TITLE PAGE

Efficacy of Non-Drug Lifestyle Measures for the Treatment of Nocturia

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ABSTRACT

Purpose: Nocturia has a major impact on quality of life and affects numerous aspects of health. Lifestyle modifications are expected to be helpful in improving nocturia; however, the efficacy of this strategy has not been established. The aim of this study is to test the efficacy of non-drug lifestyle measures as a first step to treat nocturia and to find factors predictive of the efficacy of the intervention.

Materials and Methods: We conducted a prospective evaluation on 56 patients treated at three hospitals between 2005 and 2009 for symptomatic nocturia. The patients were advised to modify their lifestyle in order to improve nocturia. Lifestyle modifications consisted of four directives - restriction of fluid intake, refraining from excess hours in bed, moderate daily exercise and keeping warm in bed. The frequency volume chart, International Prostate Symptom Score and Pittsburgh Sleep Quality Index before and 4 weeks after the intervention were used to evaluate the efficacy of the therapy.

Results: The mean number of nocturnal voids and the nocturnal urine volume significantly decreased from 3.6 to 2.7 ($p < 0.0001$) and from 923 ml to 768 ml ($p = 0.0005$), respectively. Of the 56 patients, 26 (53.1%) showed an improvement of more than one episode. This treatment was significantly more effective in patients with a larger amount

of 24 h urine production.

Conclusions: Non-drug lifestyle measures were effective in reducing the number of nocturia episodes and improving patients' quality of life. Patients with polyuria showed a better response to the treatment.

Introduction

Nocturia has a major impact on quality of life, affecting numerous aspects of health, contributing to fatigue, memory deficits, depression, increased risk of heart disease, and gastrointestinal disorders.[1-4] Nocturnal or global polyuria, reduced nocturnal bladder capacity and sleep disturbance are the possible causes of nocturia.[5,6] Medical therapy with anticholinergic agents, desmopressin and time release diuretics is often considered as first line treatment depending on the diagnosis and underlying cause; however, medication has a potential risk of adverse events and would also cause problems with national medical expenditures as the number of patients increase as a result of aging of the population. Lifestyle modifications such as fluid restriction and sleep enhancement are expected to be helpful,[1,2,7] but effectiveness of this strategy has not been established. The aim of this study was to test the efficacy of non-drug lifestyle measures as a first step to treat nocturia. We also sought to find factors predictive of the efficacy of the intervention.

Materials and methods

Of the patients who visited our outpatient clinic with a chief complaint of nocturia, those with nocturnal frequency of two or more voids were enrolled in this study. Exclusion criteria were post void residual volume of more than 50 ml, untreated urogenital malignancies or renal, cardiac or hepatic failure. The patients who strongly sought medical treatment were also excluded.

After completing a 72 h frequency volume chart (FVC), the patients were advised to modify their lifestyle in order to improve nocturia. Lifestyle modifications consisted of four directives - restriction of fluid intake, refraining from excess hours in bed, moderate daily exercise and keeping warm in bed. We paid attention to avoiding imposing too strict measures on the patients, and gave them an explanatory brochure to aid their understanding of the procedure. **In the brochure we said, "Examples of lifestyles that can be associated with nocturia are listed below. If you think one or more are applicable to you, please follow the appropriate recommendations." For fluid restriction, we instructed the patients that daily fluid intake of 2% of the body weight (i.e., 1000 ml for a person weighing 50 kg) is enough. We also told patients to restrict fluid in particular in the evening and to avoid excess alcohol or caffeine intake. Secondly, we explained that the patients should not stay in bed for a long time**

and that excess bedtime hours would make their sleep shallower, leading to worsening of the nocturia. Thirdly, as an example of moderate daily exercise, we told the patients "If you can walk, try to walk 20 minutes a day. Walking in the evening would be more effective." Finally, we suggested taking a hot water bottle to bed as one of the methods to keep warm in bed.

