Original Article: Treatment

Comparison of the efficacy and safety of tramadol/acetaminophen combination therapy and gabapentin in the treatment of painful diabetic neuropathy

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Abstract

Aims This study compared the efficacy and safety of tramadol/acetaminophen (T/A) and gabapentin in the management of painful diabetic neuropathy.

Methods An open, randomized, comparative study was conducted. Subjects with painful symmetric neuropathy in the lower limbs and mean pain-intensity score ≥ 4 on a numeric rating scale were eligible. Subjects were randomized to receive either tramadol (37.5 mg)/acetaminophen (325 mg) or gabapentin (300 mg) for 6 weeks. After 2 weeks of the titration period (1200 mg/day for gabapentin and three tablets/day for T/A), the doses were maintained if the pain was relieved. The primary efficacy outcome was a reduction in pain intensity. Secondary measures evaluated a pain relief scale, a Brief Pain Inventory, a 36-item Short Form Health Survey, average pain intensity and sleep disturbance.

Results One hundred and sixty-three subjects (T/A 79; gabapentin 84) were included. At the final visit, the mean doses were 1575 mg/day for gabapentin and 4.22 tablets/day for T/A. Both groups were similar in terms of baseline pain intensity (mean intensity: T/A 6.7 ± 1.6; gabapentin 6.3 ± 1.6, P = 0.168). At the final visit, the mean reductions in pain intensity were similar in both groups (T/A −3.1 ± 2.0; gabapentin −2.7 ± 2.1, P = 0.744). Both groups had similar improvements in every Short Form Health Survey category and Brief Pain Inventory subcategory, and in the mean pain relief scores.

Conclusion This study suggests that the T/A combination treatment is as effective as gabapentin in the treatment of painful diabetic neuropathy in patients with Type 2 diabetes.

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Keywords diabetic complication, painful diabetic neuropathy, Type 2 diabetes mellitus

Abbreviations DPN, diabetic peripheral neuropathy; GABA, γ-aminobutyric acid; NRS, numeric rating scale; T/A, tramadol/acetaminophen; TCA, tricyclic anti-depressants

Introduction

With the enormous increase in the prevalence of Type 2 diabetes mellitus worldwide and the improved survival of these patients, the complications accompanying chronic diabetes have become an inevitable issue for patients with this disease. Among such chronic complications, diabetic peripheral neuropathy is characterized by its progressive natural course and troublesome severe symptoms. The reported prevalence of diabetic peripheral neuropathy varies dramatically from 8.3% for patients with newly diagnosed Type 2 diabetes to up to 50% in patients who have had diabetes for 25 years [1,2].

Most diabetic complications can be prevented only if the glycaemic status of the patient with diabetes is maintained within a nearly normal range [3]. Poor glycaemic control also plays a

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central role in the development and progression of diabetic peripheral neuropathy both in patients with Type 1 and Type 2 diabetes [4]. However, a substantial proportion of those with good glycaemic control (HbA$_{1c}$ < 7%) have diabetic peripheral neuropathy and neuropathic pain persists in the majority of diabetic patients over periods of several years [5,6].

Although many patients with diabetic peripheral neuropathy receive treatment, neuropathic pain is not always controlled successfully [7]. In addition to its severity, this type of pain also induces sleep disturbance and depression and impacts upon quality of life [8,9]. Therefore, adequate pain control and the maintenance of glycaemia within a target range should be addressed simultaneously in the management of patients with painful diabetic peripheral neuropathy.

Gabapentin, an anticonvulsant which is structurally related to the neurotransmitter γ-aminobutyric acid (GABA) is widely used for painful neuropathy [10]. Recent clinical trials have shown that gabapentin is effective for neuropathic pain control and has an adverse-effect profile superior to that of the tricyclic antidepressants [11].

Tramadol is a centrally acting narcotic analgesic that is used in the management of moderate to severe pain, including post-herpetic neuralgia and polyneuropathies [12,13]. The drug mechanism is thought to involve a combination of weak mu-opioid agonist activity and the inhibition of norepinephrine and serotonin uptake [14]. Tramadol has been shown to have some efficacy in patients with diabetic peripheral neuropathy in a placebo-controlled multi-centre study [15]. Acetaminophen is a commonly used analgesic which can be used for combined analgesia or analgesic rescue therapy.

