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Original Article

Comparative assessment of efficacy and safety of different treatment for *de novo* overactive bladder children: A systematic review and network meta-analysis

Shi Qiu [1], Siwei Bi [1], Tianhai Lin [1], Zhuheng Wu, Qi'an Jiang, Jiwen Geng, Liangren Liu, Yige Bao, Xiang Tu, Mingjing He, Lu Yang*, Qiang Wei*

Department of Urology, Institute of Urology, West China Hospital of Sichuan University, Chengdu, China

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KEYWORDS
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Abstract *Objective:* To compare these managements focusing on the efficacy and safety to treat overactive bladder (OAB) in children through network meta-analysis (NMA).
Methods: We searched PubMed, Embase, the Cochrane Library Central Register of Controlled Trials (CENTRAL) and the reference lists up to May 1st, 2017. Data from eligible randomized controlled trails (RCT) studies including three different treatment options were extracted. The primary outcome was maximal voiding volume (MVV). We performed pairwise meta-analyses by random effects model and NMA by Bayesian model. We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework to assess the quality of evidence contributing to each network estimate.
Results: Six RCTs (462 patients) comparing three different interventions fulfilled the inclusion criteria. A low risk of bias was shown for the majority of the study items. The results of NMA showed that compared with antimuscarinic drugs, Parasacral transcutaneous electrical nerve stimulation was associated with significant improvement in the MVV (mean difference [MD] = 58.50, 95% confidential interval [CI]: 45.95–69.52), followed by urotherapy group (MD = 21.03, 95% CI: 11.85–29.97). When it comes to the constipation, antimuscarinic drugs exerted significant benefit than PTENS (odds ratio [OR]: 0.22, 95% CI: 0.01–0.46). No significant difference was found between other treatments.

* Corresponding authors.
E-mail addresses: wycleflue@163.com (L. Yang), weiqiang163163@163.com (Q. Wei).
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[1] These authors contributed equally to this work.

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Conclusion: Compared with antimuscarinic drugs, PTENS was associated with significant better efficacy considering MVV, but more constipation events in *de novo* OAB children. Antimuscarinic drugs showed remarkably better efficacy considering MVV and comparable safety profile compared with urotherapy. Clinicians should take all known safety and compliance of patients into account when choosing an optimal strategy.

1. Introduction

The International Children's Continence Society [1] defined overactive bladder (OAB) as "urinary urgency, usually accompanied by frequency and nocturia, with or without urinary incontinence, in the absence of urinary tract infection or other obvious pathology", and the children here refer to those aged 4—12 years old. OAB, affecting up to 12% of the children, is a symptom complex than a disease. In most large population studies, investigators focus on the daytime urinary urgency but not the urinary urgency. Thus, calculating the actual prevalence of OAB in children from such studies is difficult [2]. The prevalence of urinary incontinence is often correlated with gender; the peak prevalence for girls is 8.4% at 7 years old and gradually decreases to 4% at adolescence. The prevalence for boys is 1.4% and 0.9%, respectively [3,4].

OAB has a damaging effect on quality of life [5] and negatively influence the social, emotional, and behavioral well-being [6]. Children that have troubles with incontinence have a three to fold greater incidence of behavioral and psychiatric disorders than that of the age-matched general population [7]. A stepwise approach is favored to treat this pathology, beginning with urotherapy, a behavioral therapy, followed by pharmacological treatment, and invasive procedures in the end [8]. Urotherapy, starting with education of the children and their family, has several phases, including timed voiding, management of constipation and pelvic floor training. In a child whose symptoms have not responded to simple urotherapy, the treatment of choice is pharmacological [2]. The keystone of current pharmacological treatment refers to the use of muscarinic receptor antagonists [8]. Furthermore, even though the mechanism is not clear, data from many researches indicated that electrical stimulation, mostly parasacral transcutaneous electrical nerve stimulation (PTENS), can be used to suppress bladder overactivity. Parasacral stimulation involves the use of a transcutaneous electrical nerve stimulation device and parasacral conducting pads, placed parasacrally in the S2—S3 region with the electrodes connecting on the surface to a current generator.

