World Journal of Urology (2024) 42:586
https://doi.org/10.1007/s00345-024-05296-4

RESEARCH

Efficacy of high-dose vitamin D supplementation vs. solifenacin or standard urotherapy for overactive bladder dry in children: a secondary analysis of a randomized clinical trial

Hongsong Chen[1,2,3,4,5,6,7,8] · **Zhicheng Zhang**[1,2,3,4,5,6,7,8] · **Qiang Zhang**[1,2,3,4,5,6,7,8] · **Chong Wang**[1,2,3,4,5,6,7,8] · **Zhenmin Liu**[1,2,3,4,5,6,7,8] · **Zihan Ye**[1,2,3,4,5,6,7,8] · **Xiao Wang**[1,2,3,4,5,6,7,8] · **Yanxi Wang**[1,2,3,4,5,6,7,8] · **Xing Liu**[1,2,3,4,5,6,7,8] · **Guanghui Wei**[1,2,3,4,5,6,7,8]

Received: 8 August 2024 / Accepted: 26 September 2024

Abstract

Purpose To investigate the efficacy of high-dose vitamin D supplementation (VDS) plus standard urotherapy (SU) in managing pediatric overactive bladder dry (OAB-dry), specifically in children with (1) vitamin D levels between 20 and 35 ng/mL and (2) heightened baseline symptom severity.

Methods In this secondary analysis of a randomized controlled trial, eligible children ($n = 303$) were assigned to 8 weeks of VDS + SU group, solifenacin (SOL) + SU group, or SU alone group. The primary outcome was voiding frequency; secondary outcomes included urgency, nocturia, quality of life (QoL), pediatric lower urinary tract symptoms scores, and patient satisfaction.

Results Among 303 participants, 197 (65%) had vitamin D levels between 20 and 35 ng/mL, and 119 (39%) exhibited heightened baseline symptom severity. In both subgroups, VDS + SU resulted in significantly greater improvements in voiding frequency compared to SOL + SU and SU alone. In the vitamin D subgroup (20–35 ng/mL), the median difference in voids/day between VDS + SU and SOL + SU was 2.0 (95% CI, 1.0 to 3.0; $P = 0.003$) and 3.2 compared to SU alone ($P < 0.001$). In the heightened symptom subgroup, the median difference was 3.0 (95% CI, 2.0 to 4.0; $P < 0.001$) vs. SOL + SU and 5.0 (95% CI, 4.0 to 6.0; $P < 0.001$) vs. SU alone. The VDS + SU group generally outperformed the other groups in various secondary outcome measures.

Conclusion High-dose VDS plus SU has significant therapeutic benefit in children with OAB-dry in those with vitamin D levels between 20 and 35 ng/mL and with more severe symptoms, compared to SOL + SU or SU alone.

Keywords Overactive bladder · Children · Vitamin D · Solifenacin · Randomized controlled trial

✉ Xing Liu
liux@hospital.cqmu.edu.cn

[1] Department of Urology, Children's Hospital of Chongqing Medical University, 136 Zhongshan Road, Chongqing 400014, PR China

[2] Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing 400014, PR China

[3] National Clinical Research Center for Child Health and Disorders, Chongqing 400014, PR China

[4] China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Chongqing 400014, PR China

[5] Children's Hospital of Chongqing Medical University, Chongqing 400014, PR China

[6] Chongqing Key Laboratory of Pediatrics, Chongqing 400014, PR China

[7] Chongqing Key Laboratory of Structural Birth Defect and Reconstruction, Chongqing 400014, PR China

[8] Chongqing Medical University, Chongqing 400016, PR China

Published online: 22 October 2024

Introduction

Overactive bladder (OAB), a prevalent disorder among pediatric urology outpatients, significantly impacts social functioning [1, 2]. Managing of pediatric OAB presents inherent challenges, as standard urotherapy (SU) often fails to deliver satisfactory symptom relief. Additionally, the commonly used anticholinergics in children lack reassuring safety profiles and robust data, further complicating treatment decisions [3, 4]. Emerging evidence supports the involvement of vitamin D in regulating bladder functions, implying that vitamin D deficiency may contribute to the bladder symptoms experienced by OAB patients [5, 6]. In a recent randomized controlled clinical trial (RCT), we demonstrated that an 8-week, high-dose vitamin D supplementation (VDS) combined with SU proves more effective in alleviating OAB-dry symptoms (defined as OAB without urgency incontinence) in children with vitamin D levels below 35 ng/mL than solifenacin (SOL) plus SU or SU alone, with favorable tolerability [7]. These findings offer a fresh perspective on treating pediatric-OAB and provide evidence for the role of vitamin D in regulating bladder health.

