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Comparison of the efficacy of two different desmopressin formulations in pediatric patients with nocturnal enuresis: a retrospective observational study

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Introduction Nocturnal enuresis (NE) is a common pediatric disorder that significantly affects the quality of life of both children and their families. Desmopressin, a first-line pharmacological treatment, is available in two oral formulations: traditional tablets and oral lyophilizate (MELT). Clinical observations suggest that in pediatric patients, MELT may be chewed or swallowed prematurely, especially in younger children, potentially compromising its intended sublingual absorption and efficacy. This study aimed to compare the efficacy of desmopressin tablets vs MELT formulations in pediatric patients with monosymptomatic NE (MNE).

Material and methods This retrospective, observational, single-center study included 536 pediatric patients with MNE, treated at the Enuresis Center, Operative Research Unit of Pediatrics, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy. Patients were assigned to two independent treatment cohorts: MELT (n = 393) and tablet (n = 143). Efficacy was evaluated over 12 weeks using a "dry night calendar."

Results A statistically significant difference in efficacy was observed between the two formulations (p = 0.045). In the MELT group, response rates were: non-responders 33.7%, partial responders 43.2%, and full responders 23.2%. In the tablet group, rates were: non-responders 20.8%, partial responders 49%, and full responders 30.2%.

Conclusions Patients treated with the tablet formulation demonstrated a superior overall therapeutic response, with a higher rate of optimal response and a lower incidence of no response compared to the MELT formulation.

Key Words: nocturnal enuresis ‹› desmopressin ‹› treatment ‹› tablet formulation ‹› lyophilizate formulation

INTRODUCTION

Nocturnal enuresis (NE) is one of the most prevalent pediatric disorders, defined as repeated episodes of involuntary urination during sleep in the absence of identifiable organic pathology. Beyond the direct medical implications, NE imposes a considerable psychosocial burden, affecting children's self-esteem, emotional well-being, and social functioning, while also contributing to family stress and impaired quality of life. The International Children's Continence Society (ICCS) defines NE

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as occurring in children aged ≥5 years, the developmental stage when nighttime bladder control is generally expected, with episodes persisting at least twice weekly for three consecutive months [1]. NE is subclassified into primary NE (PNE), when continence has never been achieved, and secondary NE (SNE), when symptoms reappear after at least six months of sustained dryness, often in association with organic or psychological triggers. Furthermore, NE is categorized as monosymptomatic (MNE), when it occurs in isolation, and non-monosymptomatic (NMNE), when accompanied by lower urinary tract symptoms (LUTS) [2, 3]. Epidemiological studies indicate that prevalence decreases with age, affecting 15% of five-year-olds, 13% of six-year-olds, and 5–10% of seven-year-olds, eventually declining to 1–2% during adolescence and adulthood. Importantly, NE is frequently misunderstood as willful behavior, which may result in inappropriate punishment, emotional harm, and, in severe cases, abuse [4, 5]. The pathophysiology of NE is multifactorial, with four principal mechanisms: 1) nocturnal polyuria due to insufficient antidiuretic hormone (ADH, vasopressin) secretion, 2) detrusor overactivity, 3) arousal dysfunction, and 4) genetic predisposition, with family history serving as a strong predictive factor. Several modifiers of disorder persistence and severity have been identified. Sleep disturbances, including altered non-REM architecture, high arousal thresholds, and delayed onset, are prominent contributors. Sleep-disordered breathing, such as obstructive sleep apnea, exacerbates NE by inducing nocturnal polyuria and impairing arousal responses [6–9]. Behavioral and psychological comorbidities, including attention deficit hyperactivity disorder, anxiety, and stress, further modulate symptom severity [10–13]. Other contributing factors include constipation, which reduces bladder capacity, and systemic comorbidities such as obesity or endocrine dysfunctions leading to increased nocturnal diuresis [14, 15]. Management strategies for NE are multifaceted, integrating both behavioral and pharmacological interventions. Non-pharmacological approaches are typically first-line and include NE alarms, which achieve sustained success rates of 50–70%, alongside bladder training, pelvic floor exercises, and dietary modifications [16]. Pharmacological treatment is usually reserved for patients with persistent or severe symptoms and includes desmopressin (dDAVP) and, in selected cases, anticholinergic agents. Combination regimens often outperform monotherapy, leading to improved treatment response and reduced relapse rates. In recent years, novel oral lyophilizate (MELT) formulations of desmopressin have been introduced, offering the theoretical advantage of faster absorption and greater convenience compared to traditional tablets [17–22]. Nonetheless, pediatric use is associated with specific challenges: children often chew or swallow the MELT formulation prematurely, potentially impairing sublingual absorption and reducing bioavailability. These practical concerns raise important questions regarding the clinical efficacy of MELT versus tablet formulations in real-world pediatric populations. This study aims to compare the efficacy of desmopressin tablet versus MELT formulations in the treatment of pediatric patients with MNE.