Nevertheless, the parameters for efficacy measuring of existing researches various from one to another. Thus, a set of standard parameters to evaluate the overall therapeutic effectiveness of these treatments is in need to facilitate the further investigations. Moreover, given the range of different treatments, it is sometimes hard for a clinician to understand the relative effectiveness of these treatments. Considering study cost, study design, and other logistical issues, direct clinical trials would not be a reasonable choice. Network meta-analysis (NMA) is a statistical technique that provides a new way to combine previously published clinical trials to compare treatments in lieu of doing a head-to-head trial. This study used NMA to measure the efficacy and tolerability of commonly used drugs and invasive treatments involved in managing children suffering OAB.

2. Methods

This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement extension for NMA [9].

2.1. Data sources and searches

To compare the tolerability and efficacy of different strategies for pediatric OAB, a comprehensive search of literature published up to May 1st, 2017 was performed in the following databases: PubMed, Embase and the Cochrane Library Central Register of Controlled Trials (CENTRAL). We used boolean logic to incorporate discrepant terms and synonyms for concepts in each of three distinct filters: An anatomic filter for "overactive bladder" and "children", a treatment filter for "medication" or "nerve stimulation", "antimuscarinic" or "urotherapy", and a publication type filter for randomized controlled trials (RCTs). When possible, we used controlled vocabulary (such as EMTREE in Embase, MeSH in PubMed) and keywords. Reference lists of all included studies and relevant reviews were scanned. Unpublished studies were sought by locating relevant conference abstracts and contacting authors of included studies. Two independent investigators (S Qiu, S Bi) initially screened the citation titles and abstracts.

2.2. Study selection

We encompassed all RCTs comparing intervention and control groups of OAB children. Studies that met the following criteria were finally involved: (1) Trials were conducted in a homogenous group of *de novo* OAB children; (2) at least one of the interventions compared in the trial was pharmacological agents or the invasive treatments and the protocol was listed clearly in the article; (3) the publications were full length, peer reviewed research articles; and (4) at least one trial outcome was of interest for our NMA. Citations were excluded for the following reasons: Non-English text, review article, intervention and trial design. Studies including patients who were refractory to standard urotherapy or pharmacotherapy were also excluded. Any discrepancies in the study inclusion were resolved by consulting the senior author Q Wei.

2.3. Data extraction and quality assessment

The independent reviewers (S Qiu, S Bi) used a standardized form to extract information from each eligible study. Data will be collected on the following data points: (1) Research information: The first author, the site where the study was conducted, year of publication and the sample size; (2) Characteristics of the study subjects: Age, sex, numbers in each group, inclusion and exclusion of criteria of individual study; (3) Information on intervention and comparison arms: Number of groups, intervention and comparator(s) (drug, dose and route). Attempts were made to obtain missing data from the first or corresponding author of such studies. We assessed the validity of the NMA through a qualitative appraisal of study designs and methods. We executed the tool recommended by the Cochrane Collaboration to evaluate the risk of bias [10].

2.4. Outcome

The primary outcome of present study was maximal voiding volume (MVV). Our second outcome was voiding frequency, incontinence episodes and average voiding volume. We also assessed the constipation events as an alteration of adverse events.

2.5. Data synthesis and statistical analysis

We initially performed a pairwise meta-analysis by random-effects model [11]. Results were expressed as odds ratio (OR) with 95% confidence intervals (CI) for dichotomous variables (constipation), while the mean difference (MD) was used for continuous outcomes MVV, voiding frequency, incontinence episodes and average voiding volume. The level of statistical significance was set at $p < 0.05$ and all statistical tests were two-sided. The statistical heterogeneity among studies was evaluated by the Cochran's Q test and the I^2 statistic. A p-Value of 0.05 or less for the Q test or an I^2 greater than 50% was suggestive of substantial study heterogeneity.

We performed random-effects Bayesian NMA for indirect and mixed comparisons using Markov chain Monte Carlo methods in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) [12]. We report the resultant effect as posterior median OR with corresponding 95% credibility intervals (CrIs). We evaluated the relative ranking probability of each strategy and obtained the hierarchy of competing interventions using surface under the cumulative ranking curve (SUCRA) [13]. To assess the presence of inconsistency, we employed the node-splitting method [14].