The FVC, International Prostate Symptom Score (IPSS)[8] and Pittsburgh Sleep Quality Index (PSQI)[9,10] before and 4 weeks after the intervention were used to evaluate the efficacy of the therapy. **The Japanese versions of these questionnaires have been validated previously.[8,10] Outcomes were defined as excellent (nocturia decreased by ≥ 2 episodes / night), improved (nocturia decreased by ≥ 1 episode / night), or unchanged. We offered further medical therapy to the non-responders.** The PSQI is a self-rated questionnaire for evaluating subjective sleep quality. The questions are combined to obtain a global score ranging from 0-21, with higher scores indicating worse sleep quality. The global score of > 5 is considered to indicate a sleep disorder.[9]

Nocturnal urine volume (NUV) was defined as the total volume of urine passed during the night including the first morning void.[11] Nighttime was defined as the period between going to bed with the intention of sleeping and waking with the intention of rising.[12] From the FVC variables, the following measurements were derived as described elsewhere:[13] the nocturnal polyuria index (NPi: the ratio

of NUV to 24 h urine volume); the nocturia index (Ni: a measure of nocturnal urine overproduction; a higher score indicating a greater nocturnal urine overproduction); the predicted number of nocturnal voids (PNV); and the nocturnal bladder capacity index (NBCi: reflective of nocturnal bladder capacity, a higher score suggesting diminished NBC). The nighttime to daytime diuresis ratio was calculated as [NUV(ml) / nighttime(h)] / [(24h urine volume - NUV) (ml) / (24-nighttime) (h)].

For statistical analyses, a Wilcoxon signed rank test was used to compare repeated measurements of variables. Spearman correlation coefficients were used to examine the relationship between baseline parameters and the degree of improvement (change in nighttime frequency). Nominal data were analyzed using the Fisher's exact test. Results were considered significant at $p < 0.05$. Statistical analysis was performed using GraphPad Prism®, version 5.

Results

Data from 56 patients (47 men and nine women) were evaluated. The mean age was 74.5 **± 5.7** years (range 59-85) **and the mean body mass index was 21.8 ± 3.2 (range 15.0 - 30.9). Underlying medical disorders included hypertension (13 patients, 23.2 %), diabetes mellitus (12, 21.4 %), cardiac conditions (10, 17.9 %) and sleep apnea (3, 5.4 %).**

Medical prescriptions included alpha-blockers (13, 23.2 %), cholinergics (2, 3.6 %), anti-cholinergics (10, 17.9 %) for lower urinary tract symptoms, and diuretics (5, 8.9 %) for cardiac conditions. We did not change the previously prescribed drugs and just added the lifestyle modifications.

Abstracts from the FVC before and after the intervention showed significant objective improvement in the symptoms as shown in Table 1. The mean number of nocturnal voids and the NUV decreased from 3.6 ± 1.1 to 2.7 ± 1.2 ml ($p < 0.0001$, Fig. 1) and from 923 ± 332 ml to 768 ± 339 ml ($p = 0.0005$), respectively. **The percentage of patients with improved and excellent responses was 53.1 % and 24.5 %, respectively.** The 24 h frequency of micturition also decreased from 11.6 ± 2.6 to 10.7 ± 2.9 times ($p = 0.0065$). Analyses of the FVC-derived variables revealed significant improvement in NPi, Ni and NBCi (Table 1). The proportion of patients with normal NPi (less than 33 % [12]) increased from 4% to 20%. The mean nighttime to daytime diuresis ratio decreased from 1.46 ± 0.38 to 1.32 ± 0.43 ($p = 0.0052$).

Patient-reported mean number of nocturia episodes (IPSS question 7) and IPSS-QOL (quality of life) score significantly decreased after the intervention (Table 2). In 31 out of the 56 patients (54.4%), **the nocturia improved (decreased by ≥ 1 points)**. In 28 (50.0%), the IPSS-QOL score improved by 1 or more points. **There were no significant changes in the other scores (IPSS 1 through 6) before and after the**

intervention. Analyses of the PSQI revealed that although the PSQI global score did not show a significant change, the sleep quality score significantly improved after the intervention.

Of the non-responders 52 % (13 / 25) underwent medical therapy, which included anti-cholinergics, desmopressin, diuretics, or non-steroidal anti-inflammatory drugs. Other non-responders continued the lifestyle modifications instead of taking medicine.