In this study, we compared the efficacy and safety of a T/A combination with gabapentin for the management of diabetic peripheral neuropathy in patients with Type 2 diabetes. We also investigated the effects of T/A in terms of improvements in the patients' quality of life and pain relief. To the best of our knowledge, this study is the first comparative, randomized, controlled trial of a T/A combination and gabapentin for the treatment of diabetic peripheral neuropathy in patients with Type 2 diabetes.

Patients and methods

Patient enrolment

This multi-centre, randomized, open, comparative clinical trial was performed at 13 university-affiliated diabetes centres in the Republic of Korea between January 2007 and December 2008. The study was approved by the institutional ethics committee and was conducted in accordance with good clinical practice guidelines and the principles of the Declaration of Helsinki.

Patients with Type 2 diabetes, aged 25–75 years, who had experienced symptoms of painful diabetic neuropathy (including paraesthesia, dysaesthesia, hyperaesthesia, hyperalgesia and allodynia) in the upper or lower extremities for the preceding 3 months were recruited. Patients who showed an abnormal

monofilament response, decreased ankle reflex or vibration sensation, accompanied by an average daily pain intensity ≥ 4 on a numeric rating scale (0 = no pain, 10 = worst possible pain) for the preceding 48 h, were included [16].

Patients were excluded if they were more than 75 years old, were mentally ill or unable to complete the questionnaire, or if they had any severe illness, such as malignancy, severe infection or hypoglycaemia, liver cirrhosis, heart failure or alcoholism. Patients were also excluded if they suffered pain from any other cause, pain of duration exceeding 10 years, diabetic foot, amputation or if their HbA$_{1c}$ was ≥ 10.0% (86 mmol/mol).

During the observation period, other antidepressants, anticonvulsants, alpha-lipoic acid, opioid analgesics, capsaicin, steroids, COX-2 inhibitors, long-acting non-steroidal anti-inflammatory drugs and antipsychotics were prohibited. Treatment with hypoglycaemic agents was maintained.

Study design, medication and assessments

The study consisted of a 2-week titration period and a 4-week maintenance period. Patients who were eligible for the study were randomized to receive either T/A or gabapentin using a table of random sampling numbers in blocks of four according to a computer-generated random code.

The study medication comprised tablets containing either tramadol (37.5 mg)/acetaminophen (325 mg) or gabapentin (300 mg). The titration schedules were as follows. In the gabapentin group, 300 mg was given at bedtime on day 1; this was increased by 100–300 mg three times daily on days 2–7, then increased by 1200 mg/day in divided doses on days 8–14 and maintained thereafter. If there was no pain relief or the pain increased, the gabapentin dose was increased to 3600 mg/day after week 2 and maintained. In the T/A group, one tablet was given at bedtime on day 1; this was increased to one tablet twice daily on days 2–7, then one tablet three times daily on days 8–14 and this dose maintained thereafter. If there was no pain relief or the pain increased, the T/A dose was adjusted to eight tablets, given as divided doses. Acetaminophen up to 3000 mg was used as rescue medication during the titration period.

Before treatment (on day 1), the Brief Pain Inventory, 36-item Short Form Health Survey and the records of pain severity and pain relief were investigated [17–19]. The Brief Pain Inventory questionnaire consists of 11 items: pain severity (4 items—worst, least, average for the preceding week and current pain) and the interference by pain of daily function (7 items—general activity, mood, walking, sleep, normal work, relationships with others and enjoyment of life). Each item is rated on an numeric rating scale of 0 to 10 (0 = none, 10 = worst imaginable pain) [20]. The 36-item Short Form Health Survey quality-of-life questionnaire measures: physical functioning, role limitations attributable to physical problems, social functioning, bodily pain, general mental health, role limitations attributable to emotional problems, vitality and general health problems [21]. Pain relief was assessed on a six-point scale (−1 = pain aggravation, 0 = no change, 1 = a little

relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief) during weeks 2 and 4 and at the final visit.

Patients reported their average daily lower extremity pain within the preceding 24 h in a diary by scoring pain intensity (0 = no pain to 10 = worst possible pain) and sleep interference (0 = no interference to 10 = cannot sleep) on an 11-point numeric rating scale from day 1 to week 6. The Brief Pain Inventory and 36-item short Form Health Survey were assessed on visit 2 (day 1) and at the final visit (week 6).

