RESEARCH ARTICLE

Assessment of lower urinary tract symptoms among calcium channel blocker-users and its impact on quality of life

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Abstract

Objective: To investigate the prevalence and severity of lower urinary tract symptoms among calcium channel blocker users, and the impact on patients' quality of life.

Methods: The cross-sectional study was conducted at one hospital and 2 community pharmacies in Lahore, Pakistan, from November 2017 to July 2018, and comprised patients using calcium channel blockers. Data was collected using standardised scales to assess lower urinary tract symptoms and quality of life. Data was analysed using SPSS 22.

Results: Of the 410 subjects, 315 (76.8%) were males. The overall median age was 50.84 years, IQR 19 with 126 (30.7%) aged 41-50 years. Of the total, 108 (26.3%) patients were on calcium channel blockers alone, while the rest were taking it in combination with other drugs. Prevalence of lower urinary tract symptoms was 307 (74.9%); mild 103 (25.1%), moderate 201 (49.1%) and severe 106 (25.9%). The symptoms were significantly associated with reduced quality of life ($p<0.05$).

Conclusion: Majority calcium channel blockers users had clinically significant lower urinary tract symptoms which significantly reduced patients' quality of life.

Keywords: Antihypertensive agents, Calcium channel blockers, Lower urinary tract symptoms, Quality of life.
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Introduction

Historically, a number of pseudo-diagnostic terms, like "prostatism", "symptoms of benign prostatic hyperplasia" and "clinical benign prostatic hyperplasia" were used to describe urinary symptoms in men. In 1994, the term "lower urinary tract symptoms" (LUTS) was introduced to label patient complaints without implying their cause.[1] LUTS are classified into three groups of symptoms, namely voiding which is marked by weak stream, splitting/spraying, intermittent stream, hesitancy, straining and terminal dribble, storage which is marked by increased daytime frequency, nocturia, urinary urgency and incontinence, and post-micturition symptoms, like post-micturition dribble and feeling of incomplete bladder emptying.[2] These symptoms are emotionally distressing,[3] socially isolating for the patient and increase economic burden on society.[4] Published data advocates that several diseases and conditions,[5] surgeries or operations[6] and medications can contribute to LUTS.[7,8] Calcium channel blockers (CCBs) are among the perpetrators that contribute to LUTS. The blockade of L-type voltage-dependent calcium channels in detrusor urinae muscles impedes bladder contraction,[9-11] increases time to reach maximal bladder pressure, and decreases power of contraction, maximal emptying rate, and rate of bladder-filling that result in LUTS.[12] A recent systematic review indicated that there was scarcity of information related to LUTS among CCB users and its impact on the quality of life (QOL).[13] The current study was planned to evaluate the prevalence and severity of LUTS among CCB users and its impact on patients' QOL.

Patients and Methods

The cross-sectional study was conducted at the Punjab Institute of Cardiology (PIC) and 2 community pharmacies in Lahore, Pakistan, from November 2017 to July 2018. After approval from the ethics review committees of PIC and the Punjab University College of Pharmacy, University of Punjab, Lahore, the sample size was calculated using G*Power 3[14] calculator while keeping statistical power (1 - β) 80%, alpha value <0.05, effect size 0.32 and allocation ratio 3. Keeping in view potential biases and erroneously filled-out questionnaires, the sample was duly enhanced. The sample was recruited using convenience sampling method by approaching all adult patients on CCB therapy attending/visiting the study settings. Trained investigators explained the objectives and nature of the study to the prospective subjects and invited them to participate in it. Those who gave consent were inducted. Those who refused to participate, or were non-adults, or

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could not converse in Urdu, or were critically ill and, were catheterised, suffering from urinary tract infections (UTIs), prostatic diseases, urolithiasis and neurological diseases affecting urination were excluded.

The prevalence and severity of LUTS were evaluated using the Urdu version of the International Prostate Symptom Score (IPSS-Urdu) which is a valid and reliable non-gender-specific instrument to assess the frequency and severity of LUTS in Pakistani population.[15] It consists of seven questions regarding LUTS and one QOL (IPSS-QOL) question. Each symptom was measured and scored 0-5, where 0 = not at all; 1 = seldom; 2 = sometimes; 3 = often; 4 = usually; and 5 = almost always during the last month. The scores of individual symptoms were added to form a symptom score index ranging 0-35. The total symptom score (TSS) was stratified into three categories; mild 0-7, moderate 8-19 and severe 20-35. Individuals with TSS ≥ 8 were considered as having LUTS.

The operational definition of storage symptoms was score ≥4 (range 0-15) for the three questions on frequency, urgency and nocturia. Voiding symptoms were defined as score ≥5 (range 0-20) for four related questions.[16] The QOL index was obtained by scoring from 0 = delighted to 6 = terrible. Physician or clinician-assigned diagnoses were used to record the diseases/illnesses suffered by the patient.