However, several questions persist regarding this study. A fundamental query is whether it is justified to prioritize the high-dose VDS strategies in OAB-dry children with vitamin D between 20 and 35 ng/mL. This consideration stems from the observation that, in this trial, all enrolled children had vitamin D below 35 ng/mL, while the mainstream medical communities consider 20 ng/mL as the threshold for vitamin D deficiency [8]. Moreover, for children experiencing more severe symptoms, another question emerges: can the superiority of VDS + SU over SOL + SU and SU alone be sustained? This inquiry aligns with observations in neuropsychiatric disorders, as OAB is undoubtedly implicated, suggesting that the greater the baseline symptom severity, the more pronounced the difference favoring the "true" pharmacological effect [9, 10]. Investigating these inquiries would provide justification for high-dose VDS in individuals with vitamin D between 20 and 35 ng/mL and provide an opportunity to examine whether the observed effect of VDS is attributable to a placebo effect.

Herein, the objective of this study was to investigate the efficacy of high-dose VDS plus SU in two OAB-dry specific populations: (1) with vitamin D levels between 20 and 35 ng/mL; (2) with heightened baseline symptom severity, compared to SOL plus SU or SU alone. We hypothesize that the efficacy of high-dose VDS plus SU remain uncompromised in these delineated populations.

Methods

Study design, participants and procedures

This study is a secondary analysis of a RCT conducted at the National Clinical Research Center for Child Health and Disease in Chongqing, China, spanning January to June 2023, as previously detailed [7]. The protocol obtained endorsement from the Institutional Review Board of Children's Hospital of Chongqing Medical University. Written informed consent was acquired from all participants.

Briefly, enrolled patients, aged 5 to 18 years, diagnosed with OAB-dry and having serum vitamin D below 35 ng/mL, underwent a 7-day run-in period. Eligible participants, as per the protocol's detailed inclusion and exclusion criteria, were randomly assigned in a 1:1:1 ratio to one of three groups: high-dose VDS plus SU (VDS + SU group), SOL plus SU (SOL + SU group), or SU alone (SU group), for an 8-week period. While participants and practitioners were aware of group assignments, evaluators and statisticians remained blinded. Trained instructors led SU sessions, covering essential information on OAB-dry, providing behavioral modification guidance, lifestyle advice, and instructing on the use of bladder diaries for documenting voiding habits. All participants attended sessions upon enrollment and 4-week intervals, with treatment compliance assessed post each SU session and tailored recommendations offered. Participants in the VDS + SU group received high-dose VDS (vitamin D3 drops encapsulated as soft capsules, 2400 IU/d) in addition to SU. Participants in the SOL + SU group received solifenacin succinate at a daily dose of 5 mg, with a maximum limit of 10 mg once daily, along with SU. Participants in the SU group only attend SU sessions.

Baseline and outcome assessment

Participant demographics, encompassing age, gender, health indicators, and vitamin D levels, were documented at enrollment. Evaluations occurred at three time points: enrollment (T0), 4-week follow-up (T1), and 8-week follow-up (T2). The primary outcome centered on the enhancement in voiding frequency from T0 to T2, accompanied by secondary outcomes that scrutinized alterations in voiding frequency from T0 to T1. Secondary outcome parameters extended to urgency scores, nocturia frequency, quality of life (QoL) score, and pediatric lower urinary tract symptom (PLUTS) score, evaluated at both T0 to T1 and T2. Additional assessments included participants' perceptions of improvement and receptiveness to another therapy.

Statistical analysis

Data analysis was performed in June 2024. The original trial, designed with the power to discern a 1.5 voids per day difference between groups, incorporated a total of 303 children in the intention-to-treat analysis. In this study, we delineated specific subgroups by identifying children with vitamin D levels exceeding 20 ng/mL. Additionally, we pinpointed children exhibiting heightened OAB-dry symptoms, operationally defined as voiding frequency ≥ 16.0 voids/day, with a quality of life (QoL) score ≥ 2.0 and a PLUTS score ≥ 9.0 at T0.

Numerical findings were articulated through mean (SD) or median (Quartiles) representation as appropriate. The efficacy assessment adhered to an intention-to-treat framework, employing multiple imputation under the assumption of missing at random to address data gaps at T1 and T2. Differences among interventions were scrutinized using the Wilcoxon rank sum test, incorporating a Bonferroni correction. The Hodges-Lehmann estimate of location shift, accompanied by its corresponding 95% confidence interval, quantified between-group disparities. Categorical variables underwent comparison among groups using the Kruskal-Wallis test, Mann-Whitney U-test, chi-square test, or Fisher's exact test contingent upon appropriateness. Statistical significance was conferred to a two-tailed P-value < 0.05. All statistical analyses transpired through SAS version 9.4 (SAS Institute Inc.) and SPSS statistical software version 26 (IBM).

Interaction analyses for primary outcome were conducted by introducing an interaction term between the study group and the variables used to define subgroups, with outcomes reported as β (95% CI) [11]. We also examined the correlation between vitamin D level and baseline bladder diary variables, QoL scores and PLUTS scores, as well as correlation between improvements in those parameters and patient global ratings.

Results

Of the 467 participants who consented, 303 were randomized into three groups: VDS + SU ($n = 100$), SOL + SU ($n = 102$), and SU alone ($n = 101$), as outlined in the original report [7]. Among those randomized, 197 (65%) had vitamin D levels between 20 and 35 ng/mL (VDS + SU: 67, SOL + SU: 64, SU alone: 66), and 119 (39%) exhibited heightened baseline symptom severity (VDS + SU: 40, SOL + SU: 38, SU alone: 41).

