94

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RANDOMISED CONTROLLED TRIAL OF CANNABIS BASED MEDICINE (CBM, SATIVEX®) TO TREAT DETRUSOR OVERACTIVITY IN MULTIPLE SCLEROSIS

Hypothesis / aims of study

The overactive bladder (OAB) is a common and difficult problem to manage in patients suffering from multiple sclerosis (MS). Treatment at present is limited to anticholinergics with or without intermittent self catheterisation and most recently, intradetrusor injections of botulinum toxins. However patients using 'street cannabis' reported up to a 64% improvement in one of the symptoms of OAB and an improvement was also seen in an open labelled study of patient with severe MS. More recently a subset analysis of a double blind RCT (CAMS) with oral cannabis reported improvement in urgency incontinence (1). The scientific rationale for the use of cannabis is the finding of CB1 cannabinoid receptor on the rodent bladder and immunohistochemical endocannabinoid production in the human detrusor.

This study aims to report the preliminary results of a randomised double blind parallel group placebo-controlled of the use of oromucosal cannabis based medicinal extract with constituents of tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 mixture (2.7mg of THC and 2.5mg CBD per spray)

Study design, materials and methods

135 patients were randomised to receive either CBM or placebo (PLO) in a double blind parallel group study for eight weeks, with a two week baseline period. The study was powered to detect a difference between treatments of 0.5 episodes of incontinence per 24 hours. Ethical approved and written informed consent was obtained for all patients. 37 Male and 98 females were recruited from 3 European countries (UK, Belgium and Romania). The primary end point for this study was the reduction in urgency incontinence episodes as evaluated by voiding diary. Secondary end points included urgency, day frequency, nocturia, bladder symptom severity score, quality of life and Patients Global Impression of Change. Intention to treat analysis and Per-Protocol analysis was utilised, as well as subgroup analysis using recognised statistical tests.

Results

The primary end point i.e. reduction in numbers of daily incontinence at the end of treatment, did not reach significance .

CBM was superior to placebo for nocturia (CBM -0.52 PLO – 0.24, p=0.01). This was present at all levels of severity of nocturia and the size of effect was greater for more severe disease. Substantial numbers of patients became nocturia free on the active treatment.

The patient's opinion of bladder symptom severity (0 – 10 NRS) showed a significant difference in favour of CBM at the end of treatment (CBM -2.21 PLO -1.05, p=0.001). Patients on CBM were three times more likely to report an improvement of more than 30% compared with those on placebo (P = 0.006).

The reduction in the number of daytime voids also reached significance (P = 0.044) and the total number of voids per 24 hours was also significantly reduced (P = 0.001). There was no difference in the volume of urine produced between the CBM and placebo groups.

Patient's global impression of change (i.e. how much better the patient felt on medication as compared to baseline) which was highly significant in favour of CBM (p = 0.001) There was a trend in favour of improvement in Quality of Life in the treated group but this did not reach statistical significance.

CBM was well tolerated. The most common adverse events were dizziness, UTI and headache and (18% vs 7%, 6% vs 10% and 8% vs 7% for CBM and placebo respectively).

Interpretation of results

This randomised placebo controlled trial demonstrates that CBM has a major impact on bladder symptoms in patients with MS and severe urinary symptoms particularly on the nocturia and frequency. The difference that patients reported in the PGIC and bladder symptom severity scores provides strong evidence of the positive impact of CBM on their condition for the patients. None of the difference in treatment effect was due to urine volumes, as these were comparable between the two groups.

Concluding message

Our results show a beneficial effect in a double blind randomised placebo controlled trial of (Sativex®) on the symptoms of overactive bladder in multiple sclerosis.

References

(1) Neurourol Urodyn (2004); 23(5/6):607(A149).

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CLINICAL TRIAL REGISTRATION: **This clinical trial has not yet been registered in a public clinical trials registry.**

HUMAN SUBJECTS: **This study was approved by the Institute of Neurology and National Hospital for Neurology and Nerosurgery Joint REC No. 02/N053 and followed the Declaration of Helsinki Informed consent was obtained from the patients.**