Laboratory tests

Physical examinations were undertaken at the beginning of the study and biochemical laboratory tests were performed at baseline and at the endpoint. Fasting plasma glucose levels were measured with an automated enzymatic method and HbA_{1c} levels were determined by HPLC with a reference range of 4.4–6.4% (25–46 mmol/mol).

Safety evaluation

Adverse effects were monitored throughout the study (occurrence, intensity and relationship to the study drug). Patients were evaluated for safety at every visit and were instructed to report any severe adverse effects.

Statistical analysis

Sample sizes of 88 patients per group were required based on the assumption that the minimum clinically significant difference in the numeric score for pain intensity was 1.39, with 90% power [22]. All analyses used the intent-to-treat population, defined as all randomized patients using SAS statistical software (SAS Institute, Cary, NC, USA).

The primary endpoint was based on the pain intensity measured by the numeric rating score at the endpoint relative to the baseline value and the average daily intensity during the preceding 24 h from day 1 to week 6. The secondary endpoints were pain relief, 36-item Short Form Health survey, Brief Pain Inventory and sleep interference scores. The primary endpoint was calculated as the mean daily score. The Brief Pain Inventory score was calculated as the mean score and the 36-item Short Form Health Survey score was calculated as the sum of scores. Most clinical characteristics of the T/A and gabapentin groups were compared using an unpaired t-test, although some, including sex ratio and the presence of hypertension, were analysed using the χ^2-test. The Brief Pain Inventory and 36-item Short form Health Survey scores were analysed using an unpaired t-test for inter-group analysis and a paired t-test for intra-group analysis. Adverse effects were analysed using Fisher's exact test. All the results are expressed as means ± SD. $P < 0.05$ was considered significant.

Results

Clinical characteristics

Of the 163 patients, 79 were randomized to the T/A group and 84 to the gabapentin group. Fifty-nine patients (74.7%) in the T/A group and 63 (75%) in the gabapentin group completed the study (Fig. 1).

The demographic data for the study population are shown in Table 1. At baseline, the T/A group consisted of 37 men and 42 women, with a mean age of 58.6 ± 7.5 years compared with 35
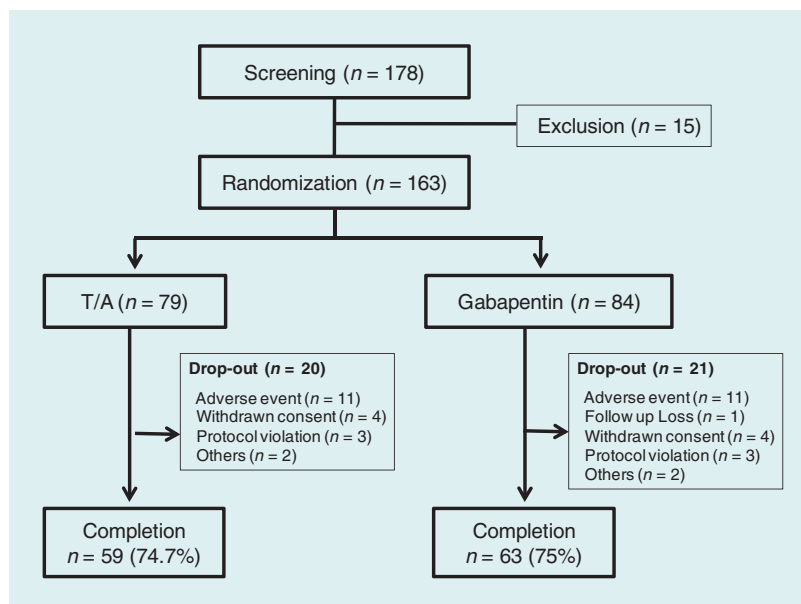

FIGURE 1 Study enrolment and follow-up. T/A, tramadol/acetaminophen.