2.6. Quality of evidence

Two researchers (S Qiu, S Bi) independently evaluated the quality of each pair of comparison. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology [15] was performed to rate the quality of evidence. In this approach, direct evidence from RCTs starts at high quality and can be downgraded based on risk of bias, indirectness, imprecision, inconsistency (or heterogeneity) and publication bias to levels of moderate, low and relatively low quality [16].

3. Results

3.1. Eligible studies

Of 268 citations identified through our search strategy, six RCTs [17–22] were included in this NMA (Fig. 1). All six trials had two comparison interventions. Overall, 462 children were randomized to three different treatment options (including PTENS, antimuscarinic drugs and urotherapy).

3.2. Study and patient characteristics

Data related to basic factors in every study are summarized in Table 1. Three studies reported outcomes of 56 patients receiving PTENS versus 59 patients receiving urotherapy [17–19]. Two trails included outcome comparisons between urotherapy versus antimuscarinic drug with 157 and 160 patients respectively [21,22]. One study compared outcomes of 13 patients underwent PTENS versus 15 patients underwent antimuscarinic drug. Urotherapy, as a fundamental treatment, was implemented in both groups of all the six studies. The patients involved from four studies were not been previously treated for a certain length of time while the rest two study did not make clear statement.

3.3. Quality assessment

We used the Cochrane Collaboration risk-of-bias tool for the measurement details of quality assessment (Figs. 2 and 3). Half of trials showed a low risk of bias for quality criteria, and the other three studies were sorted as moderate risk of bias. The risk of other bias was the most risk factor for quality assessment; the second risk factor was incomplete outcome data, given the unnecessary of reporting the whole results of a variety of parameters.

3.4. Maximal voiding volume

Five studies [18–22] including 446 patients were included in the analysis. In the pairwise meta-analysis, compared with urotherapy group, MVV of antimuscarinic drugs group was significantly increased (MD = 20.49; 95% CI: 6.80, 34.17; I^2 = 64%) (Fig. 4A). When it comes to NMA, compared with antimuscarinic drugs, PTENS was associated with significant improvement (MD = 58.50; 95% CI: 45.95–69.52; SUCRA = 100%), followed by urotherapy group (MD = 21.03; 95% CI: 11.85–29.97; SUCRA = 50%) (Table 2).

3.5. Voiding frequency

Five studies [18–22] including 446 patients were included in the analysis. In the pairwise meta-analysis, compared with patients receiving urotherapy, voiding frequency of antimuscarinic drugs group led to a significant amelioration (MD = −0.80; 95% CI: −1.29–0.31; I^2 = 0) (Fig. 4B). When considering the result of NMA, no statistic difference was found between each comparison (Table 2).