Among the baseline parameters tested, 24 h and nocturnal urine volume were significantly associated with the degree of improvement (Fig. 2). In addition, **10 patients (40 %) out of 25 presenting with a larger volume of 24 h urine production (greater than the median value) achieved an excellent response as compared to only 2 patients (8.3 %) out of 24 with less than the median value (Fisher's exact test $p = 0.018$). All 12 patients who achieved an excellent response were male and none of the female patients showed an excellent response; however, it is difficult to draw a definite conclusion about the sex difference on the efficacy of the treatment because of the small number of female patients.**

There was no significant worsening of the health status reported by the patients during this period.

Discussion

Nocturia is associated with various kinds of medical conditions such as overactive bladder, prostatic disease, diabetes mellitus, cardiovascular disease and sleep disorders.[1] Therapeutic strategies include reducing NUV, increasing nocturnal bladder capacity and treating sleep disorders. Lifestyle modification or behavioral therapy are often mentioned in the literature, mainly in an attempt to reduce nocturnal urine volume; however, their efficacy has not been established and some authors believe that these treatments are of limited efficacy and that pharmacologic therapy is the only option for the majority of patients.[6] In this study, we attempted to evaluate the efficacy of this strategy by combining four types of lifestyle modifications.

The first step in our treatment is fluid restriction. Many people, encouraged by articles in the media, believe that a high water intake will help to prevent ischemic heart disease or cerebrovascular disease and they indeed drink a lot of water; however, there is no definite evidence that stroke or myocardial infarction can be prevented by increasing the water intake in daily life, and that a high intake of water will actually decrease blood viscosity.[14] Reducing fluid intake has already been recommended in patients whose nocturia is secondary to nocturnal polyuria;[1,15] however, there has been no recommendation stating the actual means of fluid restriction. As total 24 h urine volume in healthy individuals was reported to be 23.0 ±

1.7 ml/kg [16] and this is roughly equivalent to drinking fluid of 2–2.5% of body weight, **we made a recommendation as described in the Methods section.**

Second, we recommended shortening the time spent in bed to improve sleep quality. We previously reported that patients with nocturia spent a significantly longer time in bed than controls.[17,18]

The third measure was to maintain moderate daily exercise. Asplund and Aberg reported that lack of regular exercise was associated with an increased number of nocturnal micturition episodes,[19] and Sugaya et al. showed the efficacy of walking exercise in the treatment of nocturia.[20] By using the protocol of 30 min rapid walking in the evening or night for 8 weeks, they achieved a significant reduction in the number of nocturia episodes from 3.3 to 1.9. It is a very useful behavioral therapy; however, we were afraid that some of the elderly patients would find difficulty in carrying out this practice. In order to make the protocol suitable for as many patients as possible including those with impaired activities of daily living, **we made a recommendation of moderate exercise, where possible, as described in the Methods section.**

Finally, we included a recommendation to keep warm in bed. Cold exposure is known to increase urine output by inducing "cold diuresis" through a combination of increased venous return, activation of atrial natriuretic peptide, decreased levels of antidiuretic hormone and

renal antidiuretic hormone receptor, and tubular dysfunction.[21,22] In our previous study using a self-reported questionnaire on the reasons for change in night time frequency in patients with symptomatic nocturia, feeling cold in bed was the third most prevalent answer next to increased fluid intake and longer duration in bed.[18] We have also shown that urinary symptoms including nocturia worsen in winter in the general population.[23]

The major limitation of our study is the lack of a control group. Although the gold standard for study design is a randomized controlled trial, it is difficult to set a control group in this kind of study. A possible placebo effect and a patient selection bias should therefore be kept in mind in interpreting the results. Nevertheless, the objective improvements shown in the FVC analyses strongly support the efficacy of the therapy. Another weakness of the study is that **we did not structurally obtain the information about the degree to which the patients actually incorporated the behavioral recommendations. Although that is an important issue, we did not want to frustrate the patients by burdening them with writing down the details of their lifestyle in addition to keeping the FVC and answering the questionnaires. We decided that the IPSS, PSQI and FVC were the minimal requirements to evaluate the efficacy of our therapy. It is therefore difficult to assess which component worked best for each patient. The most effective and suitable intervention to the given**

baseline conditions should be determined as the next step. Finally, the long-term effect remains to be confirmed. This point should also be clarified in the future studies.

