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Title:

Does successful treatment of urinary urgency improve comorbidities in patients with nocturia?

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Does successful treatment of overactive bladder improve comorbidities in patients with nocturia?

Abstract

Objective: To investigate whether treatment of overactive bladder (OAB), one comorbidity of nocturia, could reduce waking to void and improve other co-existing symptoms.

Methods: A prospective cohort study was conducted at Royal Melbourne Hospital. Participants received 12 weeks of standard treatment, including lifestyle interventions and pharmacotherapy. Outcome measures were nocturia episodes, severity of urinary urgency/incontinence, sleep quality, daytime somnolence, anxiety and depression scores, quality of life and change in blood pressure.

Results: 20 participants completed the study. Nocturia frequency improved by one void per night. OABSS, sleep quality, first uninterrupted sleep time and systolic blood pressures improved. There were no significant changes in daytime somnolence, mood or quality of life.

Conclusion: In this pilot study, nocturia and other co-morbid dysfunctions appeared to improve when the severity of OAB was reduced. Treatment of OAB co-morbid with nocturia reduces urinary symptoms and may improve sleep parameters and positively impact return to health.

MeSH Keywords

Nocturia, Urinary urgency, Overactive bladder, Sleep disturbance

Introduction

Nocturia is defined by the International Continence Society (ICS) as “the symptom of waking at night to pass urine” [1]. Nocturia occurs when urine produced during the night (i.e. nocturnal urine volume) exceeds the individual’s maximal bladder storage volume. Nocturnal polyuria, traditionally defined as more than 33% of the total 24-hour urine volume produced overnight, is one of the most frequent causes of nocturia in adults, especially in the older population [1-4]. Nocturnal polyuria is associated with osmotic diuresis or disruption in nocturnal arginine vasopressin levels, being seen with conditions such as congestive cardiac failure, hypertension, chronic kidney disease and obstructive sleep apnea [2-4]. For example, extravascular fluid retention in the lower limbs redistributes centrally during the night leading to expansion of the intravascular volume and increased nocturnal urine production [2].

Overactive bladder (OAB) is defined by the ICS as “urgency, usually with frequency/nocturia, with or without urgency incontinence”. [4] OAB patients usually have reduced bladder capacity due to detrusor overactivity; benign prostatic obstruction, bladder pain syndrome and the use of medications can also underlie nocturia [2, 4]. Historically nocturia was considered to be the night presentation of OAB, on the basis that up to 96% of patients with OAB experience nocturia [5].

Apart from OAB, nocturia is independently associated with cardiovascular morbidities, including hypertension, cardiovascular disease and stroke [6]. Nocturia is also a common symptom in endocrine disorders, such as diabetes mellitus. Failure to lower blood pressure during sleep (or non-dipping), possibly attributed to autonomic neuropathy, is a frequent feature in diabetic

patients [7]. Conditions that lead to sleep disturbances such as obstructive sleep apnea, insomnia, and chronic pain, are frequently associated with nocturia, as are psychiatric disorders and dopamine-related diseases [4-5].

Apart from its association with multiple comorbidities, nocturia independently predicts an increased risk of mortality [2, 8-10]. The association is stronger below 65 years of age; more nocturia episodes are associated with a higher mortality risk [8]. A longitudinal cohort study also reported that nocturia of two or more voids per night significantly increased fracture risk and mortality rate over five years [9].

Nocturia is clearly more than just a lower urinary tract symptom (LUTS) [2, 11-12]. Despite its multiple negative consequences, it is often unreported by patients and under-recognised by clinicians [2, 4]. The causality of nocturia is often multifactorial, especially in the older population. There are bi-directional associations between nocturia and many co-morbid symptoms indicating that a therapeutic option that targets only a single causal pathway of nocturia may constitute suboptimal management [11-12]. Little evidence is available to guide clinicians in managing the different symptoms that interact with nocturia.

The aim of this pilot study was to investigate whether treatment of OAB, one comorbidity of nocturia, could reduce waking to void and improve other co-existing symptoms. This qualitative study aimed to quantify changes in nocturia severity and other comorbidities in patients who received standard treatment for OAB.

