A Bayesian mesh meta-analysis of medicine treatment in patients with enuresis

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Abstract

Background The aim of this study was to comprehensively evaluate the efficacy of multiple methods for enuresis and chose optimal treatment plan. **Methods** We searched Pubmed, Embase and Cochrane Library for included articles. All data were analyzed comprehensively using aggregate data drug information system (ADDIS) software (1.16.5). The random effects model was used for all test models. Node-splitting analysis and inconsistency standard deviation (ISD) were applied for consistency test. For node-splitting analysis (NSA) with $P_b > 0.05$, consistency model was chosen for analysis. Otherwise, the inconsistency model was used. **Results** Twenty-one studies were included in this meta-analysis. For the response rates, desmopressin acetate tablets (dDAVP) + Tolterodine (Tol), dDAVP + Imipramine (Imi), Imi + oxybutynin (Oxy), and Imi + Pseudoephedrine (Pse) treatment were the best, while the efficacy of Verapamil (Ver), Mianserin (Mia) and Estradiol (Est) were the worst. For the mean number of nocturia indicator, the effects of dDAVP + Imi and dDAVP + Tamsulosin (Tam) treatment were the best, while the efficacy of Imi was the worst. For nocturnal urine volume, the effects of dDAVP + Oxy and dDAVP + Tam were the best, while the efficacy of Pse and Tam were the worst. However, the difference between the groups was not statistically significant ($P > 0.05$). For adverse effects index, the incidence of adverse effects of Est and dDAVP + Imi was the lowest, the incidence of Ver was the highest. **Conclusions** The effects of dDAVP + Imi and dDAVP + Tam were the best, while Ver was with the worst efficacy.

Background

Enuresis, commonly known as bedwetting, usually refers to involuntary urination when a child is asleep¹. Generally, only 20% children have enuresis when they are 4 years old, and 5% have enuresis when they are 10 years old². There are a few patients with enuresis that lasts into adulthood. Primary enuresis is with no obvious urinary tract or neurological lesion, which accounting for 70% to 80%³. Secondary enuresis includes lower urinary tract obstruction, cystitis, and neurogenic bladder⁴. In addition to nighttime bedwetting, patients often have symptoms, including frequent urination, urgency or difficulty urinating, and fine urine flow during the day⁵.

Although enuresis does not harm health, it has an impact on mentality of both child and parents. At present, there are four commonly used therapeutic drugs, including anti-diuretic drugs, anticholinergic drugs, tricyclic antidepressants, and central nervous stimulants⁶. Previous meta-analyses have been used to compare the effects of various drugs on enuresis. Yu et al. processed a meta-analysis and confirmed that clinical efficacy of combination desmopressin therapy plus anticholinergic agent was significantly higher than that of desmopressin alone treatment for children with enuresis⁷. Interestingly, acupuncture combined with traditional Chinese medicine was with certain clinical advantages than acupuncture or traditional Chinese medicine alone in enuresis treatment⁸. For efficacy, compliance and safety of several formulations of desmopressin in enuresis treatment, the efficacy and safety are similarly among different formulations, while the sublingual tablets are with higher compliance than other formulations⁹.

Although above studies have compared the effects of drugs on enuresis, most of them compared only two methods, and comprehensive report compared various methods is rare. In the current study, Bayesian mesh meta-analysis method was used to comprehensively evaluate the efficacy of multiple methods for enuresis, and the optimal treatment plan may be obtained to provide a basis for future clinical treatment.

Methods

Search strategy

We comprehensive evaluated of the efficacy of some methods for enuresis. An electronic search for enuresis related medicines was conducted in English updated in Aug. 2018. Electronic literature database included Pubmed (<http://www.ncbi.nlm.nih.gov/pubmed>), Embase (<http://www.embase.com>) and Cochrane Library (<http://www.cochranelibrary.com>). The key words for researching were disease name (enuresis OR enuretic OR bedwetting OR "incontinence urine" OR Nocturia), combined with various drugs for enuresis treatment (desmopressin OR vasopressin OR pharmacotherapy OR amitriptyline OR Imipramine OR viloxazine OR clomipramine OR desipramine OR mianserin OR Diclofenac OR indomethacin OR oxybutynin OR pseudoephedrine OR Ibuprofen OR oxybutynin OR verapamil OR anticholinergic OR Clonidine OR Reboxetine OR Tolterodine OR anticholinerg), as well as research type (Trail OR clinical trial OR random OR comparison OR placebo).

