Nephro-Urol Mon. 2025 February; 17(1): e153413 https://doi.org/10.5812/numonthly-153413

Published Online: 2025 January 1 **Systematic Review**

Comparing Desmopressin Plus Anticholinergics Versus Desmopressin Alone for Monosymptomatic Nocturnal Enuresis: A Systematic Review and Meta-Analysis

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Received: 11 August, 2024; **Revised:** 29 October, 2024; **Accepted:** 5 December, 2024

Abstract

Context: Monosymptomatic nocturnal enuresis (MNE) is the most common type of enuresis. Desmopressin is the most widely used pharmacological treatment for MNE, while combination therapy with anticholinergics is recommended for patients who are refractory to monotherapy.

Objectives: This meta-analysis aims to evaluate the efficacy and safety of combination therapy (desmopressin with an anticholinergic agent) compared with desmopressin alone in the treatment of MNE.

Methods: A comprehensive search was conducted across multiple databases, including Cochrane, Scopus, ScienceDirect, PubMed, and Embase, along with manual searching. Clinical trials were included in this meta-analysis, specifically focusing on the comparison between desmopressin combined with an anticholinergic agent and desmopressin alone in pediatric patients with MNE. The primary outcomes assessed were complete remission (90 - 100% reduction in mean wet nights compared to baseline) and partial remission (50 - 90% reduction), with the latter being considered as part of total remission (sum of complete and partial remission). The secondary outcome measured adverse effects. The risk of bias was evaluated using Cochrane tools, and a forest plot was generated using Review Manager 5.4.

Results: Eleven studies involving 872 pediatric patients (aged 5 to 17 years) with MNE were included in this meta-analysis. The analysis assessed the efficacy of desmopressin combined with anticholinergics compared to desmopressin as monotherapy in achieving remission of enuresis at one month and three months after initiating therapy. Results demonstrated that combination therapy yielded favorable outcomes for enuresis remission. At one month, the risk ratio (RR) for complete remission favored combination therapy (RR: 1.52, 95% CI 1.14 - 2.02), as did the RR for total remission (RR: 1.15, 95% CI 1.02 - 1.30). However, both outcomes exhibited heterogeneity (I^2: 71% and 59%, respectively). At three months, the combination therapy continued to show benefits, with a RR of 1.34 (95% CI 1.11 - 1.63) for complete remission and 1.10 (95% CI 1.00 - 1.21) for total remission, although the statistical significance was weaker (P = 0.003 and P = 0.05, respectively). Both treatment groups reported minor side effects.

Conclusions: Combination therapy of desmopressin and anticholinergics showed favorable outcomes for enuresis remission. Further research is required to explore the long-term benefits and potential side effects.

Keywords: Deamino Arginine Vasopressin, Cholinergic Antagonists, Nocturnal Enuresis

1. Context

Nocturnal enuresis is a common complaint experienced by children. Nocturnal enuresis is defined as incontinence that occurs only during sleep and is experienced for at least three consecutive months in children aged over 5 years. The prevalence of nocturnal enuresis decreases with age: Around 15% of 5-year-old children experience nocturnal urinary incontinence, while only about 5 - 10% experience it at 7 years old, and 1 - 2% at ≥ 15 years old. It is known that spontaneous resolution of nocturnal enuresis occurs in up to 15% (1, 2).

In classification, nocturnal enuresis is divided into monosymptomatic nocturnal enuresis (MNE) and non-monosymptomatic nocturnal enuresis (NMNE). Monosymptomatic nocturnal enuresis is intermittent nocturnal incontinence without lower urinary tract symptoms. On the other hand, NMNE is nocturnal enuresis accompanied by lower urinary tract symptoms. Generally, enuresis can have a negative impact on a child's psychosocial development. Enuresis can also be associated with various other comorbidities such as learning disorders, neurological diseases, attention-deficit/hyperactivity disorder, and sleep disorders (1). Findings from a meta-analysis conducted by Cai et al. in 2023 showed that combination therapy was superior to desmopressin monotherapy in treating nocturnal enuresis. However, while this meta-analysis examined nocturnal enuresis as a whole, our meta-analysis will focus specifically on MNE (3).

Desmopressin, a synthetic analog of vasopressin, has been used for decades to manage nocturnal enuresis and has proven to be effective. Desmopressin works by reducing urine volume and intravesical pressure during the night. In conditions of high nighttime diuresis, desmopressin administration has shown success rates of up to 70%. However, some patients may show resistance to desmopressin or suspicion of having overactive bladder at night, so desmopressin administration can be combined with anticholinergics.

2. Objectives

This systematic review aims to evaluate the effectiveness and safety of combination therapy (desmopressin and anticholinergic agents) compared to single desmopressin therapy in managing MNE in children (2, 4, 5).