In conclusion, the present study demonstrated that lifestyle measures were effective in improving nocturia, and patients with larger 24 h urine volume showed a better response. Assessment of FVC and FVC-derived variables revealed that the number of nocturnal voids and nocturnal urine volume significantly decreased, and NPi, Ni and NBCi significantly improved after the intervention; however, bladder capacity did not show any significant change. This implies that the efficacy of this therapy is primarily attributable to the reduction of nocturnal urine volume.

Conclusions

Non-drug lifestyle measures were effective in reducing the number of nocturia episodes and improving patients' QoL. The effect of this therapy was shown to result from a reduction in NUV. Patients with polyuria showed a better response to the treatment.

Abbreviations

FVC: frequency volume chart

IPSS: International Prostate Symptom Score

NBCi: nocturnal bladder capacity index

Ni: nocturia index

NPi: nocturnal polyuria index

NUV: nocturnal urine volume

PNV: predicted number of nocturnal voids

PSQI: Pittsburgh Sleep Quality Index

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Figure Legends

Fig. 1 — Box plots showing nocturnal frequency before and after the intervention. Whiskers: 10-90 percentiles; $p < 0.001$.

Fig. 2 — The relationship between pre-treatment 24 h urine volume (A) and nocturnal urine volume (B) and decreased number of nocturia episodes. A: r = 0.3923; $p = 0.0102$; B: r = 0.3088; $p = 0.0466$.

TABLES

Table 1 — Results of frequency volume chart before and after the intervention

Variables	Before	After	*p*
NUV, ml			
Mean (SD)	923 (332)	768 (339)	
Median (range)	917 (235-1650)	707 (175-1513)	< 0.001
24 h UV, ml			
Mean (SD)	1850 (581)	1716 (607)	
Median (range)	1835 (665-3537)	1705 (675-3084)	0.024
Nocturnal frequency			
Mean (SD)	3.6 (1.1)	2.7 (1.2)	
Median (range)	3.6 (2.0-6.5)	2.8 (0.3-5.0)	< 0.001
24h frequency			
Mean (SD)	11.6 (2.6)	10.7 (2.9)	
Median (range)	11.3 (6.3-19.5)	10.0 (5.3-18.5)	0.007
MVV, ml			
Mean (SD)	309 (99)	313 (103)	
Median (range)	300 (50-530)	300 (50-600)	0.65
NPi			
Mean (SD)	50.5 (12.2)	45.9 (14.7)	
Median (range)	48.3 (25.2-75.4)	45.0 (14.6-72.6)	0.004
Ni			
Mean (SD)	3.1 (0.9)	2.6 (0.9)	
Median (range)	2.9 (1.4-5.4)	2.6 (1.2-4.3)	< 0.001
NBCi			
Mean (SD)	1.5 (0.7)	1.3 (0.6)	
Median (range)	1.6 (0.2-3.7)	1.2 (0.1-2.8)	0.002

N/D diuresis ratio			
Mean (SD)	1.46 (0.38)	1.32 (0.43)	
Median (range)	1.44 (0.64-2.52)	1.31 (0.58-2.19)	0.005