Table 1 Clinical characteristics

	T/A (n=79)	G (n=84)	*p* value
Age (years)	58.6 ± 7.5	57.1 ± 9.3	0.254
Sex (M/F)	37/42	35/49	0.507
Duration (years)	11.2 ± 7.5	10.3 ± 7.7	0.421
Body mass index (kg/m^2)	24.6 ± 3.2	25.6 ± 3.7	0.063
Hypertension	42 (53.2%)	45 (53.6%)	0.959
Laboratory measurements at baseline			
Glucose (mg/dl)	168.2 ± 75.2	163.3 ± 62.3	0.652
Creatinine (mg/dl)	0.95 ± 0.2	0.90 ± 0.2	0.142
Total cholesterol (mg/dl)	171.5 ± 40.5	174.9 ± 43.2	0.607
SGOT (IU/L)	21.5 ± 9.6	21.7 ± 7.5	0.918
SGPT (IU/L)	24.0 ± 16.5	24.0 ± 12.9	0.981
HbA$_{1c}$ (%)	7.76 ± 1.3	7.66 ± 1.4	0.644
HbA$_{1c}$ (mmol/mol)	61.3 ± 9.3	60.2 ± 8.2	
Laboratory measurements at final visit			
Glucose (mg/dl)	165.0 ± 74.4	167.2 ± 68.0	0.863
Creatinine (mg/dl)	0.95 ± 0.3	0.92 ± 0.2	0.548
Total cholesterol (mg/dl)	174.5 ± 35.3	170.1 ± 43.6	0.543
SGOT (IU/L)	21.6 ± 7.5	22.7 ± 8.4	0.439
SGPT (IU/L)	25.8 ± 16.2	23.9 ± 12.0	0.446
HbA$_{1c}$ (%)	7.4 ± 1.2	7.7 ± 1.3	0.240
HbA$_{1c}$ (mmol/mol)	57.4 ± 10.4	60.7 ± 9.3	

T/A, tramadol/acetaminophen group; G, gabapentin group.
All the results are expressed as means ± SD or medians (range).
P < 0.05 is considered significant.

men and 49 women, with a mean age of 57.1 ± 9.3 years in the gabapentin group. The mean duration of diabetes was 11.2 ± 7.5 years in the T/A group and 10.3 ± 7.7 years in the gabapentin group. There were no significant differences in the clinical characteristics or baseline laboratory values between the groups.

Pain intensity and pain relief

At baseline, the mean daily pain scores were 6.68 ± 1.6 in the T/A group and 6.30 ± 1.6 in the gabapentin group. After 2 weeks of the study period, the mean dose was 1200 mg/day for gabapentin and 3.03 tablets/day for T/A. At the endpoint, the mean dose was 1575 mg/day for gabapentin and 4.22 tablets/day for T/A, respectively. After 6 weeks, both treatments showed a statistically significant improvement in pain intensity. The primary efficacy outcome showed that T/A markedly reduced the average daily pain score from 6.68 to 3.59 (46.3% reduction, *P* < 0.001); gabapentin also reduced the score from 6.30 to 3.60 (42.9% reduction, *P* < 0.001). No significant between-group difference was found (*P* = 0.744; Fig. 2a).

The mean scores for daily pain intensity showed that both the T/A and gabapentin treatments produced significant improvements in the pain scores within the first week of treatment compared with baseline (*P* < 0.001) and this

persisted for the 6 weeks of the study (baseline vs. 6 weeks, *P* < 0.001; Fig. 2b). There was no difference in this improvement between the groups (*P* = 0.218). The pain relief scores at the final visit were 2.09 ± 1.1 for the T/A group and 2.03 ± 1.19 for the gabapentin group (*P* = 0.742).

Brief Pain Inventory and 36-item Short Form Health Survey

Both T/A and gabapentin significantly reduced pain as assessed by the Brief Pain Inventory scores (Table 2). The pain intensity score was markedly improved in both groups [T/A: 5.4 ± 1.5 to 3.5 ± 1.4 (36.6% reduction), *P* < 0.001; gabapentin: 5.3 ± 1.5 to 3.7 ± 1.8 (29% reduction), *P* < 0.001]. The pain interference score was also markedly reduced after treatment [tramadol/ acetaminophen: 4.3 ± 2.2 to 2.8 ± 3.0 (36.3% reduction), *P* < 0.001; gabapentin: 4.3 ± 2.1 to 2.9 ± 2.2 (31.3% reduction), *P* < 0.001]. There were no significant differences between the two groups in either parameter at the final visit (pain intensity score, *P* = 0.170; pain interference score, *P* = 0.453; Table 2).