3. Data Sources

3.1. Search Strategy and Selection Criteria

This review adhered to the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines. We conducted literature searches using electronic databases: Science Direct, Scopus, Cochrane, Embase, PubMed, as well as manual searching with the following keywords (Table 1). Literature searching was performed from June to August 2023. Studies were considered eligible for inclusion if they were conducted in English or Indonesian, had full-text availability, were clinical trials, participants were aged 0 - 18 years, and the studies evaluated the comparison between desmopressin and anticholinergic treatment versus desmopressin alone in pediatric patients with MNE. Articles were excluded if their type was unsuitable, such as abstracts, reviews, comments, or similar types.

3.2. Definition of Intervention and Outcomes

We defined the control group as patients receiving only desmopressin, while the intervention group consisted of patients receiving a combination of desmopressin and anticholinergic treatment. The primary outcome assessed both complete remission (90 - 100% reduction in mean wet nights compared to baseline) and partial remission (50 - 90% reduction), with the latter being considered as part of total remission, which is the sum of complete and partial remission. Meanwhile, the secondary outcome assessed the adverse effects.

3.3. Study Selection and Data Extraction

Three reviewers independently screened the titles and abstracts of studies identified through database searching and assessed the eligibility of each study based on inclusion and exclusion criteria. The chosen studies were then subjected to data extraction, which involved collecting the following information: (1) First author's surname; (2) publication year and location; (3) study design; (4) age of the population included in the study; (5) entry time of the population into the study; (6) intervention given (drug and dose); (7) outcomes at 1 month and 3 months; (8) side effects.

3.4. Quality Appraisal

The risk of bias was evaluated using tools provided by Cochrane. These evaluations were performed independently by all authors (M.A.I.M., N.A.T., and F.A.R.). Each study included was classified as "low-risk," "high-risk," or "unclear risk" based on Cochrane risk-of-bias domains. If there was any discrepancy regarding the bias assessment, it was resolved by discussion among all the authors.

3.5. Statistical Analysis

A forest plot was generated using Review Manager 5.4. Risk ratio (RR) was used to evaluate primary

Table 1. Database Search Strategy Keywords

Databases	Search Keywords
Scopus	(Nocturnal Enuresis) AND (Desmopressin) AND (anticholinergic)
Science Direct	(Nocturnal Enuresis) AND (Desmopressin) AND (anticholinergic)
Cochrane	(Nocturnal Enuresis) AND (Desmopressin) AND (anticholinergic or oxybutynin or hyoscyamine)
Embase	(Nocturnal Enuresis) AND (Desmopressin) AND (anticholinergic OR oxybutynin OR hyoscyamine)
PubMed	(Nocturnal Enuresis) AND (Desmopressin) AND (anticholinergic)
Hand searching	(Nocturnal Enuresis) AND (Desmopressin) AND (anticholinergic)

outcomes in included studies, such as the incidence of remission (at month 1 and month 3 after treatments). All meta-analyses were performed using random-effects models. Heterogeneity of the study was evaluated with I^2 statistics. When the I^2 value was greater than 50%, this indicated a high level of heterogeneity. If the P-value was < 0.05, the result was considered statistically significant. Side effects were only analyzed descriptively.

4. Results

4.1. Selection of Studies and Study Characteristics

From database searching, 446 publications were identified. From manual searching, 5 additional publications were also identified. After duplication removal, 434 articles remained for initial screening. Selected articles were the result of agreement between 3 authors (M.A.I.M., N.A.T., and F.A.R.). Four hundred seven articles were excluded as they did not meet eligibility criteria based on the title and abstract. For the remaining 27 studies, 6 studies were excluded because the population did not meet eligibility criteria, 8 studies were excluded because the intervention did not meet eligibility criteria, and 2 studies were excluded because the desired outcome was not available. In total, 16 studies were excluded. The final screening yielded 11 clinical trials that met the eligibility criteria and were then included for analysis. The PRISMA flow diagram of our study can be seen in Figure 1.

Included studies in this meta-analysis were published between 2006 and 2021, with a total of 872 pediatric patients. The therapies for each study consisted of two groups, where one group was treated with desmopressin (either orally or nasally) and the other was treated with a combination of desmopressin and anticholinergic agents, such as oxybutynin, tolterodine, solifenacin, or propiverine. A summary of the characteristics of the included studies is shown in Table 2.

The included studies generally used remission (either complete or partial) as the primary outcome. Remission rates were typically measured at month 1 and month 3 post-treatment. The primary outcomes of the included studies can be seen in Table 3.

