Randomized Placebo-Controlled Double-Blind Clinical Trial of Cannabis-Based Medicinal Product (Sativex) in Painful Diabetic Neuropathy

Depression is a major confounding factor

DINESH SELVARAJAH, MRCP, MBCHB
RAJIV GANDHI, MRCP, MBCHB
CELIA J. EMERY, PHD
SOLOMON TESFAYE, FRCP, MD

OBJECTIVE — To assess the efficacy of Sativex, a cannabis-based medicinal extract, as adjuvant treatment in painful diabetic peripheral neuropathy (DPN).

RESEARCH DESIGN AND METHODS — In this randomized controlled trial, 30 subjects with painful DPN received daily Sativex or placebo. The primary outcome measure was change in mean daily pain scores, and secondary outcome measures included quality-of-life assessments.

RESULTS — There was significant improvement in pain scores in both groups, but mean change between groups was not significant. There were no significant differences in secondary outcome measures. Patients with depression had significantly greater baseline pain scores that improved regardless of intervention.

CONCLUSIONS — This first-ever trial assessing the efficacy of cannabis has shown it to be no more efficacious than placebo in painful DPN. Depression was a major confounder and may have important implications for future trials on painful DPN.

Diabetes Care 33:128–130, 2010

Painful diabetic peripheral neuropathy (DPN) is a common and distressing complication of diabetes (1). Unfortunately, drug treatments are often ineffective and complicated by unwanted side effects. Thus, there is need for better treatment. We report the first randomized placebo-controlled trial assessing the efficacy and safety of a cannabis-based medicinal extract (Sativex) in intractable painful DPN.

RESEARCH DESIGN AND METHODS

— A total of 38 patients with chronic painful DPN (Neuropathy Total Symptom Score 6 [2] >4 and <16) for at least 6 months with stable glycemic control (A1C <11%) were assessed. Those with persistent pain, despite an adequate trial of tricyclic antidepressants, were recruited. All patients gave written informed consent. The study had Sheffield Ethics Committee approval.

A prospective randomized double-blind placebo-controlled trial design was used. Baseline pain scores were obtained prerandomization. Three modalities of pain (superficial, deep, and muscular pain) were assessed daily using a 100-mm visual analog scale (VAS). The dose of study medication was titrated over 2 weeks, followed by a 10-week maintenance phase. At baseline, depression was assessed using the seven-item depression subscale of the Hospital Anxiety and Depression Scale (HADS-D) (3). Patients continued preexisting neuropathic pain treatment during the study.

Improvement in pain, as assessed by the pain diary and Neuropathic Pain Scale (NPS [4]) questionnaire, was used as the primary outcome measure. Study end point was the final week mean pain and NPS score while taking the maximum tolerated dose of study medication. A total pain score (TPS) (average score of all three pain modalities) was also calculated. Secondary outcome measure was quality of life (QOL), assessed by McGill Pain and QOL (5), SF-36 Health Survey (6), and EuroQOL (7) questionnaires. Tolerability and side effects were evaluated using standardized forms.

Sativex (tetrahydrocannabinol [27 mg/ml] and cannabidiol [25 mg/ml]) and its matching placebo were presented as a pump-action spray. Doses were administered sublingually in divided doses up to four times a day.

Statistical analysis

An intent-to-treat analysis was undertaken. Differences in subgroup baseline characteristics were correlated to the outcome and adjustments performed at a coefficient >0.50. The distributions of outcome measures with each of the covariates were analyzed. Multiple linear regression was used for a normal distribution, while skewed distribution was initially transformed. Data on proportions was analyzed using Fisher's exact test.

In a post hoc analysis, patients were divided into individuals with depression (HADS-D score ≥10) and no depression (HADS-D score <10). Using ANCOVA, we compared mean change in TPS from baseline between these groups. The interaction between depression and treatment was assessed using two-factor ANOVA. Each treatment arm was divided into patients with and without depression, and outcomes were compared using an independent sample *t* test.

From the Diabetes Research Department, Royal Hallamshire Hospital, Sheffield, U.K.
Corresponding author: Dinesh Selvarajah, dinesh.selvarajah@gmail.com.
Received 15 June 2009 and accepted 30 September 2009. Published ahead of print at http://care.diabetesjournals.org on 6 October 2009. DOI: 10.2337/dc09-1029.