In the designated subgroups, the characteristics within each treatment arm were consistent (Table 1), signifying effective randomization. Essential features of the alternative subgroups, complementing those of interest, were also equally distributed across intervention arms (Supplementary Table 1). In subgroups with vitamin D between 20 and 35 ng/mL, the VDS + SU group demonstrated greater improvements in voiding frequency compared to the SOL + SU group (median difference, 2.0; 95% CI, 1.0 to 3.0; $P = 0.003$) and the SU alone group (median difference, 3.2; 95% CI, 2.0 to 4.2; $P < 0.001$) at T2 (Table 2). Additionally, the VDS + SU group exhibited greater improvements in voiding frequency at T1 compared to the other groups, as well as enhancements in urgency scores (mean and max), QoL scores, and PLUTS scores at both T1 and T2 (Supplementary Table 2). These findings were further supported by participants' global rating (Supplementary Table 3). Although the SOL + SU group surpassed the SU group in decreasing voiding frequency at T2, it did not improve patients' QoL scores or PLUTS scores. Furthermore, no significant difference in overall patient satisfaction was observed between the two groups. Interestingly, in subgroup with vitamin D below 20 ng/mL, the therapeutic advantage of the VDS + SU group persisted in comparison to the SOL + SU group and the SU group, while the SOL + SU group forfeited its advantage in voiding frequency when compared to the SU group (Supplementary Tables 4–5).

In subgroups with elevated baseline symptom severity, the VDS + SU group showed significant improvements in voiding frequency compared to both the SOL + SU group (median difference, 3.0; 95% CI, 2.0 to 4.0; $P < 0.001$) and the SU group (median difference, 5.0; 95% CI, 4.0 to 6.0; $P < 0.001$) at T2. The SOL + SU group also demonstrated a more pronounced change than the SU group (median difference, 1.0; 95% CI, 0.5 to 2.0; $P = 0.01$) at T2. Additionally, the VDS + SU group generally outperformed the other groups in various secondary outcome measures (Supplementary Table 6). While the SOL + SU group outperformed the SU group in enhancing voiding frequency, maximum urgency score, and nocturia frequency, it did not significantly enhance QoL scores, PLUTS scores, or treatment satisfaction at T2 (Supplementary Table 7). Subgroups with mild baseline symptom severity produced similar results (Supplementary Tables 8–9).

No significant interaction effect was observed; thus, the treatment effect on the primary outcome remained unaffected by the variables used to define the subgroups (Supplementary Table 10). Vitamin D levels showed no correlation with baseline bladder diary variables, QoL scores, or PLUTS scores (Supplementary Table 11). Enhancements in QoL scores showed either a strong or modest correlation with patient global ratings, whereas no notable correlation was identified between changes in nocturia frequency and patient global ratings (Supplementary Table 12).

Table 1 Baseline demographics and clinical characteristics of the study population within subgroups of interest

Characteristics	With vitamin D ≥ 20 ng/mL (*N*=197)				With Severe Baseline Symptom Severity (*N*=119)			
	VDS+SU group (*n*=67)	SOL+SU group (*n*=64)	SU group (*n*=66)	*P* value[a]	VDS+SU group (*n*=40)	SOL+SU group (*n*=38)	SU group (*n*=41)	*P* value[a]
Age, median (Quartiles), months[b]	79.0 (68.0 to 96.0)	77.0 (67.0 to 89.0)	80.5 (67.0 to 94.0)	0.80	83.5 (74.5 to 99.5)	85.5 (70.0 to 101.0)	81.0 (68.0 to 99.0)	0.94
BMI, mean (SD)[c]	17.31 (1.44)	17.70 (1.74)	17.37 (1.83)	0.37	17.35 (1.54)	17.60 (1.54)	17.43 (1.81)	0.80
Gender, No. (%)[d]								
Boy	45 (67)	39 (61)	41 (62)	0.73	21	21	25	0.74
Girl	22 (33)	25 (39)	25 (38)		19	17	16	
Educational status, No. (%)[d]								
Kindergarten	34 (51)	36 (56)	31 (47)	0.67	15	15	14	0.98
Primary School	32 (48)	27 (42)	35 (53)		24	22	26	
Middle School	1 (1)	1 (2)	0 (0)		1	1	1	
Parents' educational level, No. (%)[d]								
Did not complete high school	13 (19)	12 (19)	18 (27)	0.44	10	9	10	0.39
High school	29 (43)	22 (34)	24 (36)		15	10	18	
Specialty	20 (30)	18 (28)	16 (24)		11	14	6	
Undergraduate degree or above	5 (7)	12 (19)	8 (12)		4	5	7	
Actual caregiver, No. (%)[d]								
Parents	52 (78)	54 (84)	55 (83)	0.85	31	31	32	>0.99
Grandparents	13 (19)	8 (13)	9 (14)		8	7	8	
Others	2 (3)	2 (3)	2 (3)		1	0	1	
Estimated outdoor activity time, No. (%)[d]								
2 h per day or less	44 (66)	50 (78)	50 (76)	0.23	29	30	30	0.77
More than 2 h per day	23 (34)	14 (22)	16 (24)		11	8	11	
Self-reported health status, No. (%)[d]								
Poor	4 (6)	4 (6)	5 (8)	>0.99	2	4	4	0.77
Fair	11 (16)	10 (16)	11 (17)		10	6	7	
Excellent	52 (78)	50 (78)	50 (76)		28	28	30	
Vitamin D intake, No. (%)[d, e]								
Never	56 (84)	52 (81)	56 (85)	0.13	32	31	36	0.36
Sometimes	6 (9)	3 (5)	3 (5)		6	3	3	
Regular but less than 6 months (≤ 400IU/d)	4 (6)	1 (2)	4 (6)		2	1	2	
Regular and more than 6 months (≤ 400IU/d)	1 (1)	8 (13)	3 (5)		0	3	0	
Duration of OAB-dry symptom, median (Quartiles), weeks[b, f]	4.0 (2.0 to 7.0)	4.0 (3.0 to 6.0)	4.0 (2.0 to 7.0)	0.62	6.0 (3.5 to 9.5)	6.0 (3.0 to 9.0)	7.0 (3.0 to 12.0)	0.58