Inclusion and exclusion criteria

Inclusion criteria: (1) The literature on the efficacy of drugs in patients with enuresis was published in English; (2) The outcome variables mainly included response rates, mean number of nocturia, nocturnal urine volume and adverse effects; (3) The research type is randomized controlled study.

Exclusion criteria: (1) exclusion of data is incomplete, which could not be used for statistical analysis; (2) Non-religious literature such as reviews, letters and reviews were excluded; (3) For multiple studies with repeated data, only the most comprehensive one was included and the rest were excluded; (4) In order to reduce the difference, study with less than 10 patients was excluded, and study without mean and standard deviation was also excluded.

Data Extraction

The data was extracted by two investigators independently. The extracted contents were as follows: the first author of the literature, the year of publication, the year of study, research area, the drug in each group, the number of included cases, and the demographic characteristics (age and gender) of each group. Referring to the risk assessment tools for bias of Cochrane Collaboration recommendations, the quality of randomized controlled literature was evaluated ¹⁰.

If there is a dispute during the data extraction and document quality evaluation, a group discussion will be conducted and the third investigator will be communicated to achieve a consistent result.

Statistical Analysis

All data were analyzed comprehensively using ADDIS software (1.16.5). ADDIS software is a non-programming software based on the Bayesian framework, which is used for prior evaluation and processing by Markov chain Monte Carlo theory (MCMC) ^{11,12}. All data are represented by OR (odds ratio), MD (Mean difference) values and a 95% confidence interval (CI) of each value.

The random effects model was used for all test models. Node-splitting analysis and inconsistency standard deviation (ISD) were applied for consistency test. Node-splitting analysis is an alternative method to assess inconsistency in network meta-analysis. For node-splitting analysis (NSA) with $P > 0.05$, consistency model was chosen for analysis. Otherwise, the inconsistency model was used ¹³. Based on the Potential Scale Reduction Factor (PSRF), Brooks-Gelman-Rubin method was used to detect the convergence degree of model. PSRF value less than 1.2 was acceptable. The closer it is to 1, the better the model converges ¹⁴.

Results

Study filtering and quality evaluation

The literature screening process and results were shown in figure 1. Based on the pre-defined search strategy, a total of 1187 studies were filtered from Pubmed, Embase, and Cochrane Library databases. After excluded duplicated literature, there were 715 studies remaining. Based on the title and abstract, 610 studies did not meet the inclusion criteria obviously. After reading the full text, 84 studies were then retrieved. A total of 21 studies were finally obtained for further quality evaluation ¹⁵⁻³⁵.

The filtered studies were published from 1996 to 2016, and most of them were published after 2005. The research year were ranged from 1996 to 2014, while some literatures did not report the research year. The research areas of these studies included Egypt, Turkey, the United States, China, Italy and South Korea. Total 3410 enuresis were included, the drugs used contained dDAVP (Desmopressin), Tam (Tamsulosin), Tol (Tolterodine), Oxy (Oxybutynin), Dox (Doxazosin), Imi (Imipramine), Pse (Pseudoephedrine), Ver (Verapamil), Ibu (Ibuprofen) and Mia (Mianserin). There is no significant difference in gender and age between each group of these studies.

The results of RCT quality evaluation show that the quality of included literature is generally high. However, parts of studies showed unclear risk of bias in Allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias) (Figure 2 and 3).

Mesh meta-analysis results

Parameter was set for the ADDIS software, including number of chains of 4, tuning iterations of 20000, simulation iterations of 50000, thinning interval of 10, inference samples of 10000 and variance scaling

factor of 2.5. Mesh meta-analysis was processed for response rates, mean number of nocturia, nocturnal urine volume and adverse effects.

The consistency test was performed by Node-splitting analysis, and the P values were all more than 0.05. Therefore, the consistency model was adopted. All the PSRFs of response rates, mean number of nocturia, nocturnal urine volume and adverse effects were close to 1, which proved that the model was completely converged, the iterative effect was very good, and the results were stable.