Four out of 12 included studies reported side effects from both desmopressin and combination therapy. The most common side effects were constipation and dry mouth. Other side effects reported included allergic reactions, nausea, loss of appetite, headache, and nasal irritation. The summary of side effect occurrence can be seen in Table 4.

4.2. Risk of Bias

As shown in Figure 2, all of the studies included in our study were assessed using seven domains from the Cochrane risk of bias tool. The domains included were random sequence generation, allocation concealment, selective reporting, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and other bias. Risk of bias was assessed by all authors, and any differences between studies were discussed to reach a resolution. All authors participated in the risk of bias assessment and reached a consensus on the final assessment.

4.3. Quantitative Analysis

Eleven clinical studies, consisting of 872 pediatric patients, were included for quantitative analysis. Our meta-analysis showed that patients receiving combination therapy had a significantly higher probability of achieving complete remission at 1 month and 3 months after therapy, with a RR of 1.55 (95% CI: 1.17 to 2.05) and 1.43 (95% CI: 1.16 to 1.76), respectively (Figures 3 and 4).

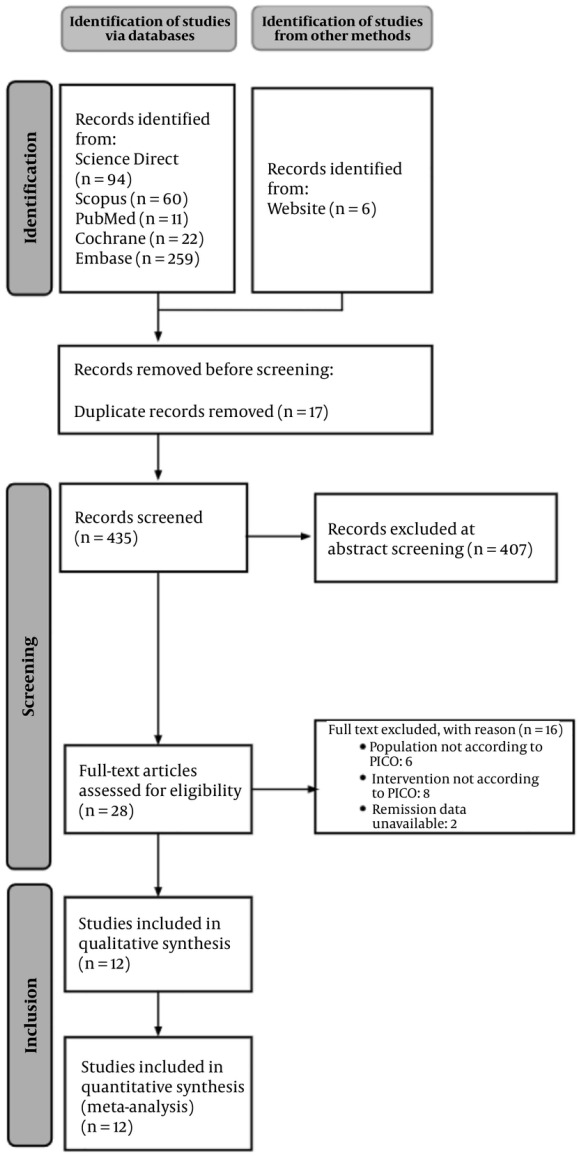

Figure 1. PRISMA flow diagram

When we analyzed patients with complete and partial remission (summed up and referred to as total remission), our analysis also showed that patients receiving combination therapy had a significantly higher probability of achieving remission at 1 month and 3 months (RR 1.16 (95% CI: 1.03 to 1.3) and 1.11 (95% CI: 1.02 to 1.19), respectively (Figures 5 and 6).

Similar side effects were observed in both the desmopressin group and the combination group. However, when conducting a meta-analysis of reported side effects, there was a slight but significant difference favoring combination therapy over desmopressin monotherapy in terms of adverse effects. The forest plot

