COMPARISION OF PREOPERATIVE TRAMADOL, PREGABALIN OR CLONIDINE ON INCIDENCE AND SEVERITY OF CATHETER RELATED BLADDER DISCOMFORT IN PATIENTS UNDERGOING PERCUTANEOUS NEPHROLITHOTOMY: A PROSPECTIVE, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL

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Abstract

Objective: Catheter related bladder discomfort is a post catheterization complication, with an incidence of 47-90%.This study evaluates the efficacy of preoperative tramadol, pregabalin or clonidine in decreasing the incidence and severity of postoperative catheter-related bladder discomfort in patients undergoing percutaneous nephrolitotomy (PCNL).

Materials and methods: 160 patients, either sex, ASA I & II, undergoing elective percutaneous nephrolithotomy, requiring bladder catheterization were randomly assigned into 4 groups to receive tramadol 100mg (Group I), pregabalin 75mg (Group II), clonidine 100mcg (Group III) and placebo (Group IV) orally 1h prior to induction of anaesthesia. Identical anaesthesia technique was utilized in all the groups. Catheter-related bladder discomfort (CRBD) was evaluated on 4-point scale (1 = no discomfort, 2 = mild, 3 = moderate, 4 = severe) on arrival (0h), 1, 2, 6, 12, 24hrs postoperatively. Patients received patient-controlled analgesia with fentanyl for postoperative pain relief.

Results: There was no difference between the demographic profile and operative variables such as surgical and anaesthesia time between the groups($p > 0.05$).The prevalence and severity of CRBD were lower in Groups I, II, III compared to group IV($p < 0.05$). Incidence and severity of CRBD between Groups I and II, II and III and I and III were comparable and statistically insignificant ($p > 0.05$). Mean fentanyl requirement were comparable between Groups I, II and III while significantly higher in Group IV ($p = 0.02$).

Conclusion: Preemptive tramadol 100mg, pregabalin 75mg and clonidine 100mcg orally one hour prior to surgery were equally effective in preventing postoperative symptoms of CRBD.

Keywords: Catheter related bladder discomfort, drugs- tramadol, pregabalin, Clonidine Percutaneous nephrolithotomy.

Registration number: Clinical Trial.gov.in (**CTRI/2017/01/007658**)

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Introduction

Catheter related bladder discomfort (CRBD) has an incidence of 47-90% in patients undergoing bladder catheterization. It manifests as an intense urge to urinate, discomfort in suprapubic region and maybe accompanied by behavioral symptoms[1-3]. Injury to proximal urethra or bladder due to indwelling catheter leads to involuntary contraction of detrusor muscle. Detrusor contraction is secondary to stimulation of muscarinic receptors by acetylcholine released from activated cholinergic nerves[4]. Patient or surgical factors implicated with increased incidence of CRBD are male gender, use of catheter >16 FG, surgical procedures involving prostate, bladder, endourology procedures of upper and lower urinary tract[5,6].

The treatment modalities of CRBD are varied with the use of anti-muscarinic agents being the mainstay of treatment[7-11]. Agents modulating the inflammatory or pain pathway also influences the pain management modalities of CRBD[12-15]. Anesthetic uses of pregabalin, tramadol or Clonidine have been shown to have favourable preoperative, intraoperative and post operative effects[16-19] and have been used in various studies to modify the CRBD pain. Literature is sparse in assessing the best agent among the three for decreasing the pain of CRBD. This study was planned to evaluate and compare the effects of preoperative pregabalin, tramadol or clonidine on prevalence and severity of CRBD in patients undergoing percutaneous nephrolithotomy.

Materials and Method

This randomized, double blind placebo controlled study was conducted after Institutional Ethical clearance (SRHU/HIMS/Ethics/2016/85) and written informed consent from 160 patients, either gender, ASA I &II, between 18-60 years of age undergoing elective percutaneous nephrolithotomy (PCNL) under general anesthesia. ASA III & IV patients, significant cardiac disease, high AV Block, renal failure (high serum creatinine >1.5mg/dl, urine output <400/day) or history of urinary tract obstruction/neurogenic/ overactive bladder were excluded from the study. The study was registered retrospectively in Clinical Trial. gov.in (**CTRI/2017/1/007658**).