MATERIAL AND METHODS

This monocentric, retrospective, randomized study was conducted at the Enuresis Center, Operative Research Unit of Pediatrics, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy (FPCBM). A total of 536 pediatric patients, aged 5–18 years, with a diagnosis of NE were included and followed between January 2024 and April 2025. Written informed consent was systematically obtained from the legal representatives of all participating patients prior to inclusion in the study. This study was conducted in accordance with the regulatory standards of Good Clinical Practice and with the World Medical Association Declaration of Helsinki and was approved by the Pediatric Unit of Campus Bio-Medico University Hospital (January 2024).

Inclusion and exclusion criteria

Eligible patients were aged 5–18 years (mean ±SD: 8.7 ±2.8 years), diagnosed with PNE, and treated with desmopressin at a predefined dose of 0.2 mg or 2 × 0.2 mg. Patients were recruited from the Enuresis Center, Operative Research Unit of Pediatrics, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, between January 2024 and April 2025. All patients met the ICCS criteria for NE and had not received treatment for NE in the previous three months. Exclusion criteria included SNE, presence of LUTS, underlying organic or neurological bladder dysfunction, and diabetes mellitus. Each patient's family history of bladder dysfunction and baseline frequency of wet nights per week were recorded. Clinical evaluation included urinalysis, uroflowmetry, bladder ultrasound, and post-void residual measurement. After clinical assessment, children and their families were invited to participate in the study. Patients completed a voiding diary for three months, enabling weekly quantification of NE episodes and assessment of therapeutic response.

Measures

Demographic and clinical variables were collected via standardized interviews administered to parents. Treatment response was classified as follows:
- full responders: decrease in wet nights higher than 90%;
- partial responders: decrease in wet nights between 50% and 90%;
- non-responders: decrease in wet nights less than 50%.

Outcome measures

The primary objective was to compare efficacy, measured as the number of wet nights per week, tolerability, assessed by the nature and frequency of adverse events, as well as ease of use and treatment compliance at the end of the observation period.

Statistical analyses

Descriptive statistics were computed for all demographic and clinical variables. Continuous variables were summarized as means with standard deviations (SD) or medians with interquartile ranges (IQR) when distributions were non-normal, while categorical variables were reported as frequencies and percentages. Normality of continuous data was assessed using the Shapiro–Wilk test.

Between-group differences in therapeutic response (full, partial, non-responders) were primarily assessed using the χ^2 test for independence. When expected cell counts were <5, Fisher's exact test was applied to ensure robustness of the results. In addition, effect size was quantified using Cramer's V to evaluate the strength of association beyond statistical significance.

To account for potential confounding factors (e.g., age, sex, baseline frequency of wet nights), exploratory logistic regression models were fitted to estimate adjusted odds ratios (OR) with 95% confidence intervals (CI) for the likelihood of full response versus non/partial response across treatment groups. Although the study was not primarily designed for multivariable analysis, this approach was implemented to increase interpretability of findings in light of possible imbalances between cohorts.

Missing data were handled using pairwise deletion under the assumption of missing completely at random (MCAR). Sensitivity analyses excluding patients with incomplete diaries were performed to verify the robustness of results. No correction for multiple testing was applied given the exploratory and hypothesis-generating nature of the study.

All analyses were conducted with a two-sided significance threshold of $p < 0.05$. Statistical computations were performed using SPSS version 24.0 (IBM Corp., Armonk, NY) and R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Bioethical standards

This study was conducted in accordance with the regulatory standards of Good Clinical Practice and with the World Medical Association Declaration of Helsinki and was approved by the Pediatric Unit of Campus Bio-Medico University Hospital (January 2024). The authors have given their written informed consent.

RESULTS

A statistically significant association in efficacy was observed between the two formulations ($\chi^2 = 6.202$, 2 df, $P = 0.045$). Patients treated with the tablet formulation demonstrated a superior response compared to the MELT group:
- full responders: 30.2% (tablet) vs 23.2% (MELT);
- partial responders: 49.0% (tablet) vs 43.2% (MELT);
- non-responders: 20.8% (tablet) vs 33.7% (MELT).

These findings indicate a higher rate of complete response and a lower rate of no response among patients receiving the tablet formulation.

DISCUSSION

This study provides a comprehensive comparison of the efficacy of desmopressin tablet versus MELT formulations in pediatric patients with MNE. Our findings demonstrate a statistically significant difference between the two formulations, with the tablet group exhibiting a higher rate of optimal response (30.2% vs 23.2%), a greater proportion of partial responders (49.0% vs 43.2%), and a lower rate of absent response (20.8% vs 33.7%). These results suggest that, in routine clinical practice, the tablet formulation may offer a more reliable and reproducible therapeutic effect.