Table 2. Study Characteristics

Studies (Year)	Location	Age	Entry Time	Intervention (Drug, Dose)	Number (Intervention/ Control)
Gozukucuk et al., 2021 (6)	Hisar Intercontinental Hospital, Dogus University, Istanbul, Turkey	6 - 16	Begin [a]	(A) Initial dose desmopressin 120 mg; non-responsive patients –> dose doubled (240 mg) after two weeks; (B) maximum dose desmopressin + 5 mg oxybutynin –> oxybutynin increased to max dose (10 mg), with 2.5 mg increases once in two weeks	183 (92/91)
Ghanavati et al., 2021 (7)	Imam Khomeini Hospital in Ahwaz	5 - 15	Begin [a]	(A) One puff of desmopressin nasal spray; (B) one puff of desmopressin nasal spray + 2 mg tolterodine; (C) one puff of desmopressin nasal spray + 5 mg solifenacin	62 (22 (A)/ 20 (B)/ 22 (C))
Shim et al., 2021 (8)	Hallym University Sacred Heart Hospital Pediatric Urology Clinic	6 - 14	Begin [a]	(A) Desmopressin lyophilisate (MELT) 120 µg only; (B) desmopressin lyophilisate (MELT) 120 µg plus propiverine 5 mg.	99 (50/49)
Kazi et al., 2020 (9)	Bahria University Medical & Dental College (PNS Shifa Hospital) and the National Institute of Child Health, Karachi	7 - 13	Begin [a]	(A) Zero point two mg desmopressin tab +5 mg oxybutynin; (B) zero point two mg desmopressin	84 (42/42)
Ravanshad et al., 2017 (10)	Ghaem Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran	5 - 15	Begin [a]	(A) Desmopressin nasal spray (10 µm/each nostril) + oxybutinin 5 mg; (B) desmopressin nasal spray (10 µm/each nostril)	59 (30/29)
Almusafer and Adel, 2017 (11)	University of Basrah	6 - 14	Begin [a]	(A) Twenty µm I/N; desmopressin + 5 mg oxybutynin, (B) Twenty µm I/N; desmopressin	41 (20/21)
Kazemi Rashed et al., 2013 (12)	Tabriz University of Medical Sciences	5 - 16	Begin [a]	(A) Tolterodine 2 mg tablets and nasal Desmopressin; with a dose of 20 µg; (B) placebo and nasal Desmopressin with a dose of 20 µg	99 (49/50)
Montaldo et al., 2012 (13)	Department of Pediatric Urology of the Second University of Naples	6 - 13	Failed [b]	(A) Two hundred forty µg desmopressin +; 5 mg Oxybutynin; (B) two hundred forty µg desmopressin + placebo	120 (61/59)
Azhir et al., 2008 (14)	Alzahra hospital, Iran	6 - 12	Begin [a]	(A) Zero point one mg desmopressin; tab + 5 mg oxybutynin, (B) zero point one mg desmopressin; tab	31 (10/21)
Austin et al., 2008 (15)	Washington University School of Medicine, St Louis Children's Hospital, St Louis, Missouri	6 - 17	Failed [b]	(A) Desmopressin (0.6 mg; total per night) and placebo; (B) desmopressin (0.6 mg; total per night) and tolterodine LA (4 mg)	34 (18/16)
Radvanska et al., 2006 (16)	Department of Pediatrics, Comenius University Medical School, Bratislava, Slovakia.	6 - 15	Failed [b]	(A) Twenty µg desmopressin; +; 5 mg oxybutynin; (B) twenty µg desmopressin	60 (19/60) sequential
Park et al, 2014 (17)	Department of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, Suwon, Republic of Korea	5 - 16	Begin [a]	(A) Desmopressin 0.2 mg daily and propiverine 10 mg daily; (B) desmopressin 0.2 mg daily	84 (42/42)

[a] Begin: No prior history of failed desmopressin therapy.

[b] Failed: Prior history of failed desmopressin therapy.

Table 3. Primary Outcome of Included Studies

Studies (Year)	1 Month						3 Months					
	Complete Remission		Partial Remission		Total Response		Complete Remission		Partial Remission		Total Response	
	D	I	D	I	D	I	D	I	D	I	D	I
Gozukucuk et al., 2021 (6)	65/91	69/92	6/91	10/92	73/91	79/92	70/91	80/92	5/91	6/92	75/91	86/92
Ghanavati et al., 2021 (7)	12/22	B: 1, C: 17, total: 32/42	NA	NA	NA	NA	14/22	B: 17, C: 19, total: 36/42	NA	NA	NA	NA
Shim et al., 2021 (8)	4/49	9/50	18/49	20/50	22/49	29/50	11/49	22/50	27/49	25/50	38/49	47/50
Kazi et al., 2020 (9)	13/42	13/42	27/42	29/42	40/42	42/42	36/42	42/42	5/42	0	41/42	42/42
Ravanshad et al., 2017 (10)	21/29	25/30	NA	NA	NA	NA	13/29	26/30	NA	NA	NA	NA
Almusafer and Adel, 2017 (11)	10/21	10/20	6/21	4/20	16/21	14/20	12/21	12/20	6/21	6/20	18/21	18/20
Kazemi Rashed et al., 2013 (12)	17/50	27/49	23/50	17/49	40/50	44/49	NA	NA	NA	NA	NA	NA
Montaldo et al., 2012 (13)	3/59	13/61	15/59	7/61	18/59	20/61	NA	NA	NA	NA	NA	NA
Azhir et al., 2008 (14)	1/21	3/10	1/21	3/10	2/21	6/10	5/21	7/10	11/21	2/10	16/21	9/10
Austin et al., 2008 (15)	1/16	3/18	4/16	5/18	5/16	8/18	NA	NA	NA	NA	NA	NA
Radvanska et al., 2006 (16)	21/60	19/19	20/60	0/19	41/60	19/19	NA	NA	NA	NA	NA	NA
Park et al, 2014 (17)	6/49	13/49	24/49	25/49	30/49	38/49	16/49	32/49	25/49	15/49	41/49	47/49