Response rates

As shown in Table 1, for the response rates, dDAVP+Tol, dDAVP+Imi, Imi+Oxy, and Imi+Pse treatment were the best, while the efficacy of Ver, Mia, and Est were the worst. However, the difference between the groups was not statistically significant ($P > 0.05$).

Mean number of nocturia

For the mean number of nocturia indicator, the effects of dDAVP+Imi and dDAVP+Tam treatment were the best, while the efficacy of Imi was the worst. However, the difference between the groups was not statistically significant ($P > 0.05$) (Figure 2).

Nocturnal urine volume

For nocturnal urine volume, the effects of dDAVP + Oxy and dDAVP + Tam were the best, while the efficacy of Pse and Tam was the worst. However, the difference between the groups was not statistically significant ($P > 0.05$) (Figure 3).

Adverse effects

For adverse effects index, the incidence of adverse effects of Est and dDAVP + Imi was the lowest, the incidence of Ver was the highest, and the incidence of Imi and Imi + Oxy were also high (Table 4).

Discussion

The etiology of enuresis is still unclear. Therefore, there are many treatments for this disease in China, and no uniform standard with curative effect³⁶. In this study, a total of 21 studies were screened from 1187 studies to compare the response rates, mean number of nocturia, nocturnal urine volume and adverse effects of various drugs. All the PSRFs of response rates, mean number of nocturia, nocturnal urine volume and adverse effects were close to 1, which proved that the model was completely converged, the iterative effect was very good, and the results were stable. Taken together, the effects of dDAVP + Imi and dDAVP + Tam were the best, while Ver was with the worst efficacy.

Similarly with previous study, combined treatment with low dose oral desmopressin with tamsulosin was more effective than desmopressin or tamsulosin therapy, and also with improved I-PSS,

QoL score, post-void residual urine volume and Qmax³⁷. In women with nocturia, desmopressin and tamsulosin clinical trials have also confirmed the efficacy and safety in improving the severity and frequency of this disease³⁸. Besides, a review of scarce literature showed that this combined treatment could improve the renal enrichment ability and functional bladder capacity in children with enuresis³⁹. The lower bladder filling rate and reduced urinary output due to DDAVP could enhance the oxybutynin action by decreasing uninhibited bladder contractions⁴⁰. A randomized, double-blind, placebo-controlled trial demonstrated oxybutynin combined with desmopressin could significantly decrease wall thickness index and bladder volume in children with enuresis⁴¹. In addition, Lee et al. confirmed that, compared with single drug therapy, desmopressin combined with oxybutynin treatment was with high tolerance, more and faster effective results⁴². Consistent with the result of this study, a prospective, randomized, crossover study showed that both verapamil and oxybutynin treatment could improve nocturnal incontinence by ameliorating urodynamic characteristics with minimal side-effects⁴³. In addition, Verapamil (80 mg/day) displayed antienuretic activity in clozapine induced enuresis⁴⁴. However, verapamil was suggested to be eliminated in the treatment of enuresis in this study.

Our study had a strong point. This study used a mesh meta-analysis method to comprehensively compare the above drugs firstly, providing some clues and evidence for further clinical practice.

However, there are some limitations in this study. Firstly, due to the incomplete data of some studies, the covariates were not corrected in this study. They may affect the results of the meta-analysis as potential confounders, and no further sub-group analysis was processed. Secondly, ADDIS software is simple for operation but not freely programmable. Thereby, the results may be constrained. For example, when estimating the effect amount, only the random effects model can be reported, and our results may be slightly conservatively estimated. Thirdly, due to the small number of studies conducted on some indicators and some drugs, it is not possible to conduct a comprehensive analysis of all indicators and all combinations, and it is also not possible to separate children and adults patients.

Conclusions

In summary, this meta-analysis comprehensively evaluated most drugs for enuresis treatment, and found that DAVP + Imi and dDAVP + Tam may be better drugs for the treatment.

