Monosymptomatic Nocturnal Enuresis Treatment Using Alarm-Therapy and Desmopressin: A Meta-analysis Approach

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ABSTRACT

Background: One of the common pediatric issues is monosymptomatic nocturnal enuresis (MNE). MNE is involuntarily urine-voiding in night sleep without lower urinary tract symptoms, such as daytime frequency, incontinence, or urgency. Alarm therapy and desmopressin have been used for treating MNE, but there is no clear comparison of the effectiveness of the two modalities. Objective: This study aimed to compare the efficacy of alarm therapy and desmopressin and strategies to improve the therapy. Methods: Study searches were conducted on PubMed, Embase, and Cochrane with a time span of 2010 to 2021. The keywords used were desmopressin, alarm therapy, pediatrics, and monosymptomatic enuresis. The study included an RCT in English, and no subjects were dropped out. Studies without a definite number of subjects were excluded. Results: As many as 12 studies were included in the meta-analysis, 9 of which looked for response rates, and 3 were for desmopressin-withdrawal optimization strategy. Alarm therapy was superior to desmopressin in well-motivated parents and patients (p=0.02), with a combined risk ratio of 1.10 in the low heterogeneity population (Z-score = 2.31; I² = 32%). A strategy that could reduce the risk of desmopressin-withdrawal was a structured dose reduction rather than a sudden dose reduction (p=0.001; I²=0%; Z-score = 3.26). However, therapy discontinuation based on time did not differ the risk (p=0.24; I²=0%; Z-score = 1.17). Conclusion: The meta-analysis shows that alarm therapy has a better response rate than desmopressin in proactive parents. However, desmopressin may be an option in the opposite subjects, and it is necessary to use structured strategies to optimize the treatment.

Keywords: Alarm therapy, desmopressin, monosymptomatic nocturnal enuresis.

1. BACKGROUND

One of the common pediatric issues is monosymptomatic nocturnal enuresis (MNE). MNE is involuntarily urine voiding in night sleep without lower urinary tract symptoms, such as daytime frequency, incontinence, or urgency (1). For decades, alarm therapy has been used to treat nocturnal enuresis in children. These alarms work as humidity sensors connected to underwear or mattress and produce sound or vibration signals. In different designs, the effect of the body sensor is better than the pad sensors (2).

Desmopressin is a synthetic vasopressin analog, which has been used in clinical practice to treat nocturnal enuresis for decades and provided a good effect (3). The usual doses for oral tablets and oral gels are 0.2 to 0.4 mg and 120 to 240 micrograms, respectively (5). Desmopressin can be administered in intranasal administration, oral tablets, and oral thawed lyophilisate (4). However, the FDA withdrew the indication of intranasal administration of desmopressin to treat nocturnal enuresis in children due to the possible occurrence of hyponatremia, seizures, and death. Although alarm therapy and desmopressin had been used for the treatment, there is no clear comparison of the effectiveness of the two modalities (1). Therefore, it is necessary to reevaluate alarm therapy and desmopressin usage to take the most advantageous strategy.

2. OBJECTIVE

This study aimed to compare the efficacy of alarm therapy and desmopressin, as well as strategies to improve through a literature review.
3. METHODS

Resources of Information and Search Strategy

This meta-analysis was carried out according to PRISMA guidelines.9 Studies were searched using electronic databases: Pubmed, Cochrane, and Embase in the period of 2010-2021. The keywords used to search the research registered in the database were “nocturnal” AND “enuresis” AND “pediatric” AND “alarm therapy” AND “desmopressin”. Full articles in English were included.

Eligibility Criteria

The studies were selected if alarm therapy and the use of desmopressin in pediatric monosymptomatic nocturnal enuresis in a randomized controlled trial design were assessed, and the full text was available. Unpublished articles, abstracts, studies not written in English were excluded. The clinical question (PICO) in this review was in patients diagnosed with monosymptomatic nocturnal enuresis, which outperformed alarm therapy and desmopressin in response rate (Table 1).

Study-Selection and Data-Collection

Study selection and data-collection were performed independently in an unblinded standardized manner by two reviewers (B.D. and P.N.) given the same portion. Discrepancies between the two authors were resolved by consensus. All studies were screened to identify duplicates once they were collected in one folder. Subsequently, the selected articles were assessed based on titles and abstracts using the inclusion and exclusion criteria described earlier. Selected studies were reviewed based on their full-text version.

Bias Assessment and Statistical Methods

The method quality in every study was assessed by the assessment tool risk of bias based on the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) by AFP. Bias assessment included allocation bias, selection, attrition, reporting, blinding, and other sources of bias.