Abbreviations: NA, not available; D, desmopressin; I, intervention (combination); B, one puff of desmopressin nasal spray + 2 mg tolterodine; C, One puff of desmopressin nasal spray + 5 mg solifenacin.

representing the reported side effects is shown in Figure 7.

Our meta-analysis may have publication bias, as indicated by the asymmetry in the funnel plot analysis for all included studies. The funnel plot representing these studies is shown in Figure 8.

To address the potential for publication bias, we performed a sensitivity analysis by excluding studies with wide confidence intervals. Specifically, we excluded four studies with 95% confidence interval ranges greater than 5.00. Based on this sensitivity analysis, patients receiving combination therapy still had a significantly higher probability of achieving complete remission at 1

Table 4. Reported Side Effects [a]

Variables	Desmopressin	Combination
Allergic reaction	7 (5)	0 (0)
Nausea	7 (5)	1 (0.7)
Loss of appetite	2 (1.4)	16 (11.3)
Headache	12 (8.5)	2 (1.4)
Constipation	26 (18.4)	21 (14.8)
Dryness of mouth	26 (18.4)	21 (14.8)
Nasal irritation	1 (0.7)	2 (1.4)
Total population	141	142

[a]Values are expressed as No. (%).

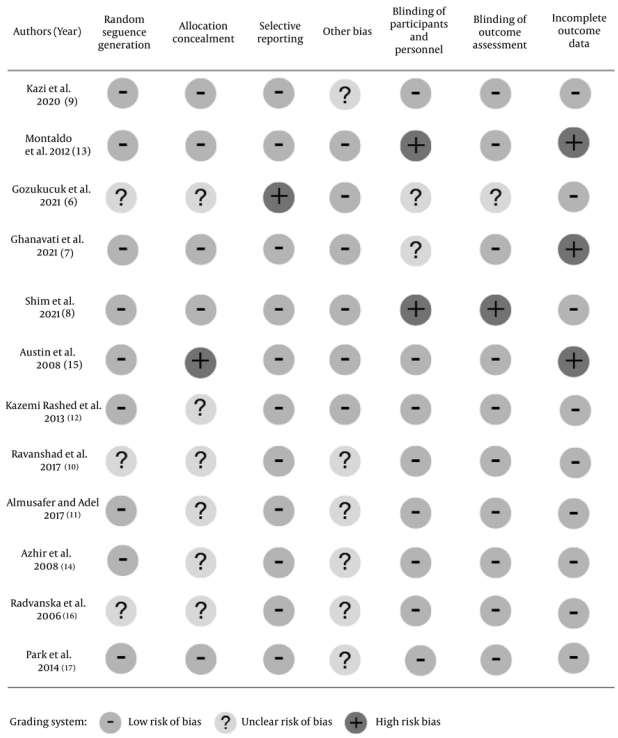

Figure 2. Risk of bias summary (6-17)

month after therapy, with a RR of 1.41 (95% CI: 1.06 to 1.86) (Figure 9).

5. Discussion

Our meta-analysis demonstrated that combination therapy of desmopressin and anticholinergics is significantly more effective in achieving remission for MNE pediatric patients compared to desmopressin monotherapy. At one month after therapy, the RR for complete remission and total remission favored the combination therapy, with a RR of 1.52 (95% CI: 1.14 - 2.02) and 1.15 (95% CI: 1.02 - 1.30), respectively. These findings suggest that pediatric patients receiving combination therapy are more likely to have reduced wet nights