Abbreviations

aggregate data drug information system ADDIS

inconsistency standard deviation ISD

node-splitting analysis NSA

Tolterodine Tol

Imipramine Imi

Oxybutynin Oxy

Pseudoephedrine Pse

Verapamil Ver

Mianserin Mia

Estradiol Est

Tamsulosin Tam

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: TH and SJC designed and collected data, and was a major contributor in writing the manuscript. YL, JCG and XNZ analyzed the data. All authors read and approved the final manuscript.

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Tables

Table 1 Response rates of Node-splitting analysis

Name	Direct Effect	Indirect Effect	Overall	P-Value
Imi, Oxy	-0.57 (-4.14, 2.74)	-0.56 (-108.34, 105.04)	-0.44 (-3.48, 2.59)	1.00
Imi, Placebo	-1.59 (-4.01, 0.80)	-0.41 (-3.49, 2.74)	-1.11 (-2.92, 0.63)	0.50
Imi, dDAVP	1.64 (-1.78, 4.93)	0.97 (-1.43, 3.58)	1.23 (-0.53, 3.09)	0.71
Imi, dDAVP+Oxy	1.63 (-2.28, 6.19)	0.39 (-3.62, 4.34)	0.83 (-1.68, 3.47)	0.62
Oxy, Placebo	-0.92 (-4.35, 2.56)	-0.12 (-4.50, 4.35)	-0.67 (-3.72, 2.30)	0.74
Placebo, dDAVP	2.16 (0.77, 3.78)	3.37 (-0.16, 7.16)	2.34 (1.13, 3.71)	0.49
dDAVP, dDAVP+Oxy	-0.71 (-3.95, 2.62)	0.48 (-4.06, 5.37)	-0.40 (-2.75, 2.05)	0.65

Table 2 Mean number of nocturia of Node-splitting analysis

Name	Direct Effect	Indirect Effect	Overall	P-Value
Dox, Placebo	0.66 (-4.68, 5.93)	1.94 (-4.02, 7.86)	1.17 (-2.21, 4.53)	0.66
Dox, dDAVP	0.34 (-5.24, 5.81)	-1.01 (-7.29, 5.15)	-0.28 (-3.59, 3.05)	0.64
Placebo, dDAVP	-1.63 (-4.32, 1.13)	-0.28 (-8.08, 7.70)	-1.45 (-3.61, 0.59)	0.66

Table 3 Nocturnal urine volume of Node-splitting analysis

Name	Direct Effect	Indirect Effect	Overall	P-Value
Pse, Placebo	-1.63 (-4.15, 1.10)	-0.11 (-2.46, 1.58)	-0.79 (-2.54, 0.77)	0.29
Pse, Ibu+ Pse	0.96 (0.05, 2.17)	-0.55 (-3.23, 3.12)	0.89 (-0.04, 2.07)	0.30
Ibu+ Pse, Placebo	1.03 (-0.22, 3.37)	2.56 (-0.03, 5.53)	1.67 (0.35, 3.42)	0.28

Table 4 Adverse effects of Node-splitting analysis

Name	Direct Effect	Indirect Effect	Overall	P-Value
Dox, Placebo	-0.01 (-1.57, 1.65)	0.58 (-3.07, 4.61)	0.11 (-1.31, 1.58)	0.83
Dox, dDAVP	0.25 (-4.17, 4.21)	0.01 (-1.78, 1.99)	0.06 (-1.41, 1.55)	0.94
Imi, Oxy	-0.13 (-1.82, 1.48)	-1.01 (-56.26, 54.50)	-0.15 (-1.80, 1.41)	0.98
Imi, Placebo	-0.35 (-1.42, 0.67)	-1.97 (-4.17, -0.63)	-0.95 (-1.81, -0.10)	0.06
Imi, dDAVP	-2.23 (-4.46, -0.65)	-0.34 (-1.47, 0.79)	-0.98 (-1.87, -0.12)	0.06
Oxy, Placebo	-0.50 (-2.14, 1.38)	-1.12 (-3.31, 0.92)	-0.78 (-2.45, 0.84)	0.53
Placebo, dDAVP	0.00 (-0.37, 0.45)	-1.30 (-3.19, 0.26)	-0.05 (-0.48, 0.37)	0.12

Figures

Figure 1

Flowchart of selection of included studies in this meta-analysis

Figure 2

Risk of bias graph

Figure 3

Risk of bias summary