Methods

This prospective cohort study was performed at the Continence Service at the Royal Melbourne Hospital, Parkville, Victoria. This study has received ethical approval from the Melbourne Health Human Research Ethics Committee (HREC number LNR/17/MH/96). Study methods are illustrated in Figure 1.

All patients who attended the Continence Service between April and September 2017 were screened for the presence of nocturia. Inclusion criteria included ≥ 40 years of age and seeking treatment for urinary urgency/incontinence. Nocturia was defined as having to wake up once or more to void at night. Exclusion criteria included current urinary tract infection, end of life care, terminal malignancies, end-stage renal disease, bladder cancer, previous pelvic radiotherapy, pregnancy, urinary catheterisation and dementia or cognitive impairment that precluded accurate completion of the study questionnaires and diaries. Participants who were not able to complete questionnaires in English were also excluded from the study.

Verbal and written informed consents were obtained from eligible participants. Prior to commencement of medication, the following baseline data were collected: demographic information, TANGO (Targeting the Aetiology of Nocturia to Guide optimal Outcomes) screening tool [11], Overactive Bladder Symptom Score (OABSS) [13], Nocturia-specific Quality of Life instrument (NQoL) [14], Epworth Sleepiness Scale (ESS) [15], Pittsburgh Sleep Quality Index (PSQI) [16], Hospital Anxiety and Depression Scale (HADS) [17] and EuroquoL-5D-5L Health Questionnaire (EQ-5D-5L) [18]. Night pain was self-rated as part of PSQI questionnaire. Participants completed a two-day bladder diary (frequency-volume chart) that captured daytime urinary frequency, nocturia frequency, maximum daytime void, average daytime void, day and night diuresis rates, nocturnal urine volume, total urine volume and nocturnal polyuria index (NPI). Participants also wore an actigraph (a watch-like arm band) to detect sleep, waking and movement over a three-day period. Postural blood pressures were collected and used as a marker of autonomic function.

Participants received standard second-line treatment for OAB, either an anticholinergic agent or a beta-3 adrenergic agonist (mirabegron) to inhibit urinary urgency or urgency incontinence. The choice of medication prescribed was determined clinically by a number of factors, including potential side effects, previous response to medications, cost and cognitive function. Intervention also included routine first-line standard care, specifically lifestyle advice, fluid modifications, bladder training and bowel management. An extra surveillance visit was conducted either in clinic or by telephone call at week 3-4 to monitor for any side effects and to up-titrate medication if clinically indicated. The maximum dose for each participant reflected dose titration according

to clinical response. All participants were reviewed by treating clinicians at week 11-12 as per standard care, at which time all study measures were repeated. Standard clinical care continued after completion of the study.

Primary outcome measures were number of nocturia episodes per night and severity of urinary urgency/incontinence. Secondary outcome measures were sleep quality, daytime somnolence, anxiety and depression scores, quality of life and changes in blood pressure. Participant adherence was assessed using self-completed questionnaire at the end of the study.

Results

A total of 20 participants, mean age of 65 (SD 13.5), completed the study. Participant characteristics are summarised in Table 1.

This relatively healthy and young cohort had a mean health status on EQ-5D-5L of 74/100 (SD 16.7) at baseline (0-100 with higher value indicating better quality of life), with no or only slight problems (scores 1-2) with mobility, usual activities, pain and mood. The cohort reported a moderate presentation of overactive bladder symptoms (OABSS of 9/15; SD 2.9). Nocturia-specific quality of life (NQoL) was 19/52 (SD 10.4), indicating a mild-to-moderate impact of nocturia on quality of life (0-52 with higher value indicating greater impact on quality of life).

The cohort reported poor sleep quality (mean global PSQI score 9/21; SD 4.2), although 65% of participants reported no significant daytime somnolence (ESS<10) with an overall average ESS score of 8/24 (i.e. the majority of the participants had normal ESS score at baseline). Two-thirds of participants had normal anxiety and depression scores based on the HADS data.

Using the TANGO nocturia causality screening tool, 79%, 63% and 58% of the participants reported concurrent symptoms in sleep, cardiovascular/metabolic and wellbeing domains respectively. Only one participant in the study complained solely of LUTS. From bladder diary data, 63% of the participants demonstrated nocturnal polyuria (i.e. $\geq 33\%$ of total urine volume produced during sleep).