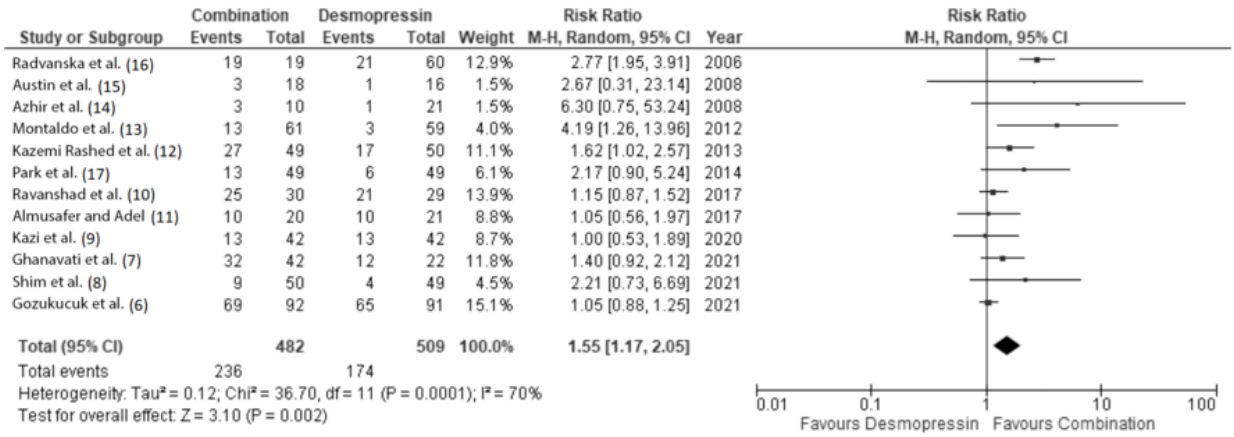

Figure 3. Forest plot of complete remission at 1 month (6-17)

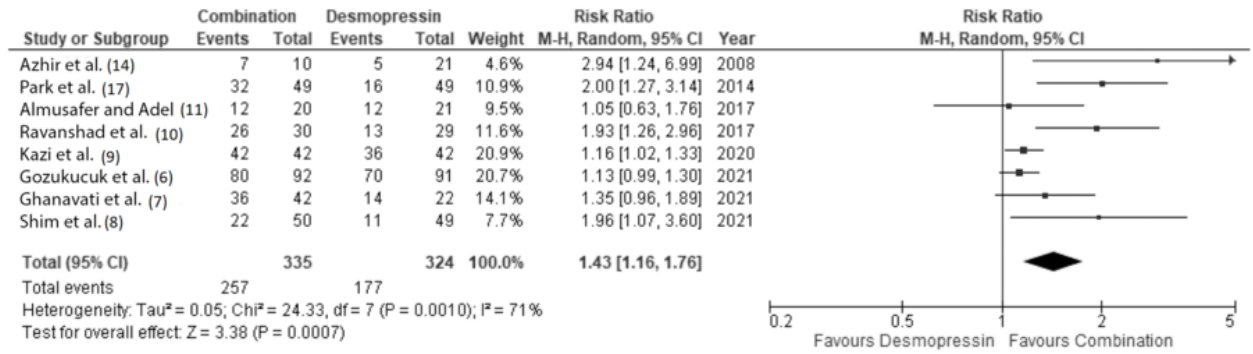

Figure 4. Forest plot of complete remission at 3 months (6-11, 14, 17)

compared to those who only received desmopressin monotherapy. These results align with previous studies that have shown increased efficacy when these two pharmacological agents are combined (12, 13, 16).

One possible mechanism to explain the efficacy of combination therapy is the enhancing mechanisms of action between desmopressin and anticholinergics. Desmopressin, an analog synthetically made to mimic vasopressin, increases water reabsorption in the kidneys, thus resulting in reduced urine production at night. On the other hand, anticholinergics could reduce detrusor activity by inhibiting muscarinic receptors in detrusor muscles. By reducing urine production and decreasing detrusor overactivity, this could result in a more comprehensive treatment for MNE. In a study conducted by Azarfar et al., 59 patients with primary MNE were selected and divided into two groups: The first group received desmopressin and oxybutynin, and the second group received desmopressin and tolterodine. The results were satisfactory, although it showed that desmopressin plus tolterodine performed better than desmopressin plus oxybutynin (18).

Our results demonstrate the superiority of combination therapy for both clinical outcomes and

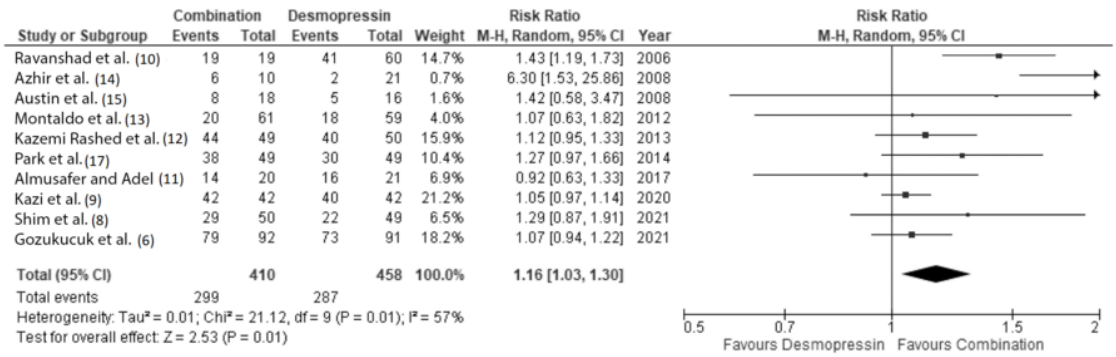

Figure 5. Forest plot of total remission at 1 month (6, 8-15, 17)