The T/A and gabapentin groups both showed significant improvement on the 36-item Short form Health Survey questionnaire in terms of both quality of life and mood (Table 3). There was no significant difference between the groups.

Sleep disturbance

The average daily sleep disturbance caused by pain in the lower extremities within the preceding 24 h was assessed by the patients' choice of a score for sleep interference (11-point numeric rating scale: 0 = no interference, 10 = cannot sleep). The T/A and gabapentin groups showed significantly reduced sleep interference scores, beginning at week 1 and continuing through to week 6. The mean reductions in the sleep interference scores for the T/A and gabapentin groups were 34.1 and 33.4%, respectively (T/A: week 1, 4.4 ± 2.5 and week 6, 2.9 ± 1.9; gabapentin: week 1, 4.1 ± 2.5 and week 6, 2.8 ± 2.1). There were no differences in the sleep interference scores for the T/A and gabapentin group from day 1 to week 6 (*P* = 0.658).

Adverse events

A total of 22 patients [T/A: 11 (13.9%), gabapentin: 11 (13.1%)] discontinued the study because of adverse effects. Treatment-related adverse events were reported in 27 patients (34.2%) in the T/A group and in 21 patients (25.0%) in the gabapentin group (*P* = 0.199). The most common adverse effect in both groups was dizziness (T/A: 11.4%; gabapentin: 8.33%; *P* = 0.512). Drowsiness (T/A: 3.8%; gabapentin: 2.4%; *P* = 0.674), nausea/vomiting (T/A: 8.9%; gabapentin: 1.2%; *P* = 0.030), constipation (T/A: 1.3%; gabapentin: 1.2%; *P* = 1.000) and indigestion (T/A: 1.3%; gabapentin: 1.2%; *P* = 1.000) were also reported. The incidence of adverse events was not significantly different
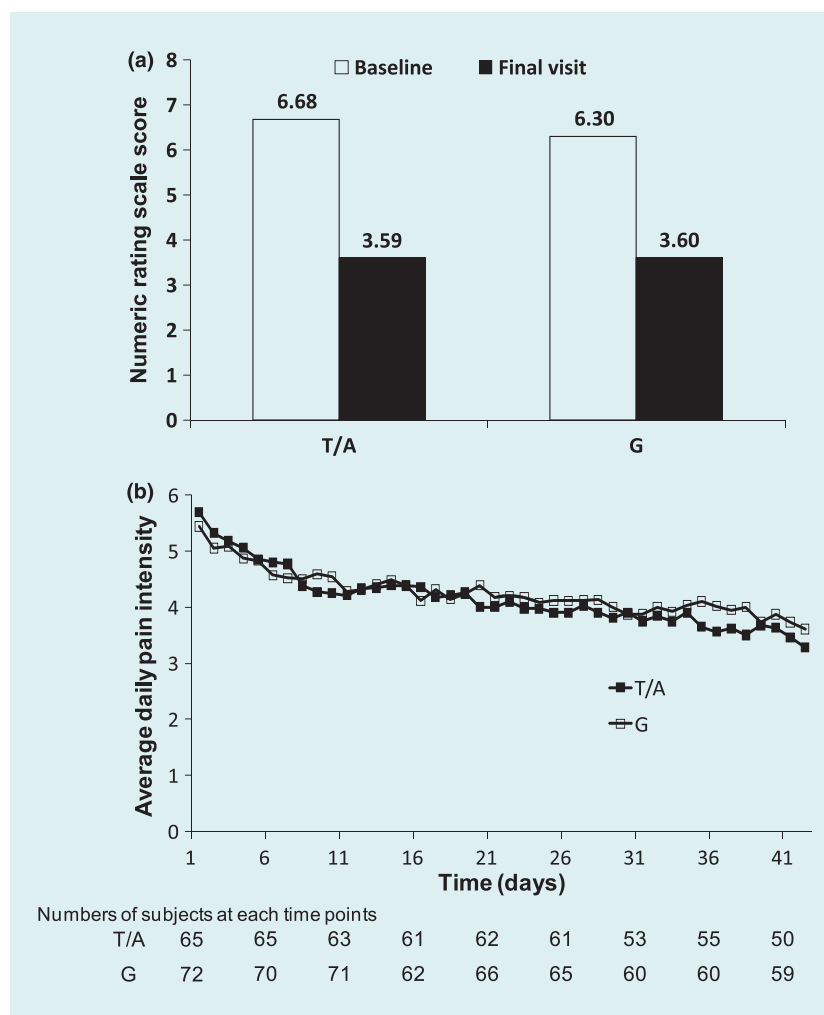
FIGURE 2 Primary outcome results after treatment using numeric rating scale (NRS) scores at the end of treatment vs. those at baseline (a) and average daily scores (b). (a) In both groups, the NRS scores were dramatically reduced after treatment (paired *t*-test), with no significant differences between the groups (unpaired *t*-test). (b) Average daily pain intensity based on the patients' diaries showed that pain was reduced within a few days of treatment and was maintained during the study period in both groups [tramadol/acetaminophen (T/A) vs. gabapentin (G), $P = 0.375$].