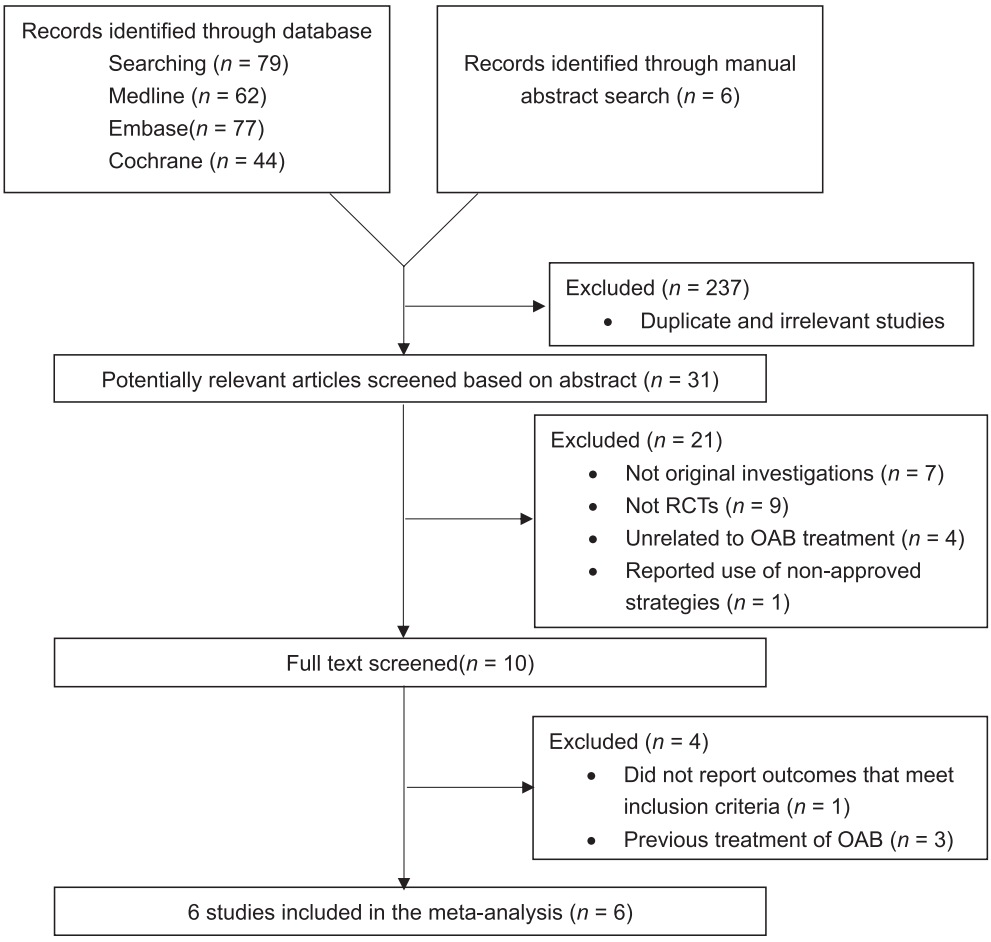

Figure 1 Flow chart of study identification and selection procedure. OAB, overactive bladder; RCTs, randomized controlled trails.

3.6. Incontinence episodes

Three studies [19,21,22] including 381 patients were included in the analysis. In the pairwise meta-analysis, incontinence episodes of antimuscarinic drugs group demonstrated a significant decrease (MD = -0.30; 95% CI: -0.54—0.05; I^2 = 0) compared with urotherapy group (Fig. 4C). However, no statistical significant difference was found between each comparison in NMA (Table 2).

3.7. Average voiding volume

Only two studies [18,20] including 65 patients were included in the analysis. In pairwise meta-analysis, no statistical significant was observed betweem PTENS and urotherapy (MD = 5.60; 95% CI = -20.04—31.23; I^2 = 35%) (Fig. 4D).

3.8. Constipation

Only two studies [17,20] including 44 patients were included in the analysis. In the pairwise analysis, a trend towards favoring PTENS than urotherapy was witnessed (OR = 0.21; 95% CI: 0.04—1.12, I^2 = 0) (Fig. 4E). The result of NMA revealed that, compared with PTENS, antimuscarinic drugs showed a significant decrease of constipation episodes (OR = 0.22; 95% CI: 0.01—0.46) (Table 2). There was no significant difference between other treatments. The surface under the cumulative ranking curve (SUCRA) values for the three treatments were 96%, 43% and 11% for antimuscarinic drugs, urotherapy and PTENS separately.

3.9. Network consistency

There was no inconsistency in the NMA estimates when we used the node-splitting approach. The differences between direct and indirect estimates in closed loops were insignificant which unable the assessment of network coherence. The total residual deviance for MVV improvement (17.6, df = 17), voiding frequency (10.6, df = 9.4), incontinence episodes (5.4, df = 5.3) and constipation episodes (3.4, df = 3.3) implied a good model fit. Convergence of chains was verified visually by looking at trace plots and inspecting the Brooks-Gelman-Rubin diagnostic statistic with values around 1.

4. Discussion

In recent years, OAB, with a significant prevalence in children, is a burdensome and challenging condition for physicians. To our knowledge, this study is the most

Table 1 The main characteristics of the included RCTs.