Three-quarters of the participants received an anticholinergic agent whilst the other participants were prescribed mirabegron (see Supplementary Table 1). At the end of the study, 78% of study participants reported full medication compliance; 15% indicated that they had missed one-to-three doses of medication. Only one participant had missed more than three doses of medication. Eighty percent of the participants who received anticholinergic agent experienced side effects, the most common one being dry mouth, compared to 20% of the mirabegron group (see Supplementary Table 1).

Outcome measures are reported in Table 2. As expected, after three months of standard therapy, the severity of urinary urgency and urge incontinence was reduced as measured by the OABSS. Both mean maximum and average daytime voids increased by 39ml and 18ml respectively (see Supplementary Table 3). Nocturia frequency, as measured on frequency-volume chart, improved by one void per night post-intervention. Overnight urine production reduced from 697ml to 573ml. The percentage of participants with nocturnal polyuria dropped from 63% to 56%. Average NPI also reduced from 38.6% to 36.3% but remained clinically relevant post-treatment.

The mean time to first nocturia or first uninterrupted sleep time (FUST) as recorded by sleep diaries improved by one hour, from 3.0 hours (SD 1.2) to 4.0 hours (SD 1.6) post-intervention. This increase correlated with better sleep quality with an average of two-point improvement as measured by the PSQI. PSQI subdomain scores are presented in Supplementary Table 4.

The mean total NQoL score reduced from 19 (SD 11) to 15 (SD 9) post-intervention. Night pain did not change (see Supplementary Table 4). Average self-perceived health status on EQ-5D-5L increased by three points. Forty-four percent of the participants reported worse or similar scores on wellbeing measures post-intervention. No significant changes were noted in anxiety or depression following intervention.

Mean systolic blood pressure did not change for the whole cohort. However, in participants with hypertension (SBP>140mmHg) at baseline, there was a clinically significant reduction in mean systolic blood pressure from 167mmHg (SD 17) to 140mmHg (SD 8) post-intervention.

Diastolic blood pressures increased post-treatment. Only one participant demonstrated postural hypotension at baseline.

Discussion

This is the first study to investigate the effects of OAB treatment on other symptoms co-morbid with nocturia. We demonstrated positive results in nocturia patients when treating OAB, specifically improvement in nocturia severity, sleep quality, duration of slow wave sleep and systolic blood pressure. Given the multiple potential underlying pathophysiologic mechanisms for nocturia, we would advocate for clinicians to perform a comprehensive all-cause assessment when managing patients with nocturia. In this study we used TANGO, a multidisciplinary screening metric developed to capture multiple and co-existing variables that may be contributing to nocturia [11]. In the study cohort, the TANGO screening tool indicated that around 95% of the study participants reported at least one other co-morbid symptom aside from OAB, highlighting the multiple potential causes of participants' nocturia.

In our study, we implemented standard clinical care for patients with OAB, including lifestyle modifications as well as pharmacotherapy. As expected after three months of standard therapy, OAB treatment resulted in less nocturia and improved OABSS. Treatment of OAB with an anticholinergic agent or beta-3 adrenergic agonist promotes detrusor muscle relaxation, and thereby increases bladder capacity. Nocturia frequency may improve as a result of larger functional bladder capacity. This change was reflected in greater maximum and average daytime voids post-intervention. Our result of an average change of one less void per night was comparable to previous study using targeted pharmacotherapy such as desmopressin [19]. This seemingly trivial improvement from two to one nocturia episode might be easily dismissed by patients and clinicians, but may reduce the risks of fracture and mortality longitudinally [8-9].

