Efficacy and safety of Fesoterodine fumarate in Neurogenic Detrusor Overactivity due to Spinal Cord Lesion (SCL) or Multiple Sclerosis (MS)

Introduction

According to the International Continence Society (ICS) Overactive Bladder (OAB) is defined as "the presence of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency incontinence, in the absence of a causative infection or obvious pathological conditions". OAB is by definition idiopathic. On the other hand Neurogenic Detrusor Overactivity (NDO) is an urodynamically confirmed bladder dysfunction secondary to an underlying neurological pathology (i.e. stroke, SCI, MS) that causes symptoms similar to OAB [1]. NDO is characterized by involuntary contractions, spontaneous or provoked, during the filling cystometry time of the UroDynamic Study (UDS) accompanied usually from low compliance, low capacity, low voiding volume and high detrusor pressure [2].

Patients with NDO usually suffer from recurrent UTI's, chronic bladder retention with increased residual volumes, hydronephrosis and eventually renal failure. The primary aims for the treatment of patients with NDO are: protection of the Upper Urinary Tract (UUT) and prevention of renal damage, achievement of urinary continence, restoration of (parts of) the LUT function and improvement of patients' QoL [3]. In patients with high detrusor pressure during the filing phase, treatment's aim is the "conversion of an active, aggressive high-pressure bladder into a passive low-pressure reservoir" despite the resulting residual urine [3]. The reduction of the detrusor pressure contributes to urinary continence and improvement in QoL, preventing simultaneously UTI.

Therapy of patients' with NDO is either non-invasive or surgical. Non-invasive therapy includes: a) assisted bladder emptying with or without intermittent self-catheterization, b) lower urinary tract rehabilitation c) drug treatment. Surgical treatment is recommended for patients not responding to non-invasive treatment and consists of botulinum toxin injections in the bladder, sacral neuromodulation, sacral rhizotomy, bladder augmentation, bladder substitution and even urine diversion [4].

Antimuscarinic drugs are the first-line choice in the treatment of patients with NDO. By blocking the cholinergic/muscarinic receptors of the bladder, they promote an inhibition of the parasympathetic pathways resulting in increased bladder capacity, bladder compliance and reduced episodes of urgency and incontinence. Nevertheless, the literature for the use of anticholinergics in Neurogenic Lower Urinary Tract Dysfunction (NLUTD) is still limited and sparse and the response of individual patients

to the treatment is variable. Hence, there is only one published meta-analysis about the efficacy of anticholinergics in the treatment of patients with NLUTD [5].

Fesoterodine fumarate is a relatively new anticholinergic drug. It is actually a prodrug that is broken down, by plasma esterases, into its active metabolite, 5-hydromethyltolterodine. The use of Fesoterodine fumarate has been approved, in many countries, for the treatment of OAB, while dry mouth, dry eyes and constipation are the most common adverse effects of its use. To the best of our knowledge no study has been yet published about the use of Fesoterodine fumarate in patients suffering from NLUTD. The aim of our study is to determine the safety and the efficacy of the use of Fesoterodine fumarate for the treatment of patients suffering from NDO.

Materials and Methods

This is an open-label prospective interventional study. All participants have signed informed consent, while the study has been approved by the Scientific and Ethics Committee of our institution. Additionally, this trial has been registered in the International Standard Randomized Controlled Trial registry database (ISRCTN ID: ISRCTN22433402).

Study population

Eligible patients have been regarded as those of 18-80 years old, with a medical history of MS or SCL and nOAB symptoms based on their bladder diaries data, which related to nDO confirmed by UDS. Patients with a recent Urinary Tract Infection (UTI), medical history of urothelial cancer, urolithiasis, stress incontinence, interstitial cystitis/ bladder pain syndrome, pelvic organ prolapse, prior pelvic surgery or pelvic radiation treatment, uncontrolled narrow-angle glaucoma, pregnancy and dementia have been excluded from the study. Furthermore, patients with MS should be clinically stable for at least 3 months before their enrollment, according to Expanded Disability Status Scale (EDSS). Asymptomatic bacteriuria is the standard case scenario in neurogenic patients, especially in Intermittent Catheterization (IC) users. According to the EAU guidelines on Neuro-urology [5], it is strongly recommended to not screen for, or treat asymptomatic bacteriuria in patients with neuro-urological disorders. We follow this strategy in our everyday clinical practice and applied the same in our study protocol.