Table 1 (continued)

Characteristics	With vitamin D ≥ 20 ng/mL (*N*=197)				With Severe Baseline Symptom Severity (*N*=119)			
	VDS+SU group (*n*=67)	SOL+SU group (*n*=64)	SU group (*n*=66)	*P* value[a]	VDS+SU group (*n*=40)	SOL+SU group (*n*=38)	SU group (*n*=41)	*P* value[a]
Serum levels of 25(OH) D, mean (SD), ng/mL[c, g]	25.37 (3.72)	26.93 (4.02)	25.58 (3.44)	0.04	22.60 (5.60)	22.31 (6.89)	22.65 (4.70)	0.97
Postvoid residual, median (Quartiles), mL[b]	3.0 (2.0 to 6.0)	4.0 (2.0 to 7.5)	3.0 (2.0 to 6.0)	0.41	3.0 (2.0 to 4.5)	4.0 (2.0 to 7.0)	3.0 (1.0 to 5.0)	0.37

Abbreviations SD, standard deviation; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); 25(OH)D, 25-hydroxy vitaminD

[a]Comparisons between groups was conducted after Bonferroni correction, and a P value of less than 0.05 was considered to be statistically significant

[b]The Kruskal-Wallis test was utilized to compare the outcomes among groups

[c]The ANOVA test or welch's ANOVA test was utilized to compare the outcomes among groups

[d]The chi-square test or Fisher's exact test was utilized to compare the outcomes among groups

[e]Vitamin D intake involves the use of medications or supplements that contain vitamin D, such as vitamin D drops or vitamin AD supplements

[f]The duration of OAB dry symptoms refers to the time between the first recognition of urinary tract symptoms, including urgency, frequency, and nocturia without incontinence, and the initial visit to our clinic. The duration measured in weeks, and period less than a week was recorded as one week

[g]Serum levels of 25-hydroxy vitamin D were measured via chemiluminescent immunoassay, convert from ng/mL to nmol/L, multiply by 2.496

Discussion

The primary trial, from which this analysis originates, established the superiority of VDS + SU over SOL + SU or SU alone in managing OAB-dry among children with vitamin D below 35 ng/mL [7]. In this study, we probed deeper into the efficacy of VDS + SU across specific subgroups and found that the benefits of VDS persisted among subgroups with vitamin D between 20 and 30 ng/mL, as well as those with more severe symptoms at enrollment.

Ancillary findings from a large-scale trial indicated that VDS did not diminish the prevalence of OAB or ameliorate its symptoms compared to placebo among older men or women [12, 13]. Nevertheless, investigations focusing on children have generated inconsistent results, with even endorsing VDS as the preferred solution over the SOL [7, 14]. Multiple factors must be considered in interpreting this inconsistency. First, the pathophysiology of OAB in children may diverge from that in adults with the latter potentially being associated with structural lesions in the pelvic floor [15–17]. Moreover, discrepancies in VDS doses, concurrent pathological conditions, and the lack of baseline vitamin D levels in adult studies may hinder the ability to formulate definitive conclusions [18, 19].

Prior researches have indicated a seasonally influenced prevalence of OAB, with a heightened incidence during colder seasons [20]. Aligned with the consensus attributing endogenous vitamin D synthesis predominantly to sunlight exposure, the hypothesis positing vitamin D deficiency as a plausible pathophysiological cause of OAB garners credibility to some extent. In the current analysis, it is suggested that when vitamin D falls below 20 ng/mL, VDS + SU retains a therapeutic advantage, while SOL + SU loses its edge compared to SU alone. However, correlation analysis revealed no association between vitamin D levels and initial symptom severity. Additionally, upon discovering vitamin D levels below 20 ng/mL, participants tended to attribute fluctuating voiding patterns more to unhealthy dietary and exercise practices than recognizing it as a condition warranting anticholinergic drugs. This inclination, combined with concerns about anticholinergic agents, particularly when contrasted with the widespread availability and safety of the vitamin D, may have compromised the efficacy of SOL and exaggerated its perceived side effects [21]. Furthermore, the dosing of SOL underwent optimization in the original trial, while the fixed high-dose VDS regimen retained theoretical constraints on its potential efficacy. These factors introduce complexities to the comparison between groups, rendering it challenging to draw more robust conclusions before conducting a more informative head-to-head RCT.