All eligible patients were kept NPO for solids for six hours and two hours for clear fluid. Tablet alprazolam 0.25mg was administered night before and two hours prior to surgery.The patients were randomized using computer generated table of random numbers into four groups to receive either Tramadol 100mg (Group I) (Cap Supridol: Neon Laboratories, India), or Pregabalin 75mg (Group II) (Cap Lyrica: Pfizer Limited, India), Clonidine 100mcg (Group III) (Tab. Arkamine: Unichem pharma, India) and placebo (Group IV) (empty Capsule). The drugs were dispensed in identical gelatin capsules prepared by pharmacy and supplied in opaque envelopes marked I, II, III, IV to be administered by a nurse in ward one hour before surgery with a sip of water.

Preoperative sedation was assessed by the Ramsay Sedation Scale (RSS) before shifting to OR. Standard anesthesia technique was employed in all the patients after attachment of vital monitors (ECG, NIBP and pulse oximetry) and establishment of intravenous (i.v) access. Anesthesia was induced with fentanyl 2mcg/kg, propofol 1.5mg/kg and vecuronium bromide 0.1mg/kg was used for facilitation of endotracheal intubation. Intubation was completed with appropriate sized cuffed endotracheal tube. Maintenance of anesthesia was done with 66% nitrous oxide in oxygen, sevoflurane (0.8-1.1 MAC) and intermittent boluses of vecuronium and fentanyl. The urethra was lubricated with 2% lignocaine jelly and 16 FG foley's catheter was inserted and inflated with 10 ml normal saline. At the end of surgery neuromuscular blockade was reversed with neostigmine and glycopyrollate in usual doses.

Patients were shifted to PACU where CRBD was assessed on 4 point scale: Grade1: No pain, Grade 2: Mild pain (revealed by asking the patient), Grade 3: Moderate pain (spontaneous complaint by the patient), Grade 4: Sever discomfort(agitation, loud complaints and attempts to remove catheter).The grades were assessed at time of shifting (0 hour),1, 2, 4, 6, 12, 24 hours after shifting. All patients received controlled analgesia with fentanyl (5 mcg/ml) by PCA pump (B. Braun Melsungen AG, Germany) for 24 hours. Total dose of fentanyl used and postoperative complications such as sedation, nausea and vomitting, decreased in

oxygen saturation, hemodynamic variability were noted in PACU.If in the postoperative ward any patient experienced VAS >6 and not relieved with additional boluses of fentanyl injection, paracetamol 1000mg or tramadol 100mg iv was administered and noted.

Sample size was calculated on basis of previous study[1] with incidence of CRBD to be 60%.Considering 25% patients will have decrease in severity of CRBD with power of 95% and α error of 0.05, 39 patients per group were needed to detect significance. We took 40 patients in each group. Data analysis was done utilizing SPSS IBM version 22 (SPSS Software, IBM Corporation Amrok, New York). The normality of numerical variables was tested using the Kolmogorov-Smirnov analysis. Numerical variables with normal distribution are presented as mean ± standard deviation (SD), and median (minimum-maximum) values are applied for non-normally distributed variables. Categorical outcomes were summarized as numbers and percentages. Repeated measures analysis of variance was used to determine within-group changes across time and group-time interactions. A $\chi 2$ test or Fisher's Exact Test was used to assess categorical outcomes among the groups. For discontinuous numerical data, a Kruskal-Wallis Test was done and a Dunn's multiple comparison tests were done to compare among the groups. A P value of <0.05 was considered statistically significant.

Results

160 patients fulfilling the eligibility criteria were included in the study (Fig. 1) between January 2015 and May 2016. All patients completed the study and there were no dropouts. Patients were not different in terms of age, weight, ASA grade, duration of anesthesia (DOA) and surgical time (DOS) (Table 1).