between the two groups, except for nausea/vomiting. None of the serious adverse events was reported to be related to the study medication and no abnormal laboratory results after treatment were reported for either group.

Discussion

This is the first randomized, controlled, open study designed to compare the efficacy and safety of T/A combination therapy with gabapentin in the treatment of diabetic peripheral neuropathy in patients with Type 2 diabetes. We have demonstrated that the T/A combination treatment is as effective as gabapentin for the treatment of painful diabetic neuropathy, not only in terms of pain control but also in the improvement of sleep disturbance and quality of life.

Diabetic peripheral neuropathy is a troublesome and common complication of diabetes. The reported prevalence varies according to the standard definition, different diagnostic

methods and variable diagnostic criteria [16]. In the literature, the prevalence of diabetic peripheral neuropathy ranges from 10 to 50% of patients with diabetes, and from 40 to 50% of those with diabetic neuropathies [1,2,10]. Several studies have reported that symptomatic neuropathy is not confined to patients with long-term diabetes, but may also affect subjects with newly diagnosed diabetes or impaired glucose tolerance [23].

These complications can be prevented only if the glycaemic status of the diabetic patient is maintained within a nearly normal range [3]. Indeed, the UK Prospective Diabetes Study demonstrated that strict blood glucose control in people with Type 2 DM was very important for the prevention of diabetic complications [24]. However, the Diabetes Control and Complications Trial demonstrated that although intensive glycaemic control slowed the progression of the neuropathy it did not improve or cure it [25,26].

The pain associated with diabetic neuropathy is severe, sometimes intractable and can affect the patient's quality of

Table 2 Changes in all measures of the Brief Pain Inventory (BPI) from baseline to the final visit

	T/A group			G group			
	Baseline (n = 66)	Final visit (n = 62)	Change	Baseline (n = 73)	Final visit (n = 67)	Change	P-value
Pain worst	7.1 ± 1.4	4.7 ± 2.1	−2.4 ± 2.0	6.9 ± 1.6	4.89 ± 2.1	−2.0 ± 2.3	0.416
Pain least	3.6 ± 1.9	2.5 ± 1.3	−1.2 ± 1.9	3.7 ± 2.1	2.7 ± 1.8	−1.0 ± 2.3	0.549
Pain average	5.8 ± 1.6	3.4 ± 1.5	−2.3 ± 1.9	5.7 ± 1.6	4.0 ± 1.8	−1.7 ± 1.9	0.082
Pain now	5.1 ± 2.3	3.2 ± 1.8	−1.9 ± 2.4	4.7 ± 2.3	3.4 ± 2.3	−1.3 ± 1.9	0.164
Pain intensity score	5.4 ± 1.5	3.5 ± 1.4	−1.9 ± 1.6	5.3 ± 1.5	3.7 ± 1.8	−1.5 ± 1.8	0.170
General activity	4.4 ± 2.7	2.7 ± 2.0	−1.7 ± 2.5	4.1 ± 2.4	3.1 ± 2.3	−1.0 ± 2.7	0.159
Mood	5.2 ± 2.3	3.2 ± 2.1	−1.9 ± 2.8	4.8 ± 2.5	3.2 ± 2.4	−1.6 ± 2.8	0.499
Walking ability	4.2 ± 3.1	2.6 ± 2.2	−1.5 ± 2.4	4.4 ± 2.7	3.1 ± 2.6	−1.3 ± 2.8	0.629
Normal work	4.6 ± 2.6	2.8 ± 2.1	−1.7 ± 2.6	4.1 ± 2.7	3.0 ± 2.4	−1.1 ± 2.7	0.185
Relations	3.1 ± 2.5	2.3 ± 2.2	−0.9 ± 3.1	3.3 ± 2.7	2.6 ± 2.6	−0.6 ± 2.5	0.536
Sleep	5.0 ± 3.1	3.0 ± 2.4	−2.0 ± 3.6	5.1 ± 2.8	3.0 ± 2.6	−2.1 ± 3.2	0.903
Enjoyment of life	4.0 ± 2.8	2.8 ± 2.2	−1.3 ± 3.1	4.1 ± 2.9	2.9 ± 2.8	−1.1 ± 2.9	0.725
Pain interference score	4.3 ± 2.2	2.8 ± 3.0	−1.6 ± 2.2	4.3 ± 2.1	2.9 ± 2.2	−1.3 ± 2.1	0.453