Table 1 —*Demographics and primary and secondary outcome measures*

	Baseline		End point		
	Sativex	Placebo	Sativex	Placebo	*P*
Age (years)	58.2 ± 8.8	54.4 ± 11.6			0.24
Sex (female)	4	7			0.38
BMI (kg/m^2)	31.9 ± 6.3	31.6 ± 8.2			0.92
Cannabis (previous use)	2	0			0.60
A1C (%)	8.64 ± 1.7	8.39 ± 1.6			0.72
Diabetes duration (years)	11.2 ± 8.4	13.7 ± 6.0			0.37
Type of diabetes (type 2)	13	11			0.23
Study medication amount (ml)			0.70 ± 0.38	0.73 ± 0.38	0.84
Pain diary scores					
Superficial pain	52.3 ± 33.0	45.9 ± 24.6	37.9 ± 32.1	30.2 ± 30.1	0.72
Deep pain	63.1 ± 29.4	47.4 ± 21.4	44.5 ± 32.7	24.9 ± 29.5	0.38
Muscular pain	52.0 ± 34.2	41.4 ± 28.3	37.9 ± 32.9	20.4 ± 29.9	0.26
TPS	55.8 ± 26.7	44.9 ± 21.5	40.1 ± 28.5	25.2 ± 28.8	0.40
Neuropathic pain scale					
Total score	67.1 ± 19.4	63.6 ± 14.0	51.6 ± 21.9	51.9 ± 24.1	0.62
McGill pain questionnaire					
Sensory scale	19.2 ± 6.9	16.3 ± 6.3	14.7 ± 7.2	12.5 ± 8.7	0.65
Affective scale	4.6 ± 4.3	5.0 ± 3.8	3.1 ± 2.3	3.6 ± 3.8	0.81
VAS	7.6 ± 1.8	6.9 ± 1.7	5.1 ± 2.2	3.8 ± 2.6	0.24
Present pain intensity	2.5 ± 1.1	2.0 ± 1.0	2.1 ± 1.1	1.4 ± 1.7	0.57
EQ-5D questionnaire					
Health status index	0.40 ± 0.21	0.43 ± 0.21	0.54 ± 0.22	0.6 ± 0.2	0.87
Health status VAS	46.0 ± 20.4	44.6 ± 21.8	58.1 ± 20.5	56.4 ± 11.7	0.92
SF-36 questionnaire					
Physical functioning	26.9 ± 15.1	30.8 ± 22.7	30.5 ± 16.6	36.5 ± 27.9	0.63
Role physical	8.9 ± 27.1	12.5 ± 23.5	12.5 ± 32.1	39.3 ± 47.7	0.12
Bodily pain	22.4 ± 15.5	25.7 ± 11.3	35.6 ± 16.6	41.2 ± 24.6	0.64
General health	33.5 ± 18.7	28.4 ± 20.8	34.1 ± 18.2	29.6 ± 19.5	0.78
Vitality	28.3 ± 23.2	30.8 ± 19.2	33.9 ± 22.4	39.6 ± 19.4	0.45
Social functioning	50.8 ± 32.5	48.2 ± 24.9	55.4 ± 25.3	67.0 ± 27.6	0.08
Role emotional	38.1 ± 41.1	33.3 ± 40.8	54.8 ± 46.4	47.6 ± 48.4	0.76
Mental health	57.9 ± 22.6	57.1 ± 19.9	64.4 ± 20.3	59.4 ± 20.6	0.76

Data are *n* or means ± SD unless otherwise indicated. Pain diary scores derived from 100 mm VAS completed daily. TPS derived from average of superficial, deep, and muscular pain scores. EQ-5D, EuroQOL quality-of-life questionnaire.

RESULTS — Of 30 patients randomized, 6 withdrew because of adverse events. We excluded one placebo-treated patient from the intent-to-treat analysis ($n = 29$) because of a protocol violation.

Primary outcome measure

Covariates used in the analysis were duration of diabetes, baseline scores, age, and sex. There was no significant difference in mean change TPS between Sativex and placebo ($P = 0.40$; SEM 9.5; 95% CI −11.3 to 27.8) at end point. Similarly, there was no difference in mean change in superficial ($P = 0.72$; 9.1; −15.3 to 21.93), deep ($P = 0.38$; 10.5; −12.2 to 30.8), and muscular ($P = 0.26$; 10.3; −9.15 to 33.0) pain VAS. Differences in NPS did not reach statistical significance ($P = 0.62$; 7.8; −20.1 to 12.1).

Eight (53%) Sativex-treated patients responded (defined as ≥30% total pain VAS improvement) versus nine (64%) placebo patients ($P = 0.55$, odds ratio 0.63, 95% CI 0.14–2.82) (Table 1).

Secondary outcome measures

The McGill pain questionnaire showed no difference in sensory scale ($P = 0.65$; SEM 3.3; 95% CI −5.39 to 8.44), affective scale ($P = 0.81$; 1.3; −3.0 to 2.4), VAS ($P = 0.24$; 1.0; −0.91 to 3.4), and present pain intensity ($P = 0.57$; 0.53; −0.79 to 1.4) between study cohorts. EuroQOL and SF-36 questionnaires showed improvement in both groups, but differences between groups were not statistically significant (Table 1).