Fig. 1
Consort flow diagram

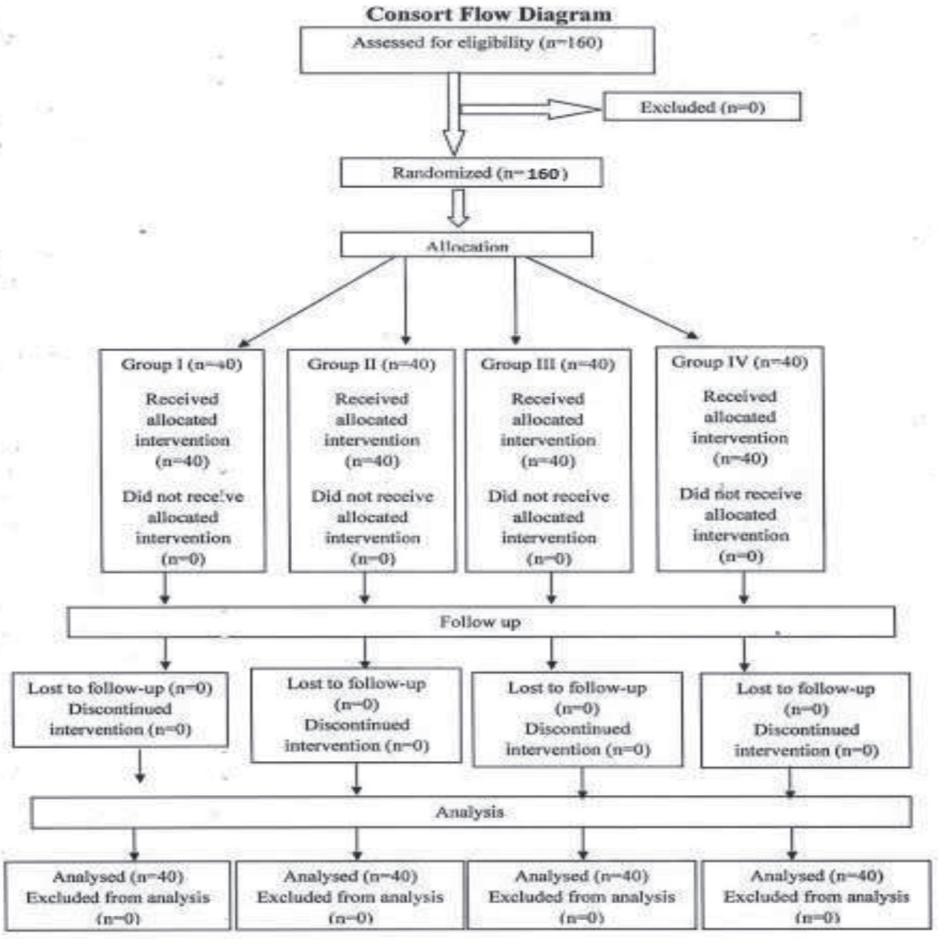


Table 1

Demographic profile, Data Is presented as mean ± Standard deviation or numbers

	Group I (n=40)	Group II (n=40)	Group III (n=40)	Group IV (n=40)	P-value
Age (years)	39.62 ± 11.58	37.18 ± 11.86	35.58 ± 11.89	41.65 ± 11.62	0.105
Sex (M:F)	25:15	23:17	26:14	17:23	0.174
ASA I/II	27/13	24/16	26/14	23/17	
DOA (min)	93.35 ± 41.06	87.70 ± 31.14	93.28 ± 31.59	82.60 ± 29.71	0.425
DO S(min)	81.40 ± 39.45	77.20 ± 31.13	80.15 ± 32.38	69.02 ± 28.74	0.340
Fentanyl requirement	652.66 ± 266.04	685.06 ± 193.03	665.71 ± 169.38	848.38 ± 311.63	0.001*

* Kruskal wallis test delete#, alpha sign

The prevalance of CRBD in different groups is shown in fig. 2. The prevalance was higher in group IV compared to all other groups at all times of observation. There was no difference in incidence of CRBD among groups I, II and III.

Pain as assessed by VAS was also higher in Group IV compared to Groups I, II, III (Table 2).