Author	Publish year	Country	Intervention group 1 (sample size)	Intervention group 2 (sample size)	stimulation frequency	Stimulation duration (min/time)	Treatment duration (week)	Treatment frequency
de Paula et al. [17]	2017	Brazil	PTENS (8)	Sham stimulation (8)	10 Hz	20	20	Once a week
Lordêlo et al. [18]	2010	Brazil	PTENS (21)	Scapular stimulation (16)	10 Hz	20	6	Three times a week
Sillén et al. [19]	2014	Sweden	PTENS and urotherapy (30)	Urotherapy (32)	10 Hz	20	12	Twice daily
Quintiliano et al. [20]	2015	Brazil	PTENS and placebo (13)	Antimuscainic (oxybutynin) and sham electric stimulation (15)	10 Hz	20	6	Three times a week
Marschall-Kehrel et al. [21]	2009	Germany	Antimuscarinic (propiverine) (87)	Placebo (84)	NA	NA	8	Twice daily
Newgreen et al. [22]	2016	Netherlands	Antimuscarinic (Solifenacin) (73)	Placebo (73)	NA	NA	12	Once daily

NA, not applicable; PTENS, parasacral transcutaneous electrical nerve stimulation; RCT, randomized controlled trail.

Figure 2 Risk of bias assessments within studies.

comprehensive and updated network meta-analysis comparing commonly treatment of *de novo* OAB children. The major findings of this study are as follows: (1) PTENS was ranked the best, followed by urotherapy when compared with antimuscarinic drugs at improving maximal voiding volume. However, PTENS displayed remarkably more constipation events than antimuscarinic drugs. (2) As for voiding frequency and incontinence episode, the evidence of NMA was limited and showed unclear difference.

In this research, PTENS demonstrated more positive remarkable impact on maximal voiding volume than urotherapy in NMA. Walsh et al. [23] and Hoebeke et al. [24] first described the use of TENS in adults in 1999 and in children in 2002, respectively. In subsequent studies, complete resolution of symptoms has ranged from 47.0% to 61.9% of children treated with this modality [17,23—25]. Studies have used stimulation at various frequencies, ranging from 10 Hz to 80 Hz, and frequencies of treatment varying from weekly to daily. Durations of stimulation have also varied, from 20 min up to 1 h daily [2]. The studies we included which focused on the influence of PTENS chose 10 Hz as their stimulation frequency and duration of stimulation lasted for 20 min per time. But the frequency of treatment was different in two studies using three times a week which would cause discrepancy results of researches and add certain amount of heterogeneity to our study.

Not only in the pairwise analysis, but also in the NMA, urotherapy was more likely to cause constipation than PTENS. To our knowledge, there is a strong link between constipation and OAB in children, though the mechanism

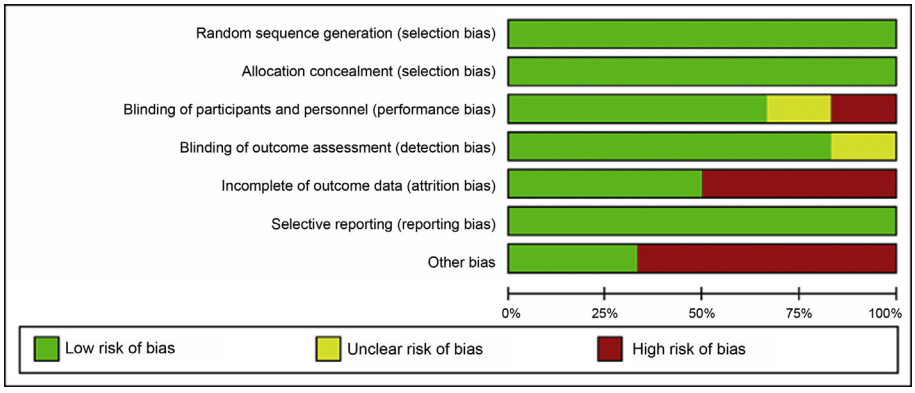

Figure 3 Risk of bias assessments for each study.