Post hoc analysis

We excluded one patient (Sativex) because baseline HADS-D was incomplete. Mean HADS-D for patients with depression ($n = 10$) and no depression ($n = 18$) were 13.4 ± 3.5 (means ± SD) and 5.94 ± 2.2, respectively. Patients with depression had significantly higher baseline TPS (62.3 ± 22.1 vs. 43.4 ± 24.3; $P = 0.05$) and greater TPS improvement (−31.6 ± 24.2 vs. −10.7 ± 25.0; $P = 0.04$, SEM 9.8, 95% CI 0.54–41.1) compared with those without depression. There was no significant interaction between treatment group and depression. However, there was a significant main effect of depression on TPS ($P = 0.05$), suggesting that in both treatment arms, patients who were depressed were more likely to respond to intervention: Sativex arm, depressed (−36.7 ± 28.6) vs. nondepressed (−4.9 ± 14.4), $P = 0.02$, −56.5 to −7.2; placebo arm, −26.5 ± 20.7 vs. −17.3 ± 33.1, $P = 0.60$, −45.9 to 27.6.

CONCLUSIONS — Despite being common, there are few effective treatments that provide symptomatic relief for painful DPN (8). For centuries, cannabinoids have been consumed for their analgesic properties and more recently studied in other neuropathic conditions (9). In this study, when compared with placebo, Sativex failed to show statistically significant improvements in primary and secondary outcome measures. Depression was identified as a major confounder of study outcome. Patients with depression had higher baseline pain scores and were also more likely to respond favorably to intervention, regardless if Sativex or placebo.

Most painful DPN trials to date either have not screened for depression or exclude individuals who have it (10,11). This study demonstrates that depression is potentially a major confounder in chronic pain trials. Future trials should consider screening for depression before recruiting patients.

As in a number of recent studies, there was a large placebo effect that may have led to a failure to show differences in outcome measures (12). This may provide an insight into the nature of pain in DPN and the placebo effect. There is a need for more robust and objective end points for use in clinical trials of painful DPN.

Use of concomitant medications may be a confounding factor. They were con-

tinued because Sativex was proposed for adjunctive use in painful DPN. Also, it was felt ethically inappropriate to discontinue treatments from which patients may be benefiting. This may have attenuated the analgesic response to Sativex. The use of specific painful DPN QOL questionnaires (13) may have captured subtle changes missed by the generic ones used in this study.

Finally, while the search for therapeutic agents to halt or reverse the neuropathic process continues, more effective treatments are required that provide better symptom control with fewer side effects. The assessment of depression may be important when designing future clinical trials into painful DPN.

Acknowledgments— This research was supported by a Diabetes U.K. grant.

No potential conflicts of interest relevant to this article were reported.

Helen Bowler and Dr. Daniel Witte are acknowledged for their invaluable contribution providing pharmaceutical and statistical advice, respectively.

References

1. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity and impact of painful diabetic peripheral neuropathy in type 2 diabetes. Diabetes Care 2006;29:518–522
2. Bastyr EJ 3rd, Price KL, Bril V, MBBQ Study Group. Development and validity testing of the neuropathy total symptom score-6: questionnaire for the study of sensory symptoms of diabetic peripheral neuropathy. Clin Ther 2005;27:1278–1294
3. Zigmond A, Snaith R. The hospital anxiety depression scale. Acto Psychiatr Scand 1983;67:361–370
4. Galer BS, Jensen MP. Development and preliminary validation of a pain measure specific to neuropathic pain: the Neuropathic Pain Scale. Neurology 1997;48:332–338
5. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. Pain 1975;1:277–299
6. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ 1993;306:1437–1440
7. The EuroQol Group. EuroQol: A new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208
8. Jensen TS, Backonja MM, Hernández Jiménez S, Tesfaye S, Valensi P, Ziegler D. New perspectives on the management of diabetic peripheral neuropathic pain. Diab Vasc Dis Res 2006;3:108–119
9. Kalant H. Medicinal use of cannabis: history and current status. Pain Res Manag 2001;6:80–91
10. Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med 1992;326:1250–1256
11. Wernicke JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, Raskin J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. Neurology 2006;67:1411–1420
12. Tesfaye S, Tandan R, Bastyr EJ 3rd, Kles KA, Skljarevski V, Price KL, the Ruboxistaurin Study Group. Factors that impact symptomatic diabetic peripheral neuropathy in placebo-administered patients from two 1-year clinical trials. Diabetes Care 2007;30:2626–2632
13. Zelman D, Gore M, Dukes E, Tai K, Brandenburget N. Validation of a modified version of the brief pain inventory for painful diabetic neuropathy. J Pain Symptom Manage 2005;9:401–410