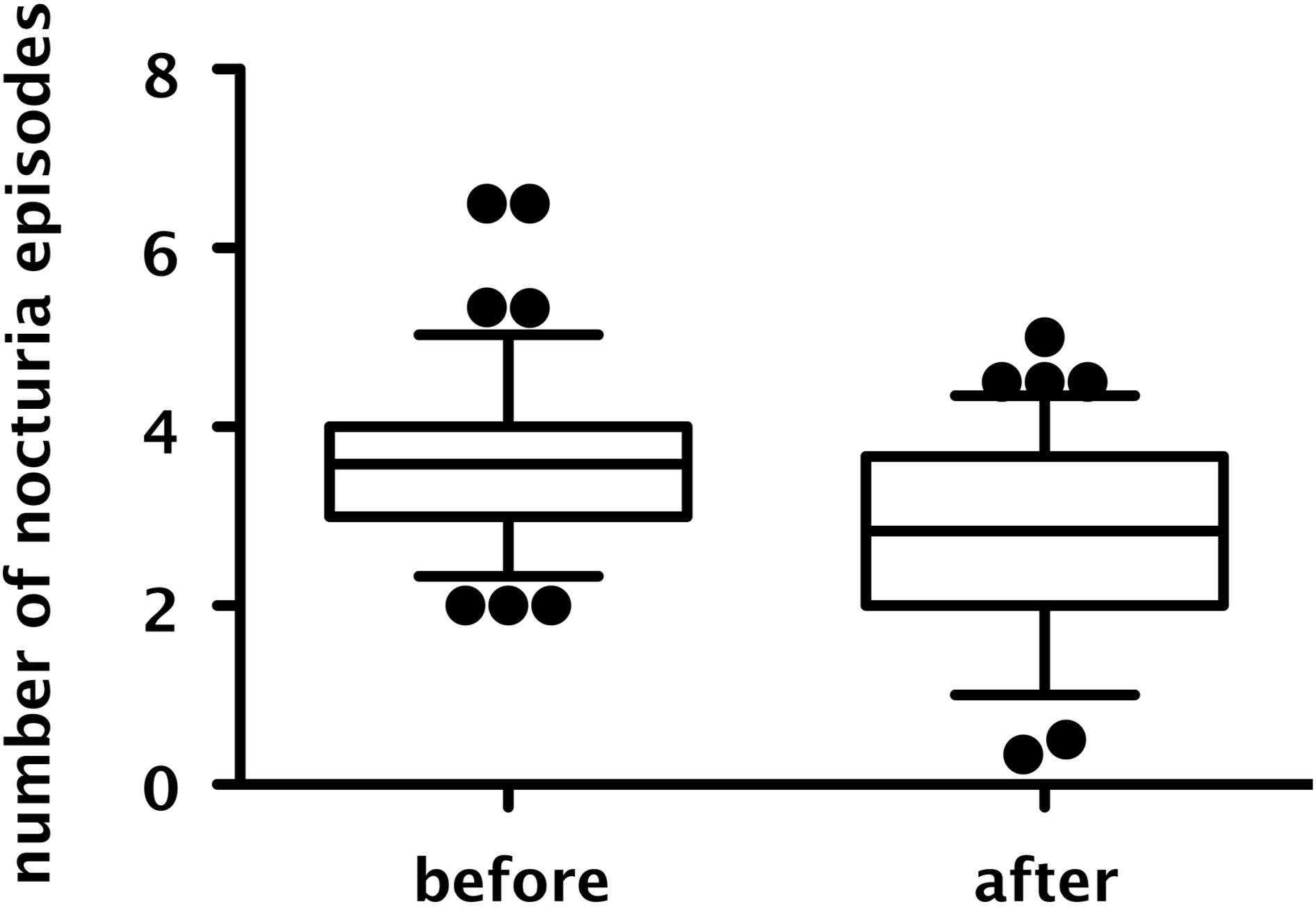
NUV = nocturnal urine volume; MVV = maximum voided volume; NPi = nocturnal polyuria index; Ni = nocturia index; NBCi= nocturnal bladder capacity index

TABLES

Table 2 — Results of IPSS and PSQI before and after the intervention

Variables	Before	After	p
IPSS - 7			
Mean (SD)	3.8 (0.8)	3.1 (1.2)	
Median (range)	4.0 (2.0-5.0)	3.0 (1.0-5.0)	<0.001
IPSS - QOL			
Mean (SD)	4.6 (1.0)	3.8 (1.4)	
Median (range)	5.0 (2.0-6.0)	4.0 (0.0-6.0)	<0.001
PSQIG			
Mean (SD)	6.56	5.95	
Median (range)	6.0 (0.0-14.0)	5.0 (0.0-14.0)	0.25
Sleep quality			
Mean (SD)	2.43 (0.80)	2.10 (0.72)	
Median (range)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	0.007
Time in bed, hours			
Mean (SD)	8.44 (1.1)	8.38 (1.2)	
Median (range)	8.5 (6.0-10.5)	8.5 (6.2-11.3)	0.99