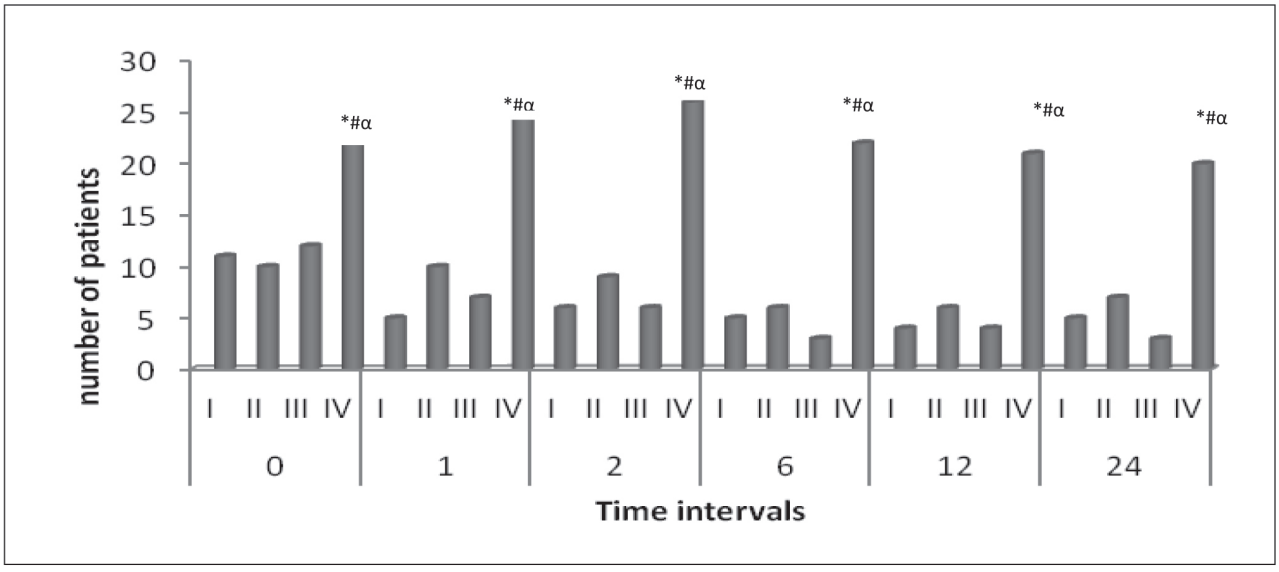
Mean postoperative fentanyl requirement was 652.66 ± 266.04 mcg (Group I), 685.06 ± 193.03 mcg (Group II), 665.71 ± 169.38 mcg (Group III) and 848.38 ± 311.63 mcg (Group IV). The amount of fentanyl used was significantly greater in Group IV ($p < 0.05$) compared to Groups I, II, III respectively. Dosage used in Groups I, II, III were comparable and statistically not significant.

Preoperative Ramsay Sedation Score (RSS) was assessed in all groups. No patient had a score of grade 4 or above. RSS1/2/3 was seen in 3/32/5 patients on Group I, 2/36/2 patients in Group II, 1/35/4 patients in Group III and 18/22/0 patients in Group IV.

Postoperative complications observed are shown in Table 3. Sedation was the most common complication. Three patients in Group IV required additional analgesics for pain control.

Fig. 2

Prevalance of CRBD at different time of Observation



* Group I, # Group II, α Group III $p < 0.05$

Table 2

Intergroup variation in Visual Analogue scale

VAS	Group I (n=40) Median (IQR)	Group II (n=40) Median (IQR)	Group III (n=40) Median (IQR)	Group IV (n=40) Median (IQR)	P-value*
T' 0	2.5 (1.0-3.75)	3.0 (2.0-4.0)*	2.0 (2.0-4.75)	5.0 (3.0-7.0)*#α	**0.003**
T' 1	3.0 (2.0-3.75)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	5.0 (3.0-7.5)*#α	**<0.001**
T' 2	2.0 (1.0-3.0)	3.0 (2.0-3.0)*	2.0 (2.0-4.0)	4.5 (2.25-6.0)*#α	**<0.001**
T' 6	2.0 (1.0-2.0)	2.0 (1.0-3.0)	2.0 (1.0-2.0)	3.0 (2.0-5.0)*#α	**<0.001**
T' 12	1.0 (1.0-2.0)	1.5 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-4.0)*#α	**0.021**
T' 24	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)	2.0 (1.0-3.0)*#	**0.034**

