethra during voiding. However, the circular smooth muscle layer of the urethra is not continuous with the detrusor and is important for maintaining urethral closure; it is more sensitive to noradrenaline than to acetylcholine. Thus, the cholinergic stimulation to the longitudinal muscle of the urethra may facilitate micturition, but stimulation to the circular muscle may oppose the micturition by increasing the bladder outlet resistance. Although cholinergic stimulation elicits a greater response from the longitudinal muscles of the urethra than from the circular muscles, it may also elicit a response in the circular muscles especially in pathological states by multitude of mechanisms; firstly, directly by stimulating Muscarinic receptors, secondly, indirectly by stimulating intramural adrenergic ganglia causing release of noradrenaline by way of a nicotinic effect, and finally, by increasing periurethral electromyography activity on central action.[10]

Urodynamic Effects of Neostigmine

The parasympathetic nervous system plays a critical role in regulating urinary bladder function. The pathway remains inactive during the filling phase and is responsible for voiding function through detrusor contraction and sphincter relaxation.[26] We found evidence of de novo DO ($P = 0.031$) and a trend of decrease in MCC ($P = 0.056$) after administration of Neostigmine. In group 2 (Table II), two patients had BOO and one DO at baseline. There was a trend of higher PVR at baseline in these patients compared to those in group 1 ($P = 0.09$; Table II). This difference may be explained by pathophysiology of BOO; bladder wall changes which take place in BOO lead to detrusor instability.[29] Nakahara et al.[30]

demonstrated biphasic contractile response of Neostigmine on rat bladder strips and concluded that it is the acetylcholinesterase rather than butylcholinesterase activity that regulates cholinergic responses in the rat bladder. They also that inferred that Neostigmine not only inhibits degradation of acetylcholine but also stimulates the endogenous release of acetylcholine. Others have also reported similar results in guinea pig model.[31,32] Bethanecol is a Muscarinic M2/M3 cholinergic agonist used for the treatment of DUA, especially in patients with incomplete lower motor neuron lesions, though the efficacy is generally considered to be low especially without concomitant use of alpha blocker.[9,33] It has been reported to decrease the PVR in patients with DUA,[34] and decrease MCC, induce DO, and improve voiding after hysterectomy.[35]

Rectal Contractile Activity With Neostigmine

Four of our patients developed rhythmic rectal contractile activity and one experienced increase over baseline after the injection of Neostigmine. Law et al.[36] conducted clinical study on human volunteers for evaluating effects of Neostigmine and bethanecol on colonic activity and found that, by virtue of stimulation of M1 receptors, the former is more efficacious in inducing phasic motor contractions and increasing urgency perception, leading to its clinical use in treating postoperative colonic pseudo-obstruction.

Limitations

The limitation of our study is small sample size and not including a placebo arm, especially for comparing analgesic efficacy of the epidural Neostigmine. In view of invasive nature of the intervention (epidural injection and UDS) the institutional ethics committee did not approve such an inclusion and only permitted pain assessment in a control group without a placebo intervention (UDS and epidural saline injection).

We do not intend to use epidural Neostigmine for these indications of cystoscopy on regular basis since nature of anesthesia would be invasive; we would rather try to change to flexible cystoscopy (which is not possible at present due to financial constraints of a government hospital in developing country). Nevertheless, our clinico-urodynamic findings may help clinicians choose this medication for transurethral procedure-related pain relief over others which may lead to voiding difficulty (e.g., morphine, bupivacaine, etc.).[22,23] Moreover, the study presents important insights into urodynamic effects as well as analgesic efficacy of Neostigmine worthy of further investigations.

CONCLUSION

Epidural Neostigmine provides significant analgesia for transurethral rigid cystoscopy at a dose of 2 μg/kg body weight with minimal side effects. It induces detrusor as well as rectal overactivity and decreases bladder capacity without adversely affecting voiding parameters. These findings may help clinician to use it for transurethral procedure-related pain relief without apprehension of increasing voiding difficulty or acute urinary retention.

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