Data are means ± SD.
Scores 0–10: 0 = no pain, 10 = worst possible pain.
Pain interference score: 0 = does not interfere, 10 = interferes completely.
G, gabapentin; T/A, tramadol/acetaminophen.

Table 3 Changes in all measures of the SF-36 from baseline to the final visit

	T/A group			G group			
	Baseline (n = 66)	Final visit (n = 62)	Change	Baseline (n = 73)	Final visit (n = 67)	Change	P-value
Physical functioning	56.6 ± 24.8	59.6 ± 24.9	4.2 ± 19.6	60.4 ± 24.2	64.8 ± 24.1	2.9 ± 20.1	0.715
Role limitations attributable to physical health	40.5 ± 42.7	51.6 ± 43.5	13.5 ± 41.7	48.3 ± 41.9	60.6 ± 41.9	11.0 ± 43.4	0.739
Pain	49.2 ± 21.2	63.8 ± 18.3	15.5 ± 22.9	50.7 ± 18.3	61.5 ± 20.3	10.5 ± 22.3	0.205
General health	38.3 ± 20.9	41.5 ± 18.0	4.7 ± 19.1	40.3 ± 18.0	45.2 ± 18.5	4.6 ± 14.1	0.988
Role limitations attributable to emotional problems	45.5 ± 44.8	55.9 ± 45.5	12.9 ± 50.3	51.1 ± 45.5	69.2 ± 40.3	18.4 ± 47.6	0.524
Energy/fatigue	39.8 ± 22.1	44.7 ± 19.4	5.9 ± 21.9	41.9 ± 19.8	51.9 ± 17.6	10.2 ± 17.9	0.219
Emotional well-being	57.8 ± 22.5	61.4 ± 17.7	5.4 ± 23.7	61.3 ± 19.0	68.5 ± 18.4	7.6 ± 15.8	0.543
Social functioning	67.4 ± 23.1	76.2 ± 19.3	10.1 ± 25.1	72.3 ± 24.9	79.3 ± 19.9	6.0 ± 24.9	0.352

Data are means ± SD.
Scores 0–10: 0 = no pain, 10 = worst possible pain.
Pain interference score: 0 = does not interfere, 10 = interferes completely.
G, gabapentin; SF-36, Short Form 36; T/A, tramadol/acetaminophen.

life. Therefore, treatment should be initiated as soon as symptoms occur. Only two drugs (duloxetine and pregabalin) have, to date, received US Food and Drug Administration approval for diabetic peripheral neuropathy, based on several multi-centre, double-blind, randomized, placebo-controlled trials in patients with Type 2 diabetes [10,27]. Nevertheless, a wide variety of medical treatments are commonly used, suggesting that there is no ideal treatment of choice for painful diabetic peripheral neuropathy.

Gabapentin is thought to act by binding to the $\alpha_2\delta$ subunits of voltage-gated calcium channels, resulting in reduced neurotransmitter release in the hyper-excited neurons [28]. In a large, controlled, double-blind study, gabapentin achieved a significant reduction in pain intensity compared with placebo at doses of 1800–3600 mg/day [9,29]. Gabapentin also produced greater sleep improvement and had a superior adverse-effect profile than the tricyclic antidepressants [30]. One recent survey reported that more than half the patients with diabetic peripheral neuropathy in Europe are treated with anticonvulsant drugs [31].