In this investigation, another subgroup stratification criterion was applied, incorporating voiding frequency,

Table 2 Changes in voiding frequency and other urinary symptoms within subgroups of the study population

Change in	Median (Quartiles)			Between-group Comparison (Median difference (95% CI); *P* value)[a]		
	VDS+SU group	SOL+SU group	SU group	VDS+SU group vs. SOL+SU group	VDS+SU group vs. SU group	SOL+SU group vs. SU group
Subgroups with Vitamin D Levels Between 20-35 ng/mL						
Number of enrollees (n)	67	64	66			
Voiding frequency (voids/d)[b]	7.0 (5.0 to 9.0)	4.8 (3.0 to 7.0)	3.0 (2.0 to 5.0)	2.0 (1.0 to 3.0) ; 0.003	3.2 (2.0 to 4.2) ; <0.001	2.0 (1.0 to 2.7) ; 0.002
Urgency score(mean)[c]	1.1 (0.7 to 1.6)	0.7 (0.3 to 1.1)	0.5 (0.1 to 0.9)	0.5 (0.3 to 0.7) ; <0.001	0.7 (0.5 to 0.9) ; <0.001	0.2 (0 to 0.4) ; 0.38
Urgency score (max)[c]	1.0 (0.2 to 2.0)	0.1 (0 to 1.0)	0 (0 to 1.0)	0.6 (0 to 1.0) ; 0.003	1.0 (0 to 1.0) ; <0.001	0 (0 to 0) ; 0.69
Mean nocturia frequency (voids/night)[d]	0.2 (-0.1 to 0.6)	0.3 (0 to 0.6)	0 (-0.2 to 0.4)	-0.1 (-0.2 to 0.1) ; 0.93	0.2 (0 to 0.3) ; 0.06	0.3 (0.1 to 0.4) ; 0.002
QoL score[e]	2.0 (1.0 to 2.0)	1.0 (0 to 1.7)	0.5 (0 to 1.0)	1.0 (1.0 to 1.0) ; <0.001	1.0 (1.0 to 1.2) ; <0.001	0 (0 to 0.9) ; >0.99
PLUTS score[f]	6.0 (4.0 to 8.0)	3.0 (1.0 to 5.0)	3.0 (1.0 to 4.0)	3.0 (2.0 to 4.0) ; <0.001	4.0 (3.0 to 4.6) ; <0.001	0.9 (0 to 1.0) ; 0.76
Subgroups with Elevated Baseline Symptom Severity						
Number of enrollees (n)	40	38	41			
Voiding frequency (voids/d)[b]	9.0 (8.0 to 10.5)	6.0 (4.0 to 7.0)	4.0 (3.0 to 5.0)	3.0 (2.0 to 4.0) ;<0.001	5.0 (4.0 to 6.0) ; <0.001	1.0 (0.5 to 2.0) ;0.01
Urgency score(mean)[c]	1.2 (0.8 to 1.7)	0.6 (0.2 to 1.0)	0.5 (0.1 to 0.9)	0.6 (0.4 to 0.9) ; <0.001	0.7 (0.4 to 1.0) ; <0.001	0.1 (-0.2 to 0.3) ; >0.99
Urgency score (max)[c]	1.0 (0.1 to 2.0)	1.0 (0 to 1.0)	0 (0 to 1.0)	0 (0 to 1.0) ; 0.06	1.0 (0.2 to 1.0) ; <0.001	0 (0 to 1.0) ; 0.03
Mean nocturia frequency (voids/night)[d]	0.2 (-0.2 to 0.6)	0.4 (0.1 to 0.6)	-0.2 (-0.4 to 0.3)	-0.1 (-0.3 to 0.1) ; >0.99	0.4 (0.1 to 0.6) ; 0.02	0.4 (0.3 to 0.6) ; 0.002
QoL score[e]	2.0 (1.0 to 2.0)	1.0 (0 to 1.7)	1.0 (0 to 1.0)	1.0 (0.3 to 1.0) ; <0.001	1.0 (1.0 to 1.0) ; <0.001	0 (0 to 0) ; >0.99
PLUTS score[f]	6.0 (4.0 to 7.5)	4.0 (2.0 to 5.0)	4.0 (2.0 to 4.0)	2.0 (1.0 to 3.0) ; <0.001	2.0 (1.0 to 3.0) ; <0.001	0 (-1.0 to 1.0) ; >0.99

Abbreviation CI, confidence interval; T0, baseline; T1, 4-week followup; T2, 8-week followup; NA, not applicable; QoL, quality of life; PLUTS, Pediatric Lower Urinary Tract Symptom

[a]Comparison of continuous variables across groups was performed using the Wilcoxon rank sum test. Hodges-Lehmann location shift estimates and 95% CIs are presented for comparisons associated with differences in medians. The p-values were adjusted after the Bonferroni correction