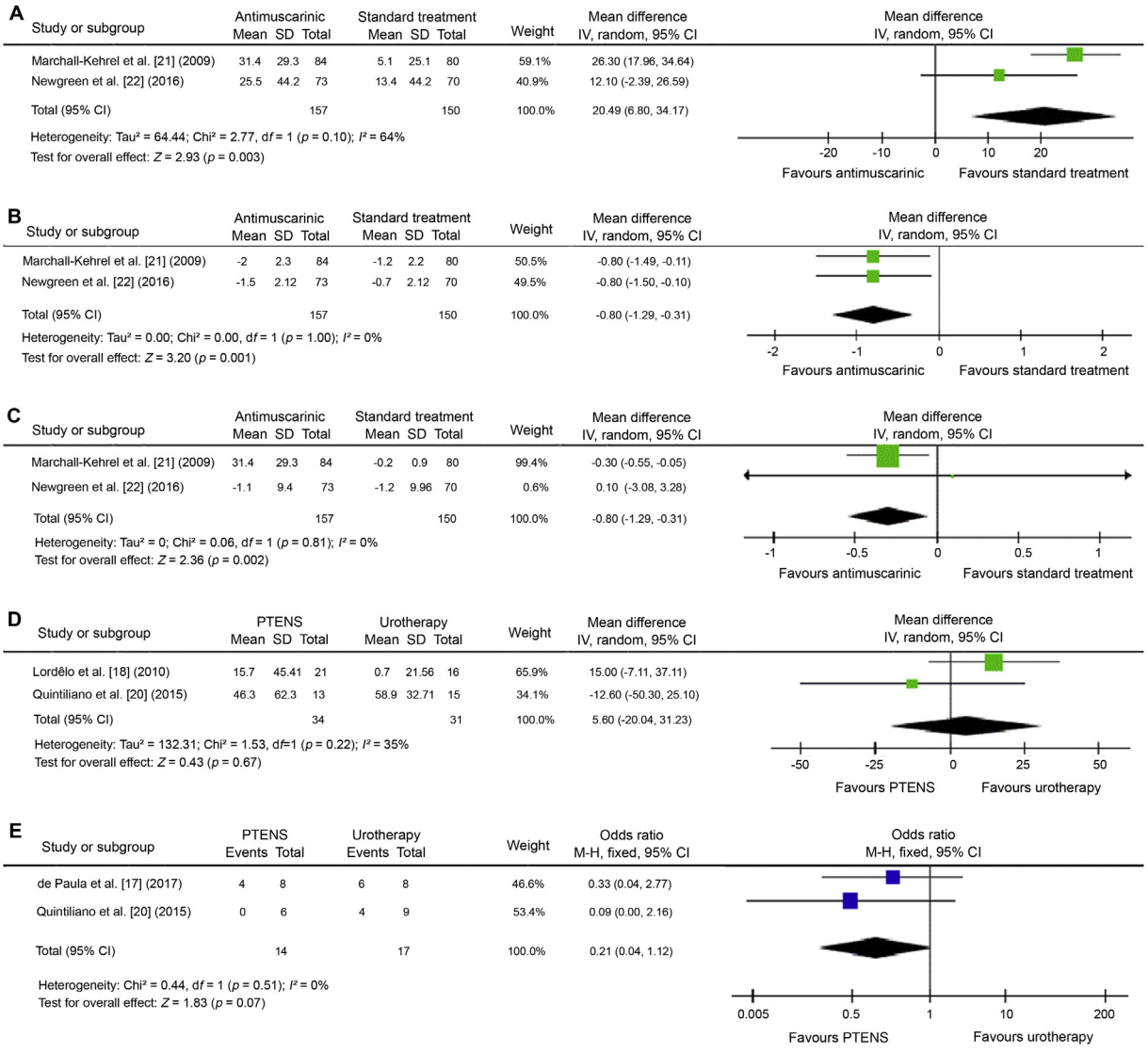

Figure 4 Forest plot for pairwise meta-analysis. (A) Change in maximal voiding volume; (B) Voiding frequency; (C) Incontinence episodes; (D) Change in average voiding volume change; (E) Constipation. The size of the boxes corresponds to each study's weight. CI, confidential interval; PTENS, parasacral transcutaneous electrical nerve stimulation. IV, Inverse variance; M-H, Mantel-Haenszel.