* Group I, # Group II, α Group III p <0.05

Table 3

Post operative complications

	Group I (n=40) Frequency (%)	Group II (n=40) Frequency (%)	Group III (n=40) Frequency (%)	Group IV (n=40) Frequency (%)	P-value
Sedation	28 (70.0%)	26 (65.0%)	28 (70.0%)	19 (47.5%)	<0.001
Hypertension	1 (2.5%)	0 (0.0%)	1 (2.5%)	5 (12.5%)	0.032
Hypotension	2 (5.0%)	1 (2.5%)	3 (7.5%)	1 (2.5%)	0.650
Tachycardia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	0.389
Bradycardia	0 (0.0%)	1 (2.5%)	2 (5%)	0(0.0%)	0.389
Insomnia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Hallucination	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Unpleasant dreams	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Diplopia	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Nausea vomiting	4 (10.0%)	0 (0.0%)	2 (5.0%)	2 (5.0%)	0.291
Respiratory depression	1 (2.5%)	2 (0.0%)	1 (2.5%)	0 (0.0%)	0.124
Delayed Extubation	1 (2.5%)	1 (2.5%)	1 (2.5%)	0 (0.0%)	0.797
Total Paracetamol	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.5%)	0.389
Total Tramadol	2 (5.0%)	2 (5.0%)	0 (0.0%)	2 (5.0%)	0.556

Discussion

Our study demonstrated the effectiveness of preoperative tramadol, clonidine and pregabalin in decreasing the prevelance and severity of catheter related bladder discomfort in the postoperative period.

The bladder receives cholinergic innervation from the pelvic nerves and adrenergic innervation from the hypogastric nerves. It has a heterogeneous population of type 2 and 3 muscarinic receptors. Although M2 receptors predominates in the bladder and modulates detrusor contraction, the subtype M3 receptors are primarily responsible for bladder contraction[20]. Acetylcholine is released by cholinergic nerves supplying bladder and is stimulated by irritation due to urinary catheter, causing muscarinic receptor-mediated involuntary contractions of the detrusor[21]. Inflammatory mediators and calcitonin gene related peptide (CGRP) are also postulated to be responsible for pain and detrusor contraction leading to CRBD. The treatment modalities of CRBD are varied with different mechanism of action ranging from their action on muscarinic receptors, peripheral and central pain modulation and decreased synthesis of prostaglandins.

Tramadol, a synthetic opioid of the aminocyclohexanol group, is centrally acting opioid analgesic with a low affinity for opioid receptors and selectivity for mu receptors and preferentially inhibits serotonin reuptake. It also has inhibitory effect on M1 and M3 muscarinic receptors, thus postulating to be beneficial for CRBD[22].

Pregabalin is an analogue of the inhibitory neurotransmitter GABA, but does not interact with GABA receptors or mimic the actions of GABA. It interacts with an auxiliary subunit (alpha2-delta subunit) of voltage-gated calcium channels[23] thus attenuating depolarization-induced calcium influx at nerve terminals, with a subsequent reduction in the central release of excitatory neurotransmitters (e.g., glutamate, substance P, calcitonin, noradrenaline, gene-related peptide)[24,25]. Peripheral release may lead to the subsequent inhibition of bladder smooth muscle contraction and to decreased amplitude of detrussor contractions. Pregabalin's capacity to suppress the release of excitatory neurotransmitters is probably responsible for its analgesic properties. This analgesic effect may increase the intervals between urgency episodes, helping to augment bladder capacity[26].

Clonidine is a centrally acting selective partial alpha 2 adrenergic agonist that acts as an antihypertensive drug by virtue of its ability to decrease sympathetic nervous system output from central nervous system. Alpha 2 receptors within the spinal cord modulate pain pathways resulting in analgesia[27]. It binds to alpha 2 receptors of which there are three subtypes alpha 2a, 2b, 2c. Alpha 2a produces sedation, analgesia and sympatholysis, alpha 2b mediates vasoconstriction and antishivering. The startle response may reflect activation of alpha 2c. Clonidine stimulates alpha 2 adrenergic inhibitory neurons in medullary vasomotor centre resulting in decrease of sympathetic nervous outflow from central nervous system to peripheral tissues, manifested as peripheral vasodilation and decrease in systemic blood pressure, heart rate and cardiac output.