Patients' QOL was assessed by the Urdu version of EurQol-5-dimension-3-level (EQ-5D-3L) which was provided by the EurQol group on researcher's request.[17] The EQ-5D-3L comprises of EQ-5D description system and the EQ visual analogue scale (EQ-VAS). The EQ-5D-3L descriptive system has 5 dimensions, namely mobility, self-care, usual activities, pain discomfort and anxiety/depression. Each dimension is divided into three levels of perceived problems; no problem, some problem and severe/extreme problem. The EQ-VAS records the respondent's self-rated health on a vertical VAS where the endpoints are labelled 'best imaginable health state' and 'worst imaginable health state'.[17]

Data was analysed using SPSS 22. Kolmogorov-Smirnov test and Shipiro-Wilk test indicated non-normal distribution of continuous variables. Therefore, median (25th and 75th percentile) values were used to present continuous variables, whereas categorical variables were presented as frequencies and percentages. Mann-Whitney U test and Kruskal-Wallis H test were used to assess the significance of continuous variables, whereas categorical variables were compared using chi-square test. Binary logistic regressions were performed to determine all the factors associated with moderate-severe (IPSS ≥8) and severe LUTS (IPSS ≥20). Covariates used for regression models were age, gender, smoking, duration of hypertension (HTN), co-morbidities, CCB user categories, and duration of CCB use. P<0.05 was considered statistically significant.

Results

Of the 756 individuals approached, 455 agreed to participate. The final sample stood at 410 with adequate data. Of the 410 subjects, 315 (76.8%) were males. The overall 50.84 years (IQR 19), with majority 126 (30.7%) aged 41-50 years. Of the total, 108 (26.3%) patients were on CCBs alone, while the rest were taking it in combination with other drugs (Table-1).

Frequency of LUTS in the study sample was 307 (74.9%); mild 103 (25.1%), moderate 201 (49.0%) and severe 106 (25.9%). Storage symptoms [312 (76.1%)] were more common than voiding [281 (65.8%)]. The most common troublesome symptom was nocturia [367 (89.5%)], followed by increased daytime urinary frequency [357 (87.1%)].

Table-1: Patient characteristics.

Variables	N (%)
Age (years)	
< 40	92 (22.4)
41-50	126 (30.7)
51-60	89 (21.7)
61-70	80 (19.5)
> 70	23 (5.6)
Gender	
Male	315 (76.8)
Female	95 (23.2)
Economic Status	
Lower class	164 (40.0)
Middle class	201 (49.0)
Upper class	45 (11.0)
Smoking	
Never smoker	190 (46.3)
Current smoker	151 (36.8)
Former smoker	69 (16.8)
Co-morbidities	
Diabetes	66 (16.1)
Dyslipidemia	179 (43.7)
Cardiovascular disease	257 (62.7)
PUD/GERD	19 (4.6)
Gout/arthritis	10 (2.4)
Medications	
CCB alone	108 (26.3)
CCB + beta-blockers	72 (17.6)
CCB + diuretics	36 (8.8)
CCB + RAAS inhibitors	65 (15.9)
CCB + beta-blockers + diuretics	29 (7.1)
CCB + beta-blockers + RAAS inhibitors	62 (15.1)
CCB + RAAS inhibitors + diuretics	22 (5.4)
CCB + beta-blockers + diuretics + RAAS inhibitors	16 (3.9)

CCB: Calcium channel blockers; GERD: Gastroesophageal reflux disease; PUD: Peptic ulcer diseases; RAAS: Renin angiotensin aldosterone system.

Table-2: Description of urinary condition-specific and overall health-related quality of life scores.

	IPSS-QOL index		EQ-5D index			EQ-VAS	p value
	Mean rank	p-value	Median	25th percentile	75th percentile	Mean rank	
Severity of LUTS							
None-mild (IPSS ≤ 7)	156.76	< 0.001	0.796	0.291	1	228.51	0.022
Moderate-severe (IPSS ≥ 8)	221.85		0.416	0.082	0.725	197.78	

LUTS: Lower urinary tract symptoms; EQVAS: EuroQol visual analogue scale; IPSS: International Prostate Symptom Score; QOL: Quality of life. EQ-5D: EuroQol 5 dimensions.

