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Immediate 1-month efficacy of desmopressin and anticholinergic combination therapy versus desmopressin monotherapy in the treatment of pediatric enuresis: A meta-analysis

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Summary

Background
Several studies have proposed the combination of desmopressin and anticholinergic as a treatment regimen to address the pathophysiology of polyuria and bladder dysfunction in pediatric enuresis. However, the available literature is inconsistent with regards to the immediate 1-month efficiency of the combination therapy in the treatment for pediatric enuresis.

Objective
The aim was to assess the immediate 1-month efficacy and safety of desmopressin and anticholinergic agent combination therapy versus desmopressin monotherapy in the treatment of pediatric enuresis using meta-analysis of randomized controlled trials (RCTs).

Study design
Systematic literature acquisition was carried out on electronic medical databases up to April 2015. RCTs relevant to the topic were critically appraised. Dichotomous data of the 1-month post-treatment response rate (defined as $\geq$90% reduction of wet nights) were extracted for calculation of the risk ratio (RR) and 95% confidence interval (CI). The Mantel–Haenszel method with the random effects model was used to pool effect estimates. Inter-study heterogeneity and publication bias were assessed. Subgroup analysis was done for the desmopressin treatment-naive versus treatment-resistant groups: PROSPERO (CRD42015017922).

Results
Four RCTs of good methodological quality without heterogeneity were included for meta-analysis. The pooled effect estimates showed that combination therapy was associated with a significantly better immediate 1-month response rate than desmopressin monotherapy. Subgroup analysis showed a greater immediate 1-month response rate among desmopressin-resistant patients than treatment-naive patients. No severe adverse events were noted among combination therapy treated groups.

Discussion
The limitation of the current meta-analyses is the small sample size, albeit with high-quality studies pooled for effect estimation. Despite the limitation, the study results were able to consistently illustrate a large treatment effect of combination therapy among desmopressin treatment-resistant patients. It was consistent with the literature review of retrospective and non-comparative studies by Alloussi et al. (2011), who summarized a similar impressive treatment outcome. However, due to the low level of evidence available at the time of their study, only a grade B–C recommendation was given to combination therapy as an approach for second-line treatment. This study also summarized that combination therapy was well tolerated and similar to desmopressin monotherapy.

Conclusion
This study was able to summarize the immediate 1-month efficacy of combination therapy compared with desmopressin monotherapy in the treatment of pediatric enuresis. For both treatment-naive and desmopressin-resistant pediatric enuresis, combination therapy of desmopressin with an anticholinergic agent is well tolerated and resulted in a significantly better immediate 1-month response rate than desmopressin monotherapy.

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Table Summary table of meta-analysis pooled effect estimate (Risk Ratio) on combination therapy versus Monotherapy.

Immediate 1-month response rate comparison	Combination therapy		Monotherapy		Risk ratio	95% CI
	>90% response rate	Total subject	>90% response rate	Total subject		
Treatment naive	49	101	28	102	1.74	(1.20–2.52)
Treatment resistant	16	79	4	75	3.77	(1.32–10.77)
Overall total treatment effect	65	180	32	177	1.89	(1.34–2.68)

Note heterogeneity and sensitivity tests: tau square = 0, chi square = 2.52; $p = 0.47$; $I^2 = 0\%$.
Total overall effect: $Z = 3.59$ ($p = 0.0003$).

Introduction

The International Children's Continence Society (ICCS) recently standardized the definition of pediatric monosymptomatic enuresis as a condition among children more than 5 years old with incontinence symptoms that occur exclusively during sleeping periods without other associated lower urinary tract symptoms [1]. The prevalence of monosymptomatic enuresis at the age of 6 years and older ranges from 8% to 12.5% [2,3]. Desmopressin is a synthetic vasopressin analogue that decreases urine production; currently it is recommended as the first-line pharmacologic treatment for pediatric enuresis [4–6]. Desmopressin monotherapy can achieve an average of 64.1% immediate response rate among monosymptomatic nocturnal enuresis patients, but resistance to desmopressin treatment is documented to be high [6]. Efforts are being made to identify new strategies with immediate maximum effectiveness and minimal related adverse events. Recent literature has elaborated the relationship of bladder overactivity and abnormal bladder functional capacity in desmopressin treatment failure of pediatric enuresis [7,8]. Hence, the proposal of desmopressin and anticholinergics as a combination therapy to address the pathophysiology of bladder dysfunction and polyuria has been described in several studies [9–14]. Owing to inconsistent results in prospective studies to date, the combination treatment regimen has not yet been clearly stated or recommended in any clinical practice guideline for treatment of pediatric monosymptomatic enuresis [6,15,16]. Hence, it is relevant to review the best available literature regarding the efficacy and safety of combination therapy in the management of pediatric monosymptomatic enuresis. We aimed to assess the efficacy and safety of desmopressin and anticholinergic agent combination therapy versus desmopressin monotherapy in the treatment of pediatric enuresis.

Materials and methods

The protocol of the meta-analysis was registered at the PROSPERO registry (CRD42015017922), and was made in consultation with a topic expert and a review methodologist. The report of the meta-analysis was made in compliance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [17]. Institutional Review Board was not necessary for systemic review of published data from randomized controlled trials.

Identification of the literature

A systematic literature search was carried out to identify published medical literatures of human studies about desmopressin and anticholinergic agents in the treatment of pediatric enuresis. The following databases were last searched during April 2015: MEDLINE, EMBASE, Science Direct, OVID SP, Wiley online library, and Clinicaltrial.gov for trial registry to search for unpublished data. All of these databases were searched using Windows Chrome. The search strategy was as follows: (Desmopressin OR Vasopressin analogue) AND (Anticholinergic OR Cholinergic antagonist OR Tolterodine OR Oxybutinin OR Solifenacin OR Propiverine OR Fesoterodine) AND (Enuresis AND Randomized Controlled Trial). The searches were not restricted by language. Hand-searching review articles and studies that met our inclusion criteria were cross-referenced for potentially relevant titles. These related studies, either published or unpublished, that were not searchable from the electronic medical databases were identified and included for consideration.

This meta-analysis included only randomized controlled trials that compare efficacy and the safety of desmopressin and anticholinergic agent combination therapy versus desmopressin monotherapy in the treatment of pediatric enuresis. Excluded studies were retrospective studies, no comparative trial, non-randomized controlled trials, combination therapy of desmopressin with other medical agents or therapy, and adult study population. Primary outcomes considered in this meta-analysis were the immediate 1-month post-treatment response rate to treatment (defined as response rate more than 90% reduction in wet nights per week) [23] comparing the treatment regimen of combination therapy versus monotherapy, and the adverse events reported among patients who received the treatment regimen. Subgroup analysis dealt with a different study population (desmopressin monotherapy-resistant versus treatment naive). Treatment-naive patients were defined as patients without previous desmopressin treatment, and treatment resistant were those who had previous desmopressin treatment with no response.