[b]Participants kept a voiding diary for a minimum of seven consecutive days, and the median urinary frequency per day was used as the measurement

[c]Urgency refers to the sudden and unexpected experience of an immediate and compelling need to void. Scores for urgency were measured on a scale of 0 to 3: 0 indicated no urgency, 1 indicated mild awareness of urgency that iseasily tolerated, 2 indicated moderate urgency discomfort that interferes with or shortens usual activity, and 3 indicated severe urgency discomfort that abruptly stops all activities or tasks.Participants documented the frequency and urgency score of their urinary urgency episodes over a period of three consecutive days. The urgency score (mean) was calculated by dividing the total urgency score by the number of episodes experienced. The urgency score (max) was considered the most severe urgency experienced during the observation period

[d]Nocturia is defined as the frequency of voids recorded in the diary between the time a participant intends to sleep and just before morning awakening, and excludes instances where children wake up for reasons other than the need to void. Participants kept a voiding diary for a minimum of seven consecutive days, and the mean nocturia frequency per night was used as the measurement

[e]The quality of life score was assessed using a scale ranging from 0 to 3, where a score of 0 indicated no impact on family, social, or academic life, a score of 1 indicated occasional impact, a score of 2 indicated significant impact, and a score of 3 indicated severe impact on family, social, or academic life

[f]The PLUTS score was designed to evaluate all lower urinary tract symptoms. In this study, questions about urinary incontinence and enuresis did not require participant responses. The PLUTS score ranged from 0 to 21 and higher scores indicated a more frequent and severe occurrence of lower urinary tract symptoms

QoL score and PLUTS score. The rationale for adopting this criterion is threefold: Firstly, the original study reported a median voiding frequency of 16 voids/day for all participants [7]. Secondly, a QoL score of 2 denotes a substantial impact on family, social, and academic facets of life according to established definitions [7]. Moreover, in alignment with the foregoing observation, a PLUTS score surpassing 8.5 is indicative of functional voiding disorders, with reported sensitivity and specificity rates of 90% [22]. We observed that the daily voiding episodes totaling 16 markedly surpass the documented 8–9 occurrences per day in other high-quality RCTs focusing on pediatric OAB [23, 24]. This deviation may be attributed to the inclusion of children predominantly experiencing incontinence, as it is reasonable to perceive a correlation between heightened incontinence and diminished frequency recording. When assessing the impact of medical therapy for OAB, commonly selected variables such as voiding frequency or incontinence episodes per day are typically favored possibly due to their ease of recording and analysis [23–25]. Nevertheless, relying solely on these individual symptoms may not adequately capture the comprehensive therapeutic outcome, namely enhanced QoL and patient satisfaction [26]. Our secondary analysis revealed that, despite achieving statistical significance, the improvements in voiding frequency and urgency scores exhibit only a weak correlation with patient global ratings. Notably, QoL scores and PLUTS scores emerged as more effective predictors of patients' responses when framed in a binary "yes or no" format. These findings underscore the importance of employing composite endpoints in OAB-associated studies, integrating both objective metrics and patient perspectives to capture what matter most to OAB patients [27].

When addressing nocturia, VDS + SU and SOL + SU demonstrate a net advantage over SU alone both in whole cohort and subgroups; however, the clinical significance of this reduction is marginal. Correlation analysis indicated that improvements in nocturia have no impact on participants' satisfaction. Indeed, in our experience, nocturia was the least commonly reported concern in OAB-dry patient within clinic, with a majority reporting symptom resolution upon falling asleep, supporting the role of neuropsychiatric factors in the pathophysiology of OAB, as previous suggested [28]. It is also conceivable that bladder diaries may have influenced drinking habits, resulting in reduction of nocturia episodes in all groups [29]. The original trial, for various reasons, omitted the establishment of a double-blind and placebo group, posing limitations in interpreting the trial results, given the notable influence of the placebo effect in studies involving OAB [30]. Our analysis suggested that the efficacy of VDS + SU was not diminished compared to SOL + SU or SU alone in children with more severe symptoms; instead, the net advantage was more pronounced. While these findings provide support to the notion of a genuine pharmacological effect of high-dose VDS, considering the theoretical attenuation of the placebo effect in this scenario, the identified differences should be viewed as hypothesis-generating rather than definitive.

This study is subject to limitations stemming from the design constraints of the original trial. The sample size calculation, originally focused on primary outcome, may have led to reduced statistical power for specific results. Criticism can be directed at the post hoc selection of subgroups, notably those with vitamin D exceeding 20 ng/mL displaying slight imbalances, despite these imbalances being likely to be attributed to chance. While informative, our findings necessitate further confirmation through additional trials.

Conclusions

High-dose VDS plus SU sustains its efficacy advantage in children with OAB-dry, in those presenting vitamin D between 20 and 35 ng/mL or heightened baseline symptom severity, compared to SOL plus SU or SU alone. Future OAB-related studies should consider utilizing composite endpoints to capture treatment-induced changes. Our analysis supports a bona fide pharmacological effect of high-dose VDS in managing OAB, rather than a placebo effect.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00345-024-05296-4.