IPSS = International Prostate Symptom Score; PSQIG = Pittsburgh Sleep Quality Index global score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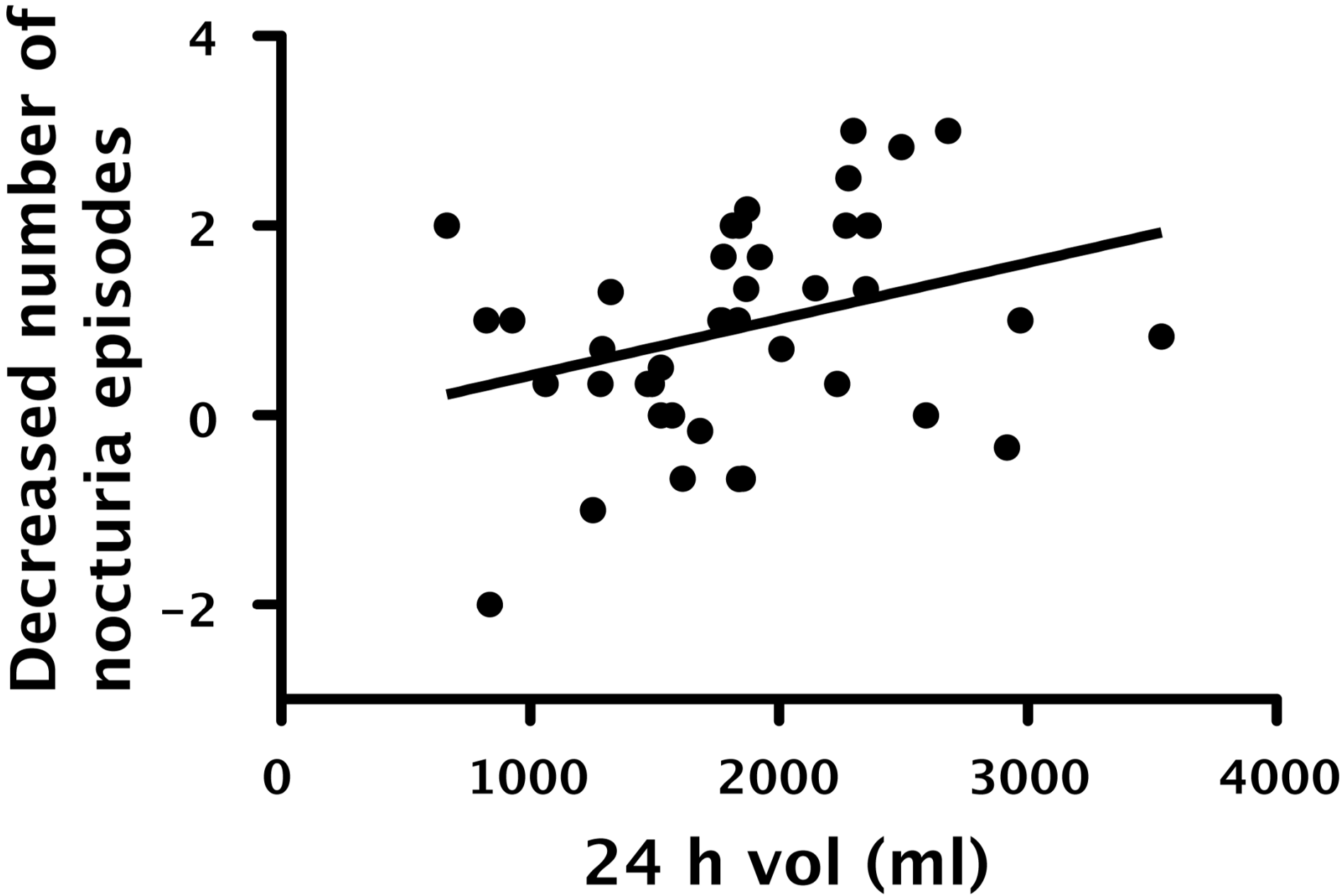
6
4
2
0
before
after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0