Table 2 Summary effect size of pairwise and network meta-analysis.

Comparison	No. of participants	No. of trials	Pairwise meta-analysis mean difference/odd ratios (95% CI)	*p*-Value	Heterogeneity, I^2	Network meta-analysis, mean difference/odds ratios (95% CrI)	Quality of evidence	Downgraded reason
Maximal voiding volume								
PTENS *vs.* urotherapy	196	2	NA	NA	NA	**37.46 (28.27, 45.24)**	⊕⊕○○ low	Inconsistency and imprecision
Antimuscarinic *vs.* urotherapy	307	2	**20.49 (6.80, 34.17)**	0.1	64%	**21.03 (11.85, 29.97)**	⊕⊕⊕○ moderate	heterogeneity
PTENS *vs.* antimuscarinic	239	0	NA	NA	NA	**58.50 (45.95, 69.52)**	⊕⊕○○ low	Heterogeneity and imprecision
Voiding frequency								
PTENS *vs.* urotherapy	196	2	NA	NA	NA	0.425 (-2.21, 2.76)	⊕⊕○○ low	Inconsistency and imprecision
Antimuscarinic *vs.* urotherapy	307	2	**-0.80 (−1.29, −0.31)**	1	0	1.09 (-1.18, 3.40)	⊕⊕○○ low	Inconsistency and imprecision
PTENS *vs.* antimuscarinic	239	0	NA	NA	NA	0.67 (-2.213, 3.71)	⊕⊕○○ low	Heterogeneity and imprecision
Incontinence episodes								
PTENS *vs.*urotherapy	219	1	NA	NA	NA	0.13 (-4.88, 5.44)	⊕⊕○○ low	Inconsistency and imprecision
Antimuscarinic *vs.* urotherapy	349	2	**-0.30 (−0.54, −0.05)**	0.81	0	0.23 (-3.41, 3.74)	⊕⊕○○ low	Inconsistency and imprecision
PTENS *vs.* antimuscarinic	190	0	NA	NA	NA	0.09 (-6.79, 6.59)	⊕⊕○○ low	Heterogeneity and imprecision
Constipation								
PTENS *vs.* urotherapy	29	1	0.21 (0.04, 1.12)	0.51	0	0.38 (0.01, 6.85)	⊕⊕⊕○ moderate	Heterogeneity
Antimuscarinic *vs.* urotherapy	23	0	NA	NA	NA	0.15 (0.25, 3.82)	⊕⊕○○ low	Heterogeneity and imprecision
PTENS *vs.* antimuscarinic	36	1	NA	NA	NA	**0.22 (0.01, 0.46)**	⊕⊕○○ low	Inconsistency and imprecision

GRADE Working Group grades of evidence— "⊕⊕⊕⊕" means high quality: Further research is very unlikely to change our confidence in the estimate of effect; "⊕⊕⊕○" means moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; "⊕⊕○○" means low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; "⊕○○○" means very low quality: We are very uncertain about the estimate. 95% CI, 95% confidence intervals; 95% CrI, 95% credible intervals; NA, not applicable; PTENS, parasacral transcutaneous electrical nerve stimulation. Results are expressed as odds ratios with 95% CI or 95% CrI for dichotomous variables (constipation). While the mean difference with 95% CI or 95% CrI was used for continuous outcomes (maximal voiding volume, voiding frequency, incontinence episodes and average voiding volume). Significant results are in bold. OR, odds ratios.

is unclear now, and when it is treated, urinary urgency presents an improvement [5,6]. Urotherapy, as mentioned above, contains the management of constipation. The PTENS has been proved in two RCTs that accelerated intestinal motility more than sham treatment [26,27]. The result of our study is consistent with Quintiliano et al. [20], in which improvement of constipation in the PTENS group was reported as 100%, but opposed to this result, de Paula et al. [17] showing that urotherapy with increased fluid intake can be effective in the treatment of constipation. The discrepancy could lie in the different frequency of treatment (once a week *vs.* three times a week). Since the results between PTENS and urotherapy are statistical insignificant, it remains unclear if PTENS is better treatment choice than urotherapy in safety concern. More researches are needed for solid conclusion.