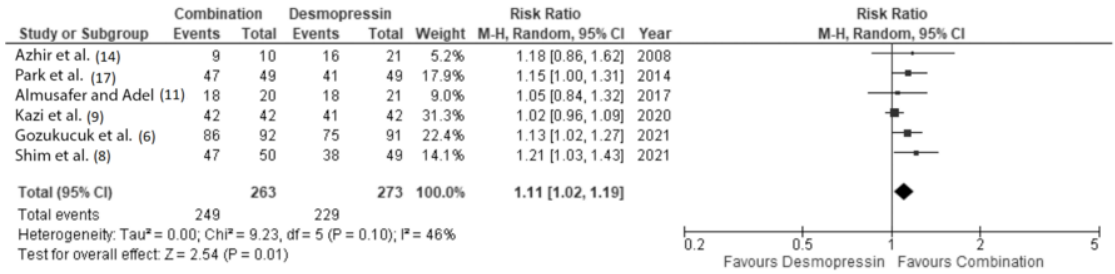

Figure 6. Forest plot of total remission at 3 months (6, 8, 9, 11, 14, 17)

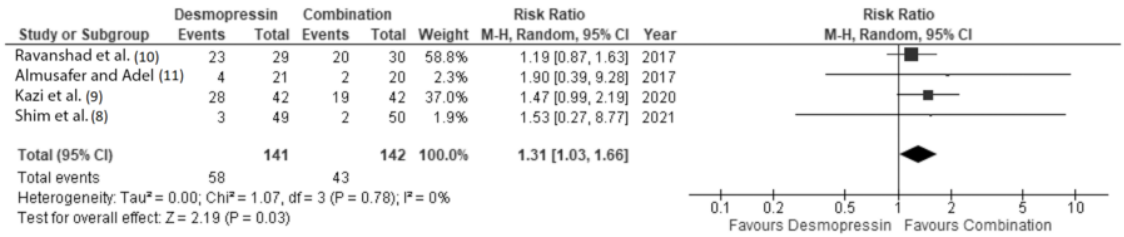

Figure 7. Forest plot of reported side effects in both groups (8-11)

adverse effects. However, our findings regarding side effects were contradicted by a meta-analysis performed by Cai et al. in 2023, which stated that the incidence of adverse reactions was not significantly different between the desmopressin and combination groups (3). The most common side effects reported were constipation and dryness of the mouth. In an article written by Ghossein et al., anticholinergics are well