Previous studies have consistently demonstrated a close relationship between nocturia and sleep [20-21]. Interrupted sleep due to nocturia has been linked to fatigue, decreased concentration, lower performance at work and increased risk of accidents [22]. Time to first nocturia episode,

quantified as first uninterrupted sleep time (FUST), is an important predictor in perceived sleep quality [23-24]. Deep sleep, or restorative slow-wave sleep (SWS), predominates in the first three-to-four hours of sleep [20]. Disruption of deep sleep, for instance by nocturia, is likely to have a greater negative impact on sleep quality and general wellbeing than waking up during rapid eye movement (REM) or light sleep [20, 24]. In our study, OAB treatment increased FUST, suggesting that participants were more likely to wake up during light sleep than deep sleep, which might subsequently lead to better overall health and quality of life. We also observed improved sleep quality as measured on PSQI. Participants took less time to fall asleep, had longer duration of restorative SWS and reported better subjective sleep quality.

Patients with OAB often present with mood disorders such as anxiety and depression, which may be a cause or effect of their urinary tract symptoms [25-26]. In our study, only a small number of participants (n=7) reported anxiety or depression at baseline and OAB treatment did not have a significant impact on mood.

Nocturia is a bothersome symptom and a marker of poor health [2]. Our study cohort had relatively good quality of life at baseline with a relatively low NQoL score and high EQ-5D-5L health status. An average reduction of one nocturia episode was associated with a four-point improvement on total NQoL score and three-point increase on EQ-5D health score. However these changes on wellbeing measures were unlikely to be clinically relevant. In our study, despite improvements in urinary symptoms and sleep quality, a large proportion of participants did not report better overall health. This might be partly attributed to the undesirable anticholinergic side effects experienced by some of the participants prescribed with anticholinergics. For example, dry mouth, a common side effect of anticholinergic agents, might have triggered increased fluid intake, resulting in urinary frequency and nocturia. High anticholinergic burden is known to be associated with poor health-related quality of life, especially in older people [27]. EQ-5D-5L as a general and non-specific measure of wellbeing could also be affected by other medical and psychosocial issues, which were not investigated in this study.

The effect of OAB treatment on blood pressure was small but clinically significant in this study. In a very small number of participants who had hypertension at baseline (n=3), systolic blood

pressures, but not diastolic blood pressures, almost normalised after three months of OAB treatment. Nocturia is commonly associated with hypertension but the underlying mechanism is not completely understood [3, 6, 28]. Previous study has suggested that hypertension causes glomerular hyperfiltration inducing nocturia [28]. Diuretics used to treat hypertension can also produce nocturia if taken in the evening. The important relationship between nocturia and blood pressure has also been reported in other study, which found systolic blood pressure as an independent and potent determinant of nocturia [29]. The positive result we observed in this study is potentially clinically relevant as hypertension is prevalent in the older population and is associated with potential end-organ damage [28-29]. However, given the very small number of participants, careful interpretation of this result is strongly recommended. In addition, the effect of “white coat hypertension” at baseline cannot be ruled out.

In contrast, we observed an increase in diastolic blood pressures, despite the readings being within normal limits at baseline and post-intervention. An uncommon adverse effect of mirabegron is elevated blood pressure, a rise reported to be less than 1mmHg, as opposed to an average of 9mmHg increase in this study [30]. Elevation in diastolic blood pressure was observed in participants on both anticholinergic agent as well as beta-3 agonist, and therefore would be unlikely to be related to mirabegron.

Limitations

The primary limitation of this non-randomised pilot study was the small number of participants. Twenty-five participants were recruited but only 20 of them completed the study, which may have resulted in the study being under-powered. The multifactorial endpoints therefore could not be statistically tested due to high standard error and chances of a false positive that include the possibility of multiple comparison issues. Hence we have treated this as a pilot hypothesis-generating study. Future investigations would be done on a much larger cohort of patients in a randomised setting with comparators, including suitably selected control group.

Bladder diaries completed over 24-72 hours by all participants were a fundamental source of diagnostic and efficacy data. These metrics are well known to be problematic and poorly

completed. Our participants completed the initial diary on 95% of occasions and the post-treatment metric 80% of the time. This is one of the first studies to use actigraphy as a source of outcome data. The logistics of capturing data in this manner was more cumbersome than expected, patients were less technologically savvy than anticipated, and the data extraction from devices was time consuming. For these reasons, the FUST variable was calculated from sleep diaries. Adherence was satisfactory overall with 95% of study participants reporting at least 96% medication compliance; suboptimal medication compliance in a small number of participants is likely to be related to medication side effects.