Tramadol, a centrally acting narcotic analgesic, probably acts through both low-affinity opioid (mu-receptor) and non-opioid activities [14,32]. These characteristics confer a better adverse-effect profile and therapeutic potential for diabetic peripheral neuropathy than those of other narcotics [25].

The tramadol/acetaminophen combination (Ultracet®; Janssen Korea, Ltd., Seoul, Republic of Korea) has been shown to be more effective in pain control than either component alone and to shorten onset time and improve tolerability compared with tramadol alone in patients with dental pain or post-surgical pain [33,34].

Tramadol also has proven efficacy in the treatment of painful diabetic peripheral neuropathy in randomized, controlled trials. Tramadol produced a significantly greater improvement in pain intensity after 6 weeks relative to that achieved in the placebo group [35]. Tramadol has also been shown to provide long-term relief of diabetic peripheral neuropathy pain over a 6-month period, with good tolerability. In this study, the low incidence (approximately 10%) of patients who discontinued because of adverse effects, such as anti-cholinergic effects and somnolence, suggests that tramadol may be a better therapeutic option than tricyclic antidepressants or anticonvulsant drugs for chronic use [32].

In our study, the overall change in pain intensity from baseline to the final visit in the T/A group was −3.11 (46.6%), compared with −2.70 (42.9%) in the gabapentin group. The score reduction after T/A therapy was similar to that in the Harati study (44%) and after gabapentin therapy (32–50%) [15,16].

In addition to causing troublesome pain, diabetic peripheral neuropathy frequently affects the quality of life of patients with Type 2 diabetes [7]. It is often associated with mood and sleep disturbances, reduced physical activity, increased fatigue and reduced quality of life [36]. Therefore, adequate treatment should play a role in both pain relief and the improvement of the patients' social lives. Depression may potentially be an important confounding factor in trials of painful diabetic neuropathy, because subjects with depression have a higher baseline pain score and, consequently, by entering a trial, respond better to treatment. In this study, the baseline Brief Pain Inventory did show a significant deficit in mood in both groups. However, both the T/A and the gabapentin treatments showed significant improvement on the 36-item Short Form Health Survey questionnaire in terms of quality of life and mood. Moreover, there were no significant differences between the T/A and gabapentin groups in the mood scores on either scale. We suggest that both gabapentin and T/A have beneficial effects on patients' quality of life, sense of well-being and mood disturbance.

In our study, both the T/A and gabapentin treatments markedly improved the pain severity and pain interference scores, with no differences between the groups. Both medications showed additional benefits in reducing the sleep interference caused by neuropathic pain.

Constipation, sweating, nausea, headache and micturition difficulties were common adverse effects of tramadol compared with placebo. However, in our study, the percentages of patients who discontinued because of adverse events did not differ between the two groups. In both groups, dizziness was the most commonly reported adverse effect and the T/A treatment showed a similar incidence of adverse effects as gabapentin.

Our study was limited by a relatively high dropout rate (approximately 25%) in both groups, although it was lower in a placebo-controlled trial with gabapentin [16]; approximately half the patients in each dropout group had experienced adverse events and all were analysed at the end of the study. Second, this study has no placebo arm and is an open-label study, although there are placebo-controlled studies of the efficacy of each treatment. Third, our study was conducted over a relatively short period. Ideally therapeutic effects on chronic pain, such as neuropathic pain, need to be investigated with longer treatment periods (> 12 weeks) to demonstrate the durability of the response and exposure at the target dose [37]. Fourth, in order to recommend T/A for chronic use, a long-term detailed comparison with the use of acetaminophen, especially in older patients or patients with diabetic nephropathy, will be required.

In conclusion, this study suggests that a T/A combination is as effective as gabapentin in the treatment of diabetic peripheral neuropathy. The T/A, therefore, represents an alternative strategy for the treatment of this condition in patients who do not respond to gabapentin or other neuropathic treatments. Further studies should be undertaken to evaluate the long-term efficacy of the tramadol/acetaminophen combination therapy for diabetic peripheral neuropathy.

Competing interests

Nothing to declare.

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