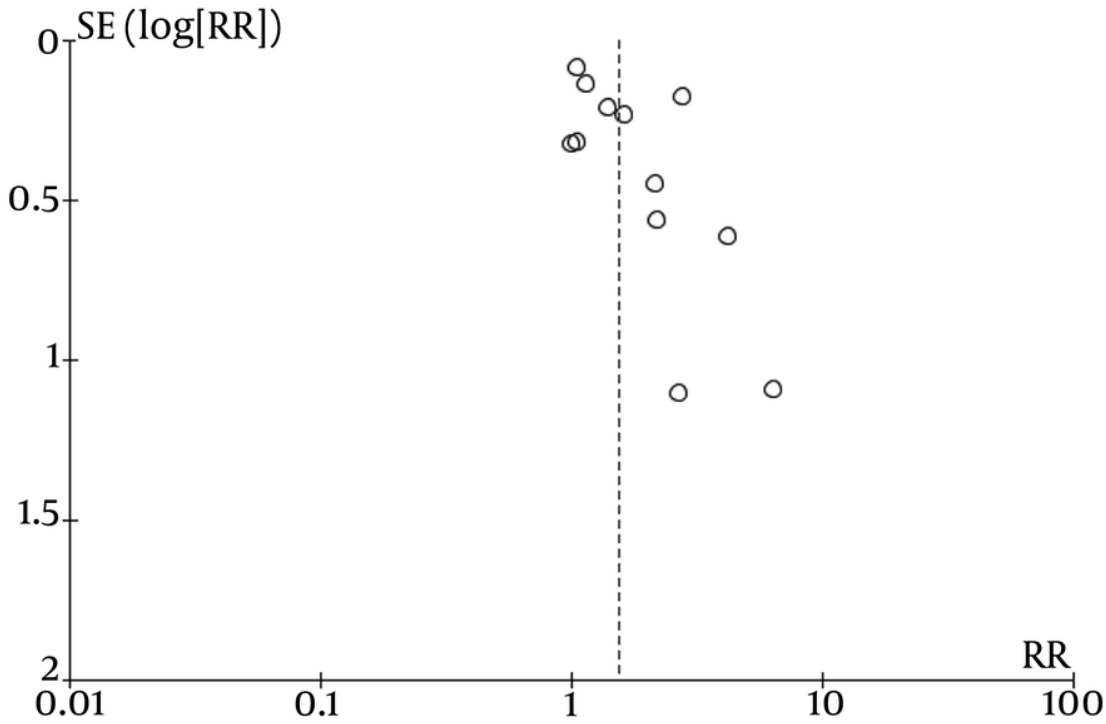

Figure 8. Funnel plot of all included studies

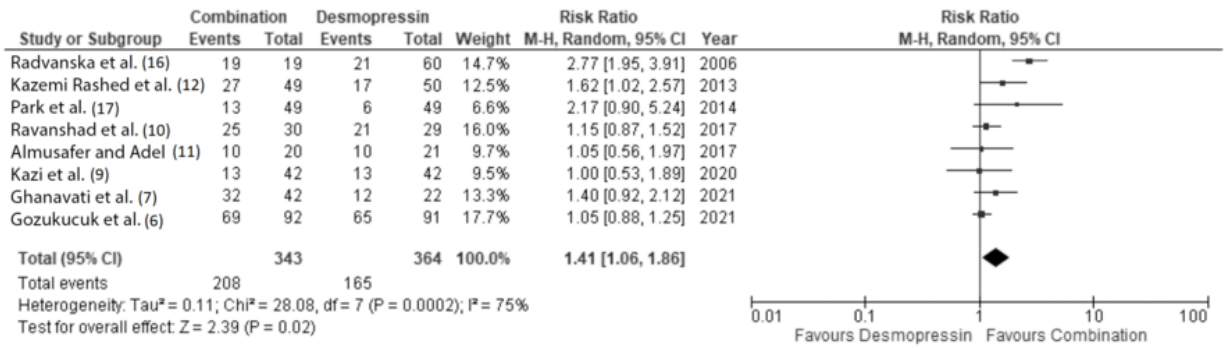

Figure 9. Sensitivity analysis of complete remission at 1 month (6, 7, 9-12, 16, 17)

known to reduce gut motility by inhibiting muscarinic receptors in the gastrointestinal tract, thus resulting in constipation (19). Meanwhile, desmopressin could also affect the balance of electrolytes, and we know that electrolyte imbalance could accelerate the occurrence of constipation (20). Anticholinergics could also cause dry mouth by interrupting the neural stimulation of saliva

secretion (21). Meanwhile, the effects of desmopressin on dryness of mouth need further studies.

5.1. Limitations

Our meta-analysis may be affected by publication bias, which could impact the overall results and the reliability of our findings. Publication bias might cause an overestimation of the true effect size. However, we conducted a sensitivity analysis, excluding studies with wide confidence intervals. This additional analysis allows us to confirm our findings and ensures that the effect size is not driven solely by potentially biased studies.

5.2. Guidelines for Future Research

Further research could focus on exploring the long-term benefits and identifying any additional potential side effects associated with desmopressin and anticholinergics. Additionally, a comprehensive cost-analysis should be conducted to calculate the economic feasibility, specifically of combination therapy with desmopressin and anticholinergics compared to desmopressin monotherapy. This research will provide more robust findings regarding the safety, efficacy, and cost-effectiveness profile, thereby supporting more effective clinical decision-making for MNE in the future.

5.3. Conclusions

Our results support the use of combination therapy consisting of desmopressin and anticholinergics as a viable option for treating MNE, especially in cases where monotherapy with desmopressin is insufficient. However, further research is still needed to uncover its long-term benefits and other potential side effects.

Footnotes

Authors' Contribution: The study concept and design were contributed by M. A. I. M. Data acquisition was carried out by M. A. I. M., N. A. T., and F. A. R. Data analysis and interpretation were performed by M. A. I. M. The manuscript was drafted by M. A. I. M. and N. A. T. Critical revision of the manuscript for important intellectual content was done by F. A. R. Statistical analysis was conducted by M. A. I. M. and N. A. T. Administrative, technical, and material support was provided by F. A. R. Study supervision was overseen by F. A. R.

Conflict of Interests Statement: The authors declared that they have no conflict of interest.

Data Availability: The data presented in this study are uploaded as a supplementary file during submission and are openly available to readers upon request.

Funding/Support: The authors declared that they have no funding/support.

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