This was a single-centre study of relatively young and healthy individuals, and therefore might not accurately reflect the general older population with more severe nocturia. As per standard practice in treating OAB, study participants were commenced on two different medications with distinct side effect profiles and cost implications. This may have influenced wellbeing measures.

Conclusion

In this pilot cohort study, nocturia and other co-morbid dysfunctions appeared to improve when the severity of OAB was reduced, indicating clinically-relevant inter-relationships between multiple medical conditions on the causal pathway to nocturia. There were positive effects on nocturia severity, sleep quality, duration of slow wave sleep and systolic blood pressure, when OAB was treated. We suggest that it is important for clinicians to recognise the inter-relationships between co-morbidities and to assess actively for the breadth of causes of nocturia. Unfortunately many patients do not mention the symptom to their doctor and the belief persists that nocturia is a normal part of ageing that cannot be resolved. Targeted treatment of OAB co-morbid with nocturia may improve urinary symptoms and other co-existing dysfunction across body systems.

Impact Statement

Nocturia is a marker of poor health. Treatment of urinary urgency appeared to reduce urinary symptoms and may improve other symptoms which frequently occur with nocturia, including sleep quality and duration of restorative sleep.

Abbreviations

BP	Blood pressure
EQ-5D-5L	Euroquo1-5D-5L Health Questionnaire
ESS	Epworth Sleepiness Scale
FUST	First uninterrupted sleep time
HADS	Hospital Anxiety and Depression Scale
LUTS	Lower urinary tract symptom
NPI	Nocturnal polyuria index
NqoL	Nocturia-specific Quality of Life Instrument
OAB	Overactive bladder
OABSS	Overactive Bladder Symptom Score
PSQI	Pittsburg Sleep Quality Index
REM	Rapid eye movement
SBP	Systolic blood pressure
SD	Standard deviation
SWS	Slow wave sleep
TANGO	Targeting the Aetiology of Nocturia to Guide optimal Outcomes

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Tables

Table 1: Participant characteristics (n=20)

Age (mean+/-SD), years	65 +/- 14
Gender (n, %)	
Female	13 (65)
Work (n, %)	
Retired	10 (50)
Employed	4 (20)
Disability pension	4 (20)
Unemployed	1 (5)
Homemaker	1 (5)
Living situation (n, %)	
Alone	4 (20)
Lives with others	16 (80)
CPAP for OSA (n, %)	
Yes	1 (5)

Table 2: Variables pre and post-intervention[#]

	Baseline	End of study	95% CI
LUTS			
Nocturia frequency, median (IQR)	2.0 (1.0-3.0)	1.0 (1.0-2.0)	0.5, 1.5
OABSS total score	8.8+/-3.0	6.8+/-3.1	0.8, 3.3
SLEEP			
First uninterrupted sleep time (FUST), hours	3.0+/-1.2	4.0+/-1.6	-1.6, -0.3
ESS score	8.1+/-6.1	8.3+/-5.2	-1.9, 1.5
PSQI total score	8.6+/-4.2	6.7+/-3.0	0.3, 3.6
MOOD			
HADS Anxiety score, median (IQR)	5.0 (3.3-9.8)	3.0 (1.0-10.0)	-3.0, 1.0
HADS Depression score, median (IQR)	4.0 (1.3-8.8)	4.0 (2.0-7.0)	-1.5, 1.0
WELLBEING			
NQoL total score	19.2+/-10.7	15.4+/-9.4	-1.1, 8.7
EQ-5D-5L health score, median (IQR)	80.0 (61.3-88.8)	82.5 (58.8-90.0)	-2.5, 7.0
BLOOD PRESSURE (BP)			
Systolic BP			
-All patients	129+/-25	130+/-17	-13, 12
-Baseline SBP>140mmHg	167+/-17	140+/-8	5, 49
Diastolic BP, median (IQR)	65 (59-75)	74 (63-80)	-1, 11

Results presented as mean (SD) unless otherwise stated. Statistical tests utilized: Paired T-Test; Wilcoxon Signed Rank Test.

^ Less than 50% of the participants had pre and post-intervention data for these variables.

Figure

Figure 1: Study methods

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Figure

Figure 1: Study methods