Author contributions Concept and design: Hongsong Chen, Zhicheng Zhang, Xing Liu. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Hongsong Chen, Zhicheng Zhang, Xing Liu. Critical revision of the manuscript for important intellectual content: Qiang Zhang, Chong Wang, Zhenmin Liu, Yanxi Wang. Statistical analysis: Hongsong Chen, Zihan Ye, Xiao Wang, Yanxi Wang, Xing Liu. Obtained funding: Hongsong Chen,Xing Liu. Administrative, technical, or material support: Xing Liu, Guanghui Wei. Supervision: Xing Liu, Guanghui Wei.

Funding This study was funded by the National Natural Science Foundation of China (Grant Number: 81970571), the Program for Youth Innovation in Future Medicine at Chongqing Medical University (Grant Number: 3001112) and the Postgraduate research and innovation projects of Chongqing Municipal Education Commission (Grant number: CYB240211). The funder of the study had no role in study design, patient recruitment, data collection and analysis, interpretation of the data, or writing of the manuscript.

Data availability Except for the patients' privacy, the study protocol, statistical analysis plan, data dictionary and de-identified results of

these analyses are available for scientific researchers upon reasonable request through the corresponding author.

Declarations

Competing interests The authors declare no competing interests.

References

1. Franco I (2016) Overactive bladder in children. Nat Rev Urol 13(9):520–532. https://doi.org/10.1038/nrurol.2016.152
2. Chung JM, Lee SD, Kang DI, Kwon DD, Kim KS, Kim SY, Kim HG, Moon DG, Park KH, Park YH, Pai KS, Suh HJ, Lee JW, Cho WY, Ha TS, Han SW (2009) Prevalence and associated factors of overactive bladder in Korean children 5–13 years old: a nationwide multicenter study. Urology 73(1) 63–7; discussion 68–9. https://doi.org/10.1016/j.urology.2008.06.063
3. Noh JW, Lee B, Kim JH (2019) Efficacy and safety of anticholinergics for children or adolescents with idiopathic overactive bladder: systematic review and meta-analysis. Int Urol Nephrol 51(9):1459–1471. https://doi.org/10.1007/s11255-019-02209-y
4. Raman G, Tunnicliffe D, Lai E, Bennett T, Caldwell P (2023) Safety and tolerability of solifenacin in children and adolescents with overactive bladder- a systematic review. J Pediatr Urol 19(1):19.e1-19.e13. https://doi.org/10.1016/j.jpurol.2022.09.014
5. Yuan P, Wang T, Li H, Lan R, Li M, Liu J (2021) Systematic Review and Meta-analysis of the association between Vitamin D Status and lower urinary tract symptoms. J Urol 205(6):1584–1594. https://doi.org/10.1097/JU.0000000000001441
6. Baer R, Tene L, Weintraub AY, Kalichman L (2022) The effect of vitamin D deficiency and supplementation on urinary incontinence: scoping review. Int Urogynecol J 33(5):1083–1090. https://doi.org/10.1007/s00192-021-04963-z
7. Chen H, Zhang Z, Wu S, Zhang D, Zhong X, Liu X, Wei G (2024) Efficacy and safety of high-dose vitamin D supplementation vs solifenacin or standard urotherapy for overactive bladder dry in children: a Randomized Clinical Trial. J Urol 211(1):26–36. https://doi.org/10.1097/JU.0000000000003763
8. Bouillon R (2017) Comparative analysis of nutritional guidelines for vitamin D. Nat Rev Endocrinol 13(8):466–479. https://doi.org/10.1038/nrendo.2017.31
9. Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT (2008) Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. Plos Med 5(2):e45. https://doi.org/10.1371/journal.pmed.0050045
10. Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, Fawcett J (2010) Antidepressant drug effects and depression severity: a patient-level meta-analysis. Jama-J Am Med Assoc 303(1):47–53. https://doi.org/10.1001/jama.2009.1943
11. Brankovic M, Kardys I, Steyerberg EW, Lemeshow S, Markovic M, Rizopoulos D, Boersma E (2019) Understanding of interaction (subgroup) analysis in clinical trials. Eur J Clin Invest 49(8):e13145. https://doi.org/10.1111/eci.13145
12. Markland AD, Vaughan C, Huang A, Kim E, Bubes VY, Tangpricha V, Buring J, Lee IM, Cook N, Manson JE, Grodstein F (2022) Effect of vitamin D supplementation on urinary incontinence in older women: ancillary findings from a randomized trial. Am J Obstet Gynecol 226(4):535e1–535e12. https://doi.org/10.1016/j.ajog.2021.10.017