Study design

The study is designed as an open label prospective interventional trial without control group. All participants will provide an inform consent and the study has the

approval of the scientific and ethics committee of our institution. It has been considered as unethical to create a placebo (or a non-therapy) control group as the increased detrusor pressure might harm the UUT of the patients. On the other hand we know from previous studies on other antimuscarinics that the placebo effect is rather "limited" in such a cohort of neurological patients.

A two-week clean period away from any treatment against nDO has been requested from those patients who were under such therapy. At the baseline, all patients underwent an invasive UDS to confirm the presence of nDO, accompanied by a bladder diary for the clinical assessment of nOAB. The status of QoL has been evaluated with the use of a relative validated questionnaire, the SF (Short Form)-Qualiveen. SF Qualiveen is a self-report measure that assesses the health-related QoL of patients with urinary disorders in neurologic conditions. All the eligible patients started medical treatment with Fesoterodine fumarate 8 mg daily for 3 months and by the end of the three-month therapy, they were re-evaluated with a new UDS and SF Qualiveen assessment. Both urodynamic studies have been performed at the same place and by the same personnel, according to ICS standards for good urodynamic practices and terms [7].

Endpoints – outcomes

The primary endpoint of the study was the confirmation of the maximum detrusor pressure (Pdetmax) reduction and the estimation of Pdetmax difference, during the filling phase in UDS, between baseline and after the three months under fesoterodine fumarate. Secondary endpoints included changes from baseline to end of treatment in other urodynamics parameters and particularly maximum bladder capacity and bladder compliance, as they are defined by the ICS standards for good urodynamic practices and terms.

A more detailed investigation for the impact of fesoterodine fumarate in the lower urinary tract function has been performed with the use of Compliance – Overactivity – Urethra - Voiding (COUV) urodynamic based classification system, obtaining information about the symptoms prognosis and treatment evaluation [8]. Moreover, during the analysis, patients will be subdivided into 4 prespecified categories according to subject's baseline bladder capacity and Pdetmax. Specifically (based on lower urinary tract function and upper urinary tract failure risk):

1. High bladder capacity > 200 ml and low Pdetmax < 40 cm H2O.
2. High bladder capacity > 200 ml and high Pdetmax > 40 cm H2O.
3. Low bladder capacity < 200 ml and low Pdetmax < 40 cm H2O.
4. Low bladder capacity < 200 ml and high Pdetmax > 40 cm H2O.

The aim of this categorization is to investigate whether the use of Fesoterodine fumarate, based on the results of the second UDS after the treatment, can “upgrade” the patients into a “more favorable” category in terms with the lower urinary tract function and the risk of upper urinary tract deterioration and impairment.

Additionally, the effect of fesoterodine fumarate treatment on QoL has been estimated by analyzing the SF Qualiveen questionnaire at baseline and after three months. Finally, incidence and severity of adverse effects of medication over the study period and discontinuation – dropout rate of the study will be recorded in order to evaluate the safety of Fesoterodine fumarate in our cohort.

Statistical Analysis

This will be a pilot study since Fesoterodine fumarate has been never again used in patients with NDO. Consequently, the estimated result of Fesoterodine fumarate will be based mainly on the results that other antimuscarinics had on P_{detmax} of patients with NDO [7].

The sample size has been based on the estimation that our study would have a 90% power with a statistical error type I a=0.05 to detect a 10cmH2O decrease in Pdetmax after the use of Fesoterodine fumarate with a Standard Deviation (SD) of 30cmH2O [10]. Based on current literature, a 15% drop-out rate was estimated and therefore total recruitment of 135 patients would compose a sufficient sample for further analysis. Data has been collected and statistically analyzed with SPSS v26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) using Wilcoxon test for non-parametric samples, regarding that a p-value less than 0.05 indicates statistical significance.

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