Output Measures and Statistical Analysis

The primary outcome was the response rate of alarm therapy and desmopressin on disease progression. Pooled Risk Ratio (RR) was calculated to find the outcome. Nocturnal enuresis definition was used as the basis for the analysis due to varied definitions. The effect size was using a 95% confidence interval. The heterogeneity of study results was determined using the Cochrane Q test. Random Effect (REM) was used if statis-
tical heterogeneity was found in the study ($I^2 > 50\%$), while Fixed Effect Model (FEM) was used if $p \leq 0.05$ (2 sided) was considered statistically significant.

4. RESULTS
We collect the relevant papers by searching in respective search engines. Study searches were conducted on PubMed, Embase, and Cochrane with a time span of 2010 to 2021. Four-hundred twenty one records were identified through database searching, however due to duplication we removed 214 records. Two-hundred seven records excluded due to insufficient quantitative data provided and 5 publication excluded due to inconclusive amount of control. This study includes 12 studies in the pooled analysis.

Alarm therapy was significantly better than desmopressin in well-motivated parents and patients ($p=0.02$), with a pooled risk ratio of 1.10 in a low heterogeneity population ($Z$-score = 2.31; $I^2 = 32\%$). The described strategies for improving desmopressin withdrawal were entirely conducive to structured strategies, rather than sudden dose dependent manner ($p=0.001$; $I^2=0\%$; $Z$-score = 3.26) but not with time dependent parameter ($p=0.24$; $I^2=0\%$; $Z$-score = 1.17).

5. DISCUSSION
Desmopressin is an endogenous synthetic analog of the antidiuretic hormone, or vasopressin, which mainly reduces urine production. (12,13). Treatment with desmopressin with a structured withdrawal technique (dose reduction, therapy discontinuation) resulted in a better relapse-free rate than abrupt drug discontinuation. A structured discontinuation method based on dose shows improved results. According to some reviews, desmopressin can produce an immediate response but provides a high relapse rate after abrupt discontinuation. Applying the clinical and physiological principles mentioned above can clarify the basis for the high recurrence rate in children with nocturnal enuresis after abrupt drug discontinuation. Several studies have been conducted to study structured, gradual discontinuation of desmopressin as a way to maintain long-term efficacy and prevent recurrence (14).

Several studies have shown that desmopressin has a better-sustained response rate when discontinued systematically (structured?) than a single enuresis alarm (15). However, to date, no studies clearly state and explain the biological mechanisms that play a role in increasing the response to desmopressin therapy with gradual systematic discontinuation.

A plausible explanation of the mechanism for a better response to desmopressin administration with systematic discontinuation might be continuous stimulation and maturation of posterior pituitary antidiuretic hormone and maintenance of circadian rhythms. However, existing studies do not show sustained urinary osmolality levels of desmopressin responders after structural withdrawal (16-18). In contrast, several studies have shown that desmopressin may have more mechanisms of action in the treatment of nocturnal enuresis, such as
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| Study or Subgroup | Structured Strategy | Abrupt Strategy | Risk Ratio | Risk Ratio |
|-------------------|---------------------|----------------|-----------|-----------|
|                   | Events | Total | Events | Total | Weight | M-H, Fixed, 95% CI | M-H, Fixed, 95% CI |
| Gökke 2014        | 39     | 71    | 30     | 71    | 51.0%  | 1.30 [0.32, 1.63] |
| Tang 2010         | 46     | 50    | 28     | 47    | 49.0%  | 1.54 [1.20, 1.99] |
| **Total (95% CI)**| 85     | 118   | 118    | 100.0%| 1.42 [1.15, 1.75] |

Figure 5: Forest Plot of desmopressin withdrawal – dose parameter

Figure 6: Forest plot of desmopressin withdrawal – time parameter

Central nervous signal transduction, wakefulness, circadian rhythm, and renal tubular proteins; thus, gradual discontinuation of therapy may improve response continuity (19-20). Further studies exploring and explaining the mechanism of therapy effectiveness with a structured gradual discontinuation method were suggested.

6. CONCLUSION

This meta-analysis showed that alarm therapy has a better response rate than desmopressin in proactive parents. However, in different subjects, desmopressin is still a preferred strategy of gradual dose reduction to optimize the treatment.

- **Author’s Contribution:** The investigation was arranged by AFP, BD, and PN who also performed research, provided research materials, and collated and processed data. AFP and BD were responsible for data analysis and interpretation. AFP, BD, and PN contributed with the initial and final versions of the article as well as practical assistance. All authors were in control of the manuscript’s substance after critically reviewing and approving the final text.
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