In multivariate regression analysis, longer duration of hypertension (≤1 year: 1.00 [reference]; >1-5 years: odds ratio [OR] 6.65, p<0.001; >5-9 years: OR 12.24, p<0.001; ≥10 years: OR 6.08, p=0.005] and cardiovascular disease: OR 2.38, p=0.009) were associated with higher odds of moderate-severe LUTS. However, in multivariate analysis for severe LUTS, in addition to cardiovascular disease (OR 2.93, p=0.004), combinations of CCBs with other antihypertensive drugs (CCB alone: 1.00 [reference]; CCB + beta-blockers: OR 3.64, p=0.008; CCB + diuretics: OR 5.04, p=0.003; CCB + renin angiotensin aldosterone system [RAAS] inhibitors: OR 2.67, p=0.059; CCB + beta-blockers + diuretics: OR 7.59, p<0.001; CCB + beta-blockers + RAAS inhibitors: OR 4.65, p=0.002; CCB + RAAS inhibitors + diuretics: OR 2.34, p=0.209; CCB + beta-blockers + diuretics + RAAS inhibitors: OR 4.40, p=0.028) were associated with increased likelihood of severe LUTS. Patients with moderate-severe LUTS reported significantly worse QOL in all dimensions compared to those with none-mild LUTS (p<0.05). EQ-VAS, EQ-5D index and IPSS-QOL index reconfirmed the findings (Table-2).

Discussion

There was a high prevalence of LUTS among CCB users which was associated with significant QOL worsening. Overall 75% prevalence of LUTS in the current study was similar to that noted in a previous study.[18] Also, similar to the findings of earlier studies,[19-21] storage symptoms were more prevalent than voiding symptoms, and the most common troublesome symptoms were also comparable.[18] Regarding the severity of LUTS among CCB users, the findings were also comparable to results of an earlier study.[18] Contrary to the results of a Elhebir and colleagues,[18] there was no significant difference in LUTS prevalence among male and female CCB users. This was noted by a systematic review as well.[22] No significant differences of LUTS were observed among dihydropyridine (DHP) and non-DHP (NDHP) CCB users in the current study. A study,[18] however, reported that NDHP were more likely to cause LUTS than DHP. Since the number of NDHP users in that study was low (n=11), further investigations are required to assess the role of NDHP in LUTS.

In the present study, no patient was prescribed lercanidipine, whereas 1 patient was prescribed felodipine, therefore we were not able to examine the impact of highly vascular selective CCB on LUTS. A previous study revealed that felodipine and lercanidipine were less likely to have an impact on LUTS compared to amlodipine, nifidipine, diltiazem and verapamil.[18] The authors commented that 'high vascular selectivity of both felodipine and lercanidipine appeared to be associated with lower bladder selectivity'.[18] Another study[23] reported that lercanidipine had 177 times higher selectivity to aorta than bladder. Elhebir et al.[24] revealed that a significantly higher proportion of CCB users took treatment for LUTS comparable to non-users. By contrast, only 5 patients were prescribed alpha-antagonists treatment for their urinary symptoms in the current study.

EQ-5D index is used to represent an individual's health state and it ranges from 1.000 to 0.594. A value of 1.000 (health state 11111) reflects no problem in all 5 dimensions of EQ-5D, whereas -0.594 (health state 33333) reflects severe problems in all dimensions.[25] In the present study, median EQ-5D index of the study participants was 0.621. Moreover, median (25th and 75th percentile) EQ-5D index of patients with non-mild and moderate-severe LUTS were 0.796 (0.291 and 1.000) and 0.416 (0.082 and 0.725), respectively. This indicated that patients with moderate-severe LUTS had poor QOL than those with non-mild LUTS, which was similar to earlier findings.[21,24] Despite significantly worsened QOL due to urinary symptoms in the present study, patients were reluctant to visit and seek medical advice from urologists considering it a normal aging-related phenomenon. Inappropriate health-seeking behaviour may also be due to the perceived stigma associated with these symptoms. A study[26] reported that emotions related to urinary symptoms were feeling embarrassment, despair, fear, anxiety and apprehension about future, about its worsening and about leaving the home. These findings indicate that urinary symptoms are emotionally distressing and socially isolating, and, therefore, earlier identification and management need to be ensured. Moreover, patients need to be counselled about notifying their healthcare providers if they notice urinary symptoms or any other adverse effects so that appropriate measures can be taken in order to improve every domain of QOL. It is recommended that the ageing

population must be educated regarding the conservative measures, such as bladder training, bladder reflex triggering, bladder expression, pelvic floor muscle exercises, and diet and fluid intake management to help resolve mild urinary symptoms affecting their daily activities.

The current study has some limitations as it used IPSS-Urdu to evaluate LUTS which lacked any item to assess urinary incontinence, and, therefore, the prevalence and types of urinary incontinence were not determined. Moreover, only one patient was taking highly vascular CCB and that was not enough to compare LUTS between highly vascular CCB users and other CCB users. Also, convenience sampling was used which is a non-probability technique, and has shortcomings, such as selection bias and under or over-representation of population. A large urodynamic study among CCB users is recommended to provide a clear picture of CCB involvement in LUTS.

Conclusion

Around three quarter of CCB users suffered from LUTS, with multiple factors contributing to it. Moreover, LUTS had significant adverse impact on patients' overall QOL.

Disclaimer: The text is based on a PhD thesis.

Conflict of Interest: None.

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