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Ghei M[1], Malone-Lee J[1]
1. University College London

DATA TO SUPPORT A HEAD-TO-HEAD COMPARATIVE STUDY OF BLADDER RETRAINING AGAINST AN ANTIMUSCARINIC AGENT IN THE TREATMENT OF THE OVERACTIVE BLADDER

Hypothesis / aims of study

Despite many drug trials on the overactive bladder only a single small, imperfect study has compared an antimuscarinic to bladder retraining [(1)]. It may be that the paucity of data available to power a comparison of bladder retraining against an active drug inhibits sponsors of such studies. Since clinical trials of treatments for the overactive bladder were first attempted, the sample sizes used have been increasing. Two recent controlled trials randomised 911 and 1081 patients [(2)] [(3)], respectively in order to detect a between groups differences of 1 micturition episode per 24 hours. However, in 1999 a similar study randomised 316 patients in order to effect the same analysis. This experiment was designed to test the power potential of a number of different clinical trial designs that could be deployed to test the efficacy of a drug against bladder retraining. It was also intended to discover the sample dimensions necessary for early Phase 2 “Proof of concept studies” using placebo in the overactive bladder

Study design, materials and methods

This was an observational cohort study. Data was collected prospectively from patients treated for an overactive bladder by antimuscarinic agents with bladder retraining, or by bladder retraining alone. At initiation and at follow-up data on frequency, incontinence, urgency and urge incontinence were collected. Data from visits up to sixteen weeks of treatment were analysed using the parametric methods. 708 patients were studied, 44 males and 664 females, and their mean age was 54 (sd=22). 52 patients used pure bladder retraining and 656 used bladder retraining and an antimuscarinic agent. The drug was either oxybutynin, tolterodine, or imipramine combined with either oxybutynin or tolterodine as “combination therapy”. The bladder retraining group had a higher daily frequency ($Z=-3.2$, $p=0.001$, 95% CI for bladder retraining = 10 – 11, 95% CI for antimuscarinic group = 10 - 12) and a lower daily incontinence compared to the antimuscarinic group ($Z=-3.4$, $p<0.001$, 95% CI of median for bladder retraining = 0.75, 0.85, 95% CI of median for antimuscarinic group = 0.75, 1.75). 431 (61%) patients were receiving no treatment prior to initiation. 221 (31%) patients were taking other medication unrelated to the bladder and 56 (8%) of patients being prescribed antimuscarinic agents had previously failed bladder retraining at another centre.

Results

A between groups analysis demonstrated that Bladder Retraining was associated with a greater improvement in urinary frequency compared to antimuscarinic therapy ($Z = -4.6$, 95% CI of difference = -3.3, -1.4, $p < 0.001$) whereas antimuscarinic therapy was associated with a greater improvement in incontinence compared to bladder retraining ($Z = -2.6$, 95% CI of difference = -0.93, -0.27, $p=0.024$). The within group change in incontinence episodes in the bladder retraining group did not appear to show an effect (95% CI of change = -0.19, 0.43). A subgroup showing greatest change in incontinence (Δ Inc) was sought. Boxplots of Δ Inc against age group, sex and the grading of symptoms were examined for maximum effect. Female sex, age group of 50>= and patients describing urge incontinence demonstrated the greatest Δ Inc. Their mean daily frequency was 11.45 (sd=6.1) and incontinence 1.6 (sd=2.1). A sample with such characteristics would be most sensitive to treatment effect.

Interpretation of results

The table illustrates the sample sizes necessary for achieving an adequately powered study depending on different designs.

Parallel Group Comparison		
Unenriched Sample	**N (Group)**	**N (Total Sample)**
Incontinence (primary outcome)	390	780
Frequency (primary outcome)	200	400
Enriched Sample	**N (Group)**	**N (Total Sample)**
Incontinence (primary outcome)	50	100
Frequency (primary outcome)	3000	6000
Cross-over Group Comparison		
Unenriched Sample	**N (Group)**	**N (Total Sample)**
Incontinence (primary outcome)	100	100
Frequency (primary outcome)	80	80
Enriched Sample	**N (Group)**	**N (Total Sample)**
Incontinence (primary outcome)	20	20
Frequency (primary outcome)	20	20

Concluding message

Δ freq is a poor outcome measure, Δ Inc is significantly superior. An antimuscarinic tested against bladder retraining, using Δ Inc for outcome, would probably compare favourably.