−2
0
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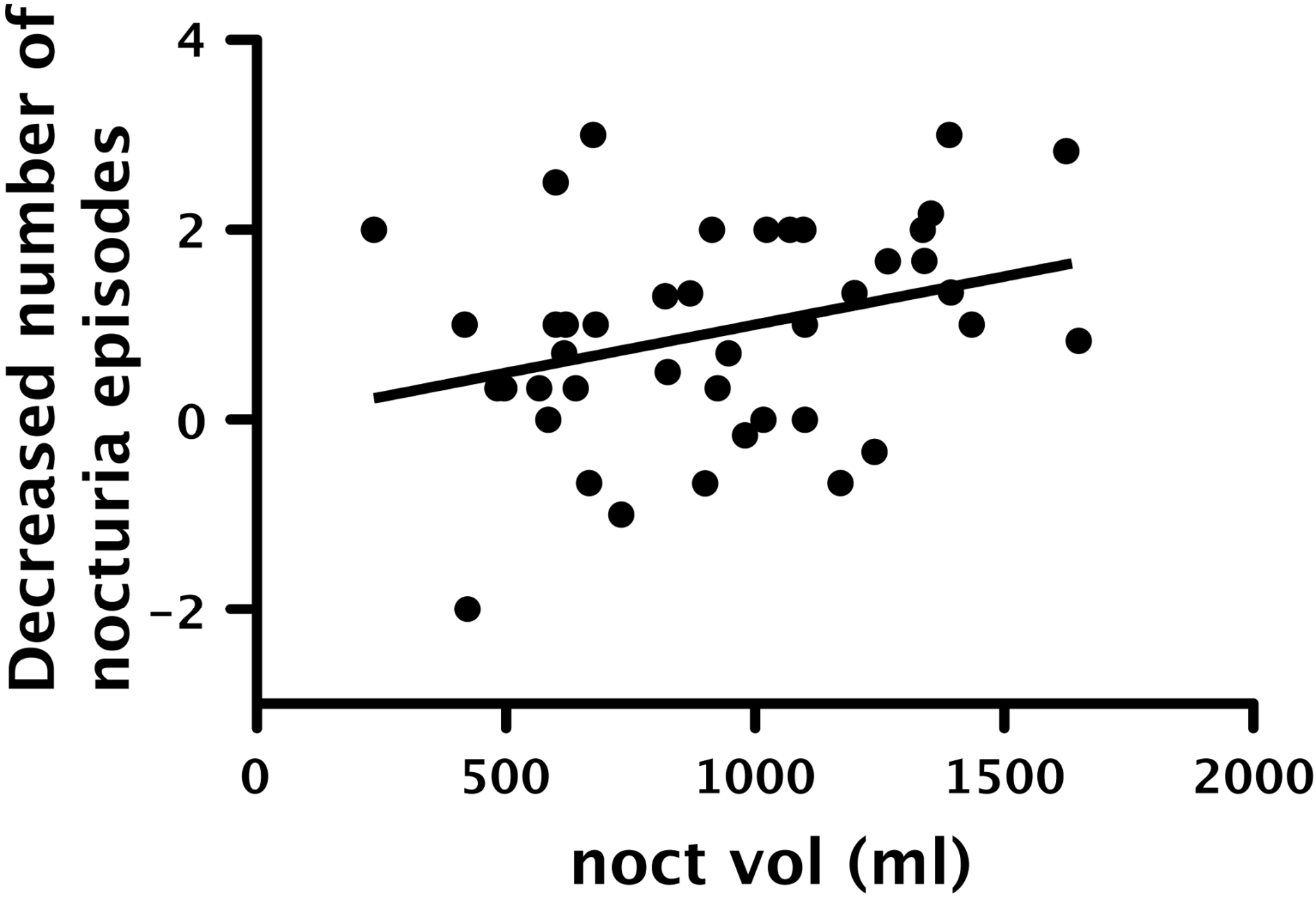
2000
3000
4000
24 h vol (ml)


Decreased number of nocturia episodes
4
2
0
−2
0
500
1000
1500
2000
noct vol (ml)