Safety and efficacy of beta 3 adrenergic agonist in treating neurogenic LUTD: Systematic review and meta analysis

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Objectives and content of the study

• Lower urinary tract has two functions
  • Urine storage
  • Bladder emptying
  • These two relies on coordinated multi-level neurological inputs including central and peripheral nerve system
• Neurogenic lower urinary tract dysfunction (NLUTD)
  • Results from neurological disease.
  • May lead to dysfunction in bladder storage and/or emptying depend on the level of neurological lesion.
  • NULTD patients are at high risk for recurrent UTI, incontinence, VUR and renal impairment.
Objectives and content of the study

• Anticholinergic agents
  • Often prescribed as a 1st line treatment for storage symptom in NULTD patients.
  • Side effects are well known
    • Dry mouth, constipation, voiding difficulty or acute urinary retention and potential cognitive impairment.

• In order to avoid these adverse effects, a novel effective and safe therapeutic agents are needed
Need for research

• Beta 3 adrenoceptor agonist has been shown to be effective in treatment of idiopathic overactive bladder (OAB).
• Through stimulation of beta 3 receptor in the bladder, induce relaxation of detrusor muscle relaxation.

We are planned to conduct a systematic review and meta analysis to assess the efficacy and safety of beta 3 agonist as a treatment for NLUTD patients.
Research strategy and method

• International prospective register of systematic reviews database (PROSPERO) registered
• Systematic literature search
  • Databases
    • EMBASE, MEDLINE, Cochrane library, SCOPUS, Web of Science, LILACS, WHO, CADTH, Grey literature, clinicaltrials.gov
  • Search term
    • Neurogenic bladder, meta-analysis, adrenergic beta-3, receptor agonists, mirabegron, randomized controlled trial, treatment outcome.
• Search strategy was designed by a discussion with investigator and librarian.
Research strategy and method

• Population
  • Inclusion criteria
    • Patients with neurogenic lower urinary tract dysfunction from any neurologic disorders.

• Exclusion criteria
  1. Patient with Foley catheter, vesicostomy
  2. Intravesical Botox injection with in 1 year
  3. BPH medication history (alpha blocker, 5ARI) 3 month before the study
  4. Post voiding volume more than 250cc
  5. Patient with 2ndary parkinsonism syndromes
  6. Previous deep brain stimulation history
  7. Daily urine output > 3000cc polyuria patient
  8. History of urological surgery that may affect bladder function within 6 months
Research strategy and method

• Exclusion criteria
  9. Urinary tract infection
  10. Risk of Prostate cancer patient
  11. Presence of urinary stone
  12. History of pelvic RTx
  13. Patient with pelvic organ prolapse
  14. Significant EKG abnormality or taking drugs that prolong the QT interval
  15. Intractable HTN,
  16. Cognitive impairment patient
  17. Renal impairment patient (GFR <30ml/min) or moderate to severe hepatic impairment (Child-pugh B&C)
  18. Orthostatic hypotension, hypokalemia and obstructing galucoma
Research strategy and method

• Intervention
  • Beta-3 adrenergic agonists
Research strategy and method

• Comparator
  1. Beta-3 adrenergic agonist vs Placebo
  2. Beta-3 adrenergic agonist vs medical treatment
  3. Beta-3 adrenergic agonist with other medical treatment vs other medical treatment
Research strategy and method

• Primary outcome
  • Change of the baseline symptom score
    • Overactive bladder symptoms score (OABSS)
    • Overactive bladder questionnaire short form (OAB-q SF)
    • Neurogenic bladder symptoms score (NBSS)
    • International consolation on Incontinence questionnaire (ICIQ)
    • Patient perception of bladder condition (PPBC)
  • Change of the baseline quality of life
    • Neurogenic bladder symptoms score (NBSS)
    • Quality of Life (I-QOL) questionnaire
    • International Consultation on Incontinence Questionnaire (ICIQ)

• Major adverse events
  • Cardiovascular side effects.
Research strategy and method

- Secondary outcome
  - Complications
    - Urinary tract infection
    - Acute urinary retention
    - Renal insufficiency
    - Changes of voiding diary: number of voiding per 24 hours, urgency episodes per 24 hours
Study design

• Study selection
  • Identify records, duplication removal
  • Screening by abstract, title. (2 independent authors)
  • All randomized control trials were included
  • Full text review after screening

• Data extraction
  • 2 review authors will classify studies independently (using EndNote, Rayyan)
  • Discrepancies will be consulted to third review author

• Risk of bias (quality) assessment
  • 2 review authors will assess risk of bias each independently using Cochrane’s Risk of bias assessment tool 2.0
  • Disagreements will be consulted to third review author.
Study design

• We will interpret random-effects meta analysis with due consideration of whole distribution of effects

• Statistical analysis
  • Cochrane Handbook for Systematic Reviews of Interventions
  • Dichotomous outcomes: Mantel-Haenszel method
  • Continuous outcome: inverse variance method
  • Subgroup analysis: age, sex, OABSS. Neurogenic disease type
Research strategy and method

Systematic review process

• Conducting systematic review based on published a priority protocol.
• Performing comprehensive search with no restrictions on the language of publication or publication status.
• Two review author will independently screen the literatures, extract data, assess risk of bias and rated certainty of evidence according to GRADE.
Importance of research results

• Recently medical information is rapidly consumed
  • Social network services (SNS)
  • Misinformation often occurs due to an excess of information which is not fully checked.

• Through this study, it is expected that the beta 3 adrenergic agonist will be administered to the appropriate patients.
Researchers

- Chief director. **Jang Hwan Kim**
  - Professor of Yonsei University College of Medicine.
- **Jinu Kim**
  - Clinical Fellow of Yonsei University College of Medicine.
- **Mohamed El Khashab**
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- **Alqahtani Abdullah Mari**
  - Specialist at Prince Sultan military medical city, Riyadh, Saudi Arabia.
- Advisor: **Jae Hung Jung**
  - Professor of Yonsei University Wonju College of Medicine. Director of Center of Evidence Based Medicine, Institute of Convergence Science.
Thank You.