In our NMA analysis, there is a significant trend that favors antimuscarinic drugs when compared with PTENS in the occurrence of constipation. Constipation is common in children administrated with antimuscarinic drugs as the nonselective antimuscarinic action [14]. Thus, we expected that the arm with treatment of antimuscarinic drug would present most probability of constipation, though not same with ours result. It could be interpreted as the small number of the study and population involved in the analysis. Further network analysis including large scale of population would serve a more reliable outcome.

We found in our two pairwise analyses about voiding frequency and incontinence episodes, though not so conspicuous, antimuscarinic drugs exhibited better safety profile than urotherapy. Meanwhile, antimuscarinic drugs were more effective when it comes to increasing the maximal voiding volume in our NMA. We currently included three kinds of antimuscarinic drugs, oxybutynin, solifenacin and propiverine, as the treatment arm of antimuscarinic drug. They are applied in different areas: Oxybutynin in Brazil while solifenacin and propiverine in Netherland and Germany, respectively. The daily dose of oxybutynin is 0.6 mg, which obeys the recommended dose. As for solifenacin and propiverine, the doses are based on children's weight. It is notable that in this arm, even though the results of pairwise analysis and NMA both favor antimuscarinic drugs, many issues would add heterogeneity and inconsistency to our study, such as the types and doses of drugs. In the near future, more specific NMA would focus on one single drug and throw light on the effects of different doses. Besides, findings were imprecise for comparison between antimuscarinic drugs and PTENS in regard to voiding frequency and incontinence episodes. Therefore, no definite evidence of superiority could be supported for any particular intervention when it comes to these two endpoints.

This study is the first NMA to research efficiency and safety of pharmacological and invasive treatment for the *de novo* OAB children. All the studies referred are RCT from Science Citation Index (SCI) database. For the high sensitivity and specificity detection of records correlated to the question of the systematic review, the quality of the search strategies was designed for each database. Although the present study is the first meta-analysis to research efficiency and safety of pharmacological and invasive treatment for the OAB in children, some pitfalls should be clarified. Firstly, given the rarity of the literature included in our study, the results derived may not consistent with the current opinions of clinicians and their experiences. This limitation does not mean that the methodological quality is inevitably bad or good. However, since the Cochrane Collaboration tool is the best tool available to evaluate quality and it requires an adequate report to properly weigh the items, this rarity could incur underestimation of the quality of our study. Secondly, positive studies are more likely to be published than negative, and the present results might have been affected by publication bias. Thirdly, the results of most of studies were documented by children's parents under the instruction of clinicians which would surely increase the subjectivity. Furthermore, it was difficult to extract data with different endpoints presented in different forms. Therefore, the results derived would be less reliable and should be interpreted with discretion. Further standardization of OAB treatment endpoints and accurate treatment targets will definitely help in patient management. This will also be helpful in genesis of future data for more convenient and more unbiased research results. Finally, four studies in our study included children without treatment for a certain time, and the other two did not made clear statement. The doses and means of administration varied between the antimuscarinic drugs. Thus, further studies can be stricter in the inclusion criteria of the study including restriction in the population characteristic, sample size, doses and types of drugs.

5. Conclusion

In this study, we showed that PTENS was more efficacious than urotherapy and antimuscarinic drugs but less tolerated than antimuscarinic drugs. Clinicians should take all known safety and compliance of patients into account when choosing an optimal strategy. Since limited quantity and small sample size of included studies, further well-designed, double-blinded, multi-centric RCTs are strongly encouraged to address the clinical question.

Author contributions

Study design: Qiang Wei, Lu Yang.
Data acquisition: Shi Qiu, Siwei Bi.
Data analysis: Siwei Bi, Xiang Tu.
Drafting of manuscript: Shi Qiu, Siwei Bi.
Critical revision of the manuscript: Qiang Wei, Lu Yang.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

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