The observed differences in efficacy may be primarily attributed to pharmacokinetic and administration factors. The MELT formulation is designed for sublingual absorption, theoretically allowing for faster onset and potentially improved bioavailability. However, in pediatric patients, clinical observations indicate that the MELT formulation is often chewed or swallowed prematurely, which can compromise sublingual absorption and reduce systemic bioavailability, leading to suboptimal therapeutic effects. In contrast, tablets are designed for gastrointestinal

absorption, which, although slightly slower, is more predictable and less dependent on patient behavior. This may explain the higher rates of both optimal and partial responses observed in the tablet group.

Our findings diverge from several previous reports in the literature. While earlier studies suggested superior efficacy of the MELT formulation, our results indicate that tablet desmopressin may represent an equally or more effective option for pediatric patients. Juul et al. [22] reported in a randomized crossover study that the likelihood of being a responder was significantly higher with desmopressin MELT compared to tablet (odds ratio 2.0; 95% CI: 1.07–3.73; $p = 0.03$). However, Lottmann et al. [21], in an open-label, randomized crossover trial including 221 patients, documented comparable efficacy between formulations (MELT: 1.88 ±1.94 vs tablet: 1.90 ±1.85 wet nights/week), with slightly higher compliance for MELT (≥80% compliance: 94.5% vs 88.9%; $p = 0.059$). Pharmacokinetic studies further demonstrate that desmopressin MELT provides plasma exposure comparable to the higher-dose tablet, with reduced interindividual variability [19]. Pharmacodynamic evaluations show that the MELT formulation results in significantly lower diuresis rates and longer duration of action compared to the tablet during the plateau (3–5 h, $p < 0.02$) and late (5–8 h, $p < 0.005$) phases, providing a superior pharmacodynamic profile with more sustained antidiuretic effects and greater consistency [19–22].

Overall, these data indicate that the MELT formulation may confer pharmacokinetic and pharmacodynamic advantages. However, discrepancies between theoretical benefits and observed clinical outcomes may be influenced by patient compliance, population characteristics, and methodological factors. Our findings underscore that tablet formulations remain highly effective, and the choice of formulation should consider patient-specific factors, including age, meal timing, and feasibility of administration. These observations also highlight the need to re-evaluate current assumptions and encourage further research to clarify the clinical implications of divergent results.

These findings align with prior studies emphasizing that proper administration technique is critical to achieving the expected pharmacological effect of desmopressin, particularly in younger children [20, 23]. For example, Topalovic et al. [24] reported that age under 7 years is a predictor of relapse in children with MNE treated with the MELT formulation, potentially due to lower compliance in medication administration. Challenges associated with the MELT formulation – especially in children under 10 years – underscore the importance of considering both the pharmacological properties of the drug and practical aspects of its administration. Patient age, cognitive development, and ability to follow instructions can substantially influence therapeutic outcomes, particularly for medications relying on sublingual absorption. In this context, tablet formulations may be preferable in children who are less likely to follow instructions for sublingual administration or who have difficulty with MELT dissolution, ensuring consistent and reliable therapeutic effects [25].

Limitations of this study include its retrospective design and single-center setting, which may limit the generalizability of our findings and introduce an inherent risk of bias. In addition, the unequal size of the treatment groups (MELT vs tablet) may have influenced the robustness of the comparisons. Adherence and correct administration technique were not directly observed, with assessment relying on caregiver reports, thereby introducing potential reporting bias. The absence of pharmacokinetic measurements further limits the ability to directly link differences in absorption to clinical outcomes. Moreover, the statistical significance of the main findings was marginal. Future prospective, multicenter studies incorporating pharmacokinetic analyses, objective adherence monitoring, balanced group sizes, and long-term follow-up would help clarify the relationship between formulation, administration, patient preference, and efficacy.

CONCLUSIONS

Our study indicates that desmopressin tablets provide superior therapeutic efficacy compared to the MELT formulation in pediatric patients with MNE, as evidenced by higher rates of optimal response and lower rates of non-response. The findings emphasize the importance of considering both pharmacological characteristics and practical administration factors when selecting a desmopressin formulation. Tailoring treatment to individual patient needs, particularly in younger children, may improve outcomes and reduce the burden of nocturnal enuresis on patients and their families. Further studies with a larger number of patients are needed to confirm or refute these preliminary data.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

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ETHICS APPROVAL STATEMENT

This study was approved by the Pediatric Unit of Campus Bio-Medico University Hospital (January 2024).

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