Our study is different from previous studies in regards to dosage, time and route of administration. Srivastava VK[28] et al in their study on 60 patients undergoing elective spine surgery evaluated the effect of preoperative 150mg Pregabalin with placebo on incidence and severity of CRBD and found a significant decrease in incidence at 0hr, 1hr, 2hrs, and 6hrs.

Two studies[29,30] evaluated the effects of preoperative tramadol 1.5mg/kg iv on the incidence and severity of CRBD and found significant decrease in the incidence of CRBD upto 6 hours of observation, however increased adverse effects like sedation, nausea and vomiting were also noted.

Two studies evaluated the efficacy of dexemedetomidine on postoperative CRBD. Akca B et al evaluated the efficacy of prophylactic 1mcg/kg of dexmedetomidine i.v 5 minutes before the end of surgery[31] whereas Kim HC et al studied effect of intraoperative dexmedetomidine 1.5 mcg/kg loading followed by 0.5 mcg/kg/h infusion on postoperative CRBD[32]. Both the studies reported lower incidence of CRBD as compared to control group.

In our study preoperative use of 75mg Pregabalin decreased the incidence and severity of CRBD at 0h, at 1h, at 2h and at 6h. Our study differed from the previous studies in 2 aspects: firstly the dose of pregabalin used was 75mg as compared to 150mg in the study done

by Srivastava VK et al[28], thus indicating that smaller doses of pregabalin are equally effective in decreasing the incidence and severity of CRBD. Secondly, in our study the incidence of CRBD was lower compared to the above study even though the patients underwent endourological procedures. Compared to the study of Agarwal A et al that used tramadol, our study differed both in doses and route of administration. We found that the incidence of CRBD were approximately equal at time 0h; however the incidence of CRBD were very low at 1h, 2h and 6h being 12.5%,15% and 12.5% respectively in our study as compared to 32%, 28% and 20% in study of Agarwal A et al.

The role of dexmedetomidine has been evaluated, its use was associated with a decrease in the incidence and severity of CRBD[32,33]. Clonidine belonging to same group as Dexmedetomidine has never been evaluated, though the mechanism of action may be different for CRBD. Dexmedetomidine along with its spinal and supraspinal effects has antimuscarinic effects owing to its action on muscarinic type 3 receptors present in bladder. Clonidine on the other hand has no antimuscarinic effect. The effect of clonidine in decreasing CRBD in our study was 30%vs 57.5% at 0h, 17.5%vs 62.5% at 1h, 15%vs65% at 2h and 7.5%vs 55% at 6h and may probably be due to its effect on descending adrenergic system modulating pain relief.

Most of the studies have compared individual drugs with placebo. A wide variation of effects on CRBD between individual drug and placebo was seen. Our study is probably the first study where these three drugs are compared with each other and found to produces comparable results in decreasing CRBD.

Side effects like dry mouth, facial flushing, blurred vision, sedation, PONV on perioperative use of tramadol, pregabalin and clonidine are reported by various authors[9,10]. Agarwal A et al in their study of use of perioperative intravenous Tramadol for CRBD reported side effects as sedation, vomiting and nausea. Similarly Srivastava VK[28] et al reported higher levels of sedation in comparison to control group with the use of pregabalin. In a study by Akca B et al hypotension and bradycardia were the most common side effects in patients receiving Dexmedetomidine[31].

In our study postoperative sedation was the most common complication observed. 12.5% patients in Group IV had hypertension whereas 7.5% patients had hypotension and 5% patients had bradycardia in Group III. 10% patients experienced nausea and vomiting in Group I. Respiratory depression and delayed extubation was observed in 2.5% patients each in Groups I, II and III, while none of the patients experienced insomnia, hallucinations, unpleasant dreams or diplopia in the postoperative period.

In conclusion premedication with Tramadol, Pregabalin and Clonidine is equally effective in controlling catheter related bladder discomfort along with favourable perioperative and postoperative conditions though postoperative sedation may be of a concern.

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