13. Markland AD, Vaughan CP, Huang AJ, Kim E, Bubes VY, Tangpricha V, Buring JR, Lee IM, Cook NR, Manson JE, Grodstein F (2023) Effect of vitamin D supplementation on overactive bladder and urinary incontinence symptoms in older men: ancillary findings from a Randomized Trial. J Urol 209(1):243–252. https://doi.org/10.1097/JU.0000000000002942
14. Ozcift B, Micoogullari U (2022) The effect of vitamin D deficiency in children with overactive bladder related urinary incontinence. Int Braz J Urol 48(2):316–325. https://doi.org/10.1590/S1677-5538.IBJU.2021.0645
15. Franco I (2007) Pediatric overactive bladder syndrome: pathophysiology and management. Pediatr Drugs 9(6):379–390. https://doi.org/10.2165/00148581-200709060-00005
16. Blaivas JG, Marks BK, Weiss JP, Panagopoulos G, Somaroo C (2009) Differential diagnosis of overactive bladder in men. J Urol 182(6):2814–2817. https://doi.org/10.1016/j.juro.2009.08.039
17. Peyronnet B, Mironska E, Chapple C, Cardozo L, Oelke M, Dmochowski R, Amarenco G, Game X, Kirby R, Van Der Aa F, Cornu JN (2019) A Comprehensive Review of overactive bladder pathophysiology: on the way to tailored treatment. Eur Urol 75(6):988–1000. https://doi.org/10.1016/j.eururo.2019.02.038
18. Markland AD, Tangpricha V, Mark BT, Vaughan CP, Richter HE, Burgio KL, Goode PS (2019) Comparing vitamin D supplementation Versus Placebo for urgency urinary incontinence: a pilot study. J Am Geriatr Soc 67(3):570–575. https://doi.org/10.1111/jgs.15711
19. Arjmand M, Abbasi H, Behforouz A (2023) The effect of vitamin D on urgent urinary incontinence in postmenopausal women. Int Urogynecol J 34(8):1955–1960. https://doi.org/10.1007/s00192-023-05486-5
20. Kim JW, Ahn HK, Ko J, Lee D, Ha JS, Kim JH, Park SJ, Cho KS (2021) Seasonal variations in overactive bladder drug prescription rates in women: a nationwide population-based study. World J Urol 39(3):877–882. https://doi.org/10.1007/s00345-020-03257-1
21. Mostafaei H, Mori K, Quhal F, Miura N, Motlagh RS, Pradere B, Laukhtina E, Lysenko I, Ghaffari S, Hajebrahimi S, Shariat SF (2021) Nocebo Response in the Pharmacological Management of overactive bladder: a systematic review and Meta-analysis. Eur Urol Focus 7(5):1143–1156. https://doi.org/10.1016/j.euf.2020.10.010
22. Akbal C, Genc Y, Burgu B, Ozden E, Tekgul S (2005) Dysfunctional voiding and incontinence scoring system: quantitative evaluation of incontinence symptoms in pediatric population. J Urol 173(3):969–973. https://doi.org/10.1097/01.ju.0000152183.91888.f6
23. Newgreen D, Bosman B, Hollestein-Havelaar A, Dahler E, Besuyen R, Sawyer W, Bolduc S, Rittig S (2017) Solifenacin in children and adolescents with overactive bladder: results of a phase 3 Randomised Clinical Trial. Eur Urol 71(3):483–490. https://doi.org/10.1016/j.eururo.2016.08.061
24. Newgreen D, Bosman B, Hollestein-Havelaar A, Dahler E, Besuyen R, Snijder R, Sawyer W, Rittig S, Bolduc S (2017) Long-term safety and efficacy of Solifenacin in Children and adolescents with overactive bladder. J Urol 198(4):928–936. https://doi.org/10.1016/j.juro.2017.05.038
25. Burgio KL, Kraus SR, Johnson TN, Markland AD, Vaughan CP, Li P, Redden DT, Goode PS (2020) Effectiveness of combined behavioral and drug therapy for overactive bladder symptoms in men: a Randomized Clinical Trial. Jama Intern Med 180(3):411–419. https://doi.org/10.1001/jamainternmed.2019.6398
26. Payne CK, Kelleher C (2007) Redefining response in overactive bladder syndrome. Bju Int 99(1):101–106. https://doi.org/10.1111/j.1464-410X.2007.06517.x
27. Chapple CR, Kelleher CJ, Evans CJ, Kopp Z, Siddiqui E, Johnson N, Mako M (2016) A narrative review of patient-reported outcomes in overactive bladder: what is the way of

the future? Eur Urol 70(5):799–805. https://doi.org/10.1016/j.eururo.2016.04.033
28. Vrijens D, Drossaerts J, van Koeveringe G, Van Kerrebroeck P, van Os J, Leue C (2015) Affective symptoms and the overactive bladder - a systematic review. J Psychosom Res 78(2):95–108. https://doi.org/10.1016/j.jpsychores.2014.11.019
29. Sand PK, Dmochowski RR, Reddy J, van der Meulen EA (2013) Efficacy and safety of low dose desmopressin orally disintegrating tablet in women with nocturia: results of a multicenter, randomized, double-blind, placebo controlled, parallel group study. J Urol 190(3):958–964. https://doi.org/10.1016/j.juro.2013.02.037
30. Mangera A, Chapple CR, Kopp ZS, Plested M (2011) The placebo effect in overactive bladder syndrome. Nat Rev Urol 8(9):495–503. https://doi.org/10.1038/nrurol.2011.99