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Observational studies on the efficacy of carbamazepine and ascorbyl palmitate in managing trigeminal neuralgia

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Abstract. – OBJECTIVE: Ascorbyl palmitate is a fat-soluble ester of vitamin C and is used as an antioxidant food additive. While literature reports that ascorbyl palmitate can prevent exacerbation of pain and improve the quality of life of patients suffering from pain, this is not yet supported by clinical trial data. Our study aimed to investigate the effectiveness of ascorbyl palmitate in managing trigeminal neuralgia.

PATIENTS AND METHODS: This study was carried out in a single-centre clinical trial in which subjects suffering from trigeminal neuralgia (N=11) were included. All patients were on carbamazepine when first included and, after washout period, received Ascorbyl palmitate. Eligible patients had the most severe trigeminal neuralgia pain in the oral cavity or pain on touching trigger zones, aged 20 years or older, were capable of proper assessment of the severity of pain and their condition, and had experienced multiple episodes of intraoral pain for at least 3 months with a pain intensity of more than 4 points on the numerical rating scale. The Brief Pain Questionnaire was used to evaluate patient's quality of life.

RESULTS: A total of 11 patients were included with a mean age 55.36±10.67 years (7 males, 4 females). Most patients had compression by the superior cerebellar artery and vascular loops upon magnetic resonance examination. The mean numerical rating scale score for carbamazepine after one month was 7.9±0.56 (95% CI 7.49, 8.30). Similarly, for ascorbyl palmitate was 5.5±1.50 (95% CI 4.42, 6.57) (p<0.001).

CONCLUSIONS: Ascorbyl palmitate can be used as an adjunct intervention in managing trigeminal neuralgia pain. According to the results, ascorbyl palmitate prevents frequent exacerbation of pain and improves patient quality of life.

Key Words:
Trigeminal nerve, Trigeminal neuralgia, Patient reported outcome measure, Ascorbylpalmitate, Lancinating pain.

Abbreviations

TN – Trigeminal Neuralgia; AP – Ascorbyl almitate; NMA – Network Meta-analysis; RCT's – Randomised controlled trials.

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Introduction

Trigeminal neuralgia (TN) has a global prevalence between 0.03% and 0.3%[1]. Although in India the prevalence and incidence rates cannot be established owing to few relevant studies, it has been shown to predominate in rural relative to urban areas, with a ratio of 1.7:1[2]. Females are most affected, with a higher incidence in the age range of 37-67 years[3].

TN is characterized by pain on the unilateral side of the face affecting most commonly maxillary and mandibular branches of TN[1]. Almost all patients with TN suffer from symptoms that have lancinating, sharp shooting, radiating pain, and specific trigger pain zones. It is elicited upon chewing, cleaning teeth, speaking and applying cold water to the face. Hence, it substantially reduces patient quality of life and affects oral health. TN is managed by single and combination therapy. The most common treatment employed is the prescription of carbamazepine. Other therapeutic approaches include gabapentin, alcohol injection, decompression, peripheral neurotomy and surgical procedures[4]. The effectiveness of these treatments varies between 23% and 60% but studies have shown that these management strategies have poor outcomes and morbidity. A series of network meta-analyses on the efficacy and acceptability of different interventions have been conducted. Based on 13 clinical studies involving 14 different interventions and data from 672 patients with TN, lidocaine, botulinum toxin and combined continuous and pulsed radiofrequency thermo-coagulation significantly reduced pain[5,6]. However, these interventions were found to have short term relief usually for hours and days, immediate and long-term side effects, and increased cost of treatment.

A case review highlighted the benefits of Ascorbyl palmitate (AP) in combination with fish oil in managing TN[7,8]. AP is a fat-soluble ester of vitamin C commonly used as an antioxidant food additive (E number E304)[9]. It is absorbed in the blood stream after breaking down into ascorbic and palmitic acid[9]. Fish oil (Omega 3), owing to its platelet-stabilizing and anti-vasospastic actions, is also used in managing migraines[10]. AP has anti-mutagenic, anti-neoplastic and antioxidant properties[11]. Overall, strong evidence exists that oral nutritional supplements have a good outcome in preventing and managing various pain conditions[12].

Given the large unmet need for additional effective therapeutic options, this clinical trial was designed to investigate the effectiveness of AP compared with the gold standard of carbamazepine for treating TN. The main aim was to encompass the spectrum of trigeminal neuralgia cases and its care (from the time of TN initiation to chronic patient care and consultation period). This report presents an innovative approach and our aim was to contribute to the literature for future direction of TN management in clinics.

Patients and Methods

Trial Design

The trial was registered in the clinical trial registry India (Reg: CTRI/2018/07/015021) and Ethical approval was taken from the Central Ethical Committee (CEC) at Nitte (Deemed to be University) (Ref:NU/CEC/2018/0198). The trial was conducted between October 2018- March 2020 and was stopped once the required sample size was met with a follow-up of three months' duration. Subjects were evaluated at Nitte (Deemed to be University).

The designed study was a single centre study in patients suffering from trigeminal neuralgia. The study included 10 subjects as decided by statistician for the calculations. The statistician was blinded; however, it was not possible to blind the participants as they were cautious and would like to be informed about the intervention (before and during the treatment). After screening and informed consent, subjects were evaluated at the clinical unit.

All patients who were diagnosed with TN preoperatively were subjected to routine blood and magnetic resonance imaging (MRI) to rule out the cause[4]. Any previous medication was stopped 24 hours before the study to avoid any confounding analgesic effect. Previous medication was resumed if pain recurred or the treatment failed to relieve pain. Carbamazepine (200 mg) was administered to those subjects who were not already on medication for pain owing to TN. Subjects who were on medication for three months or more with carbamazepine 200 mg B.I.D. for managing pain in TN were continued as first intervention (Figure 1). Subjects were crossed to the other arm (AP) after a 20-day minimum washout period. Subjects in the AP (powder) group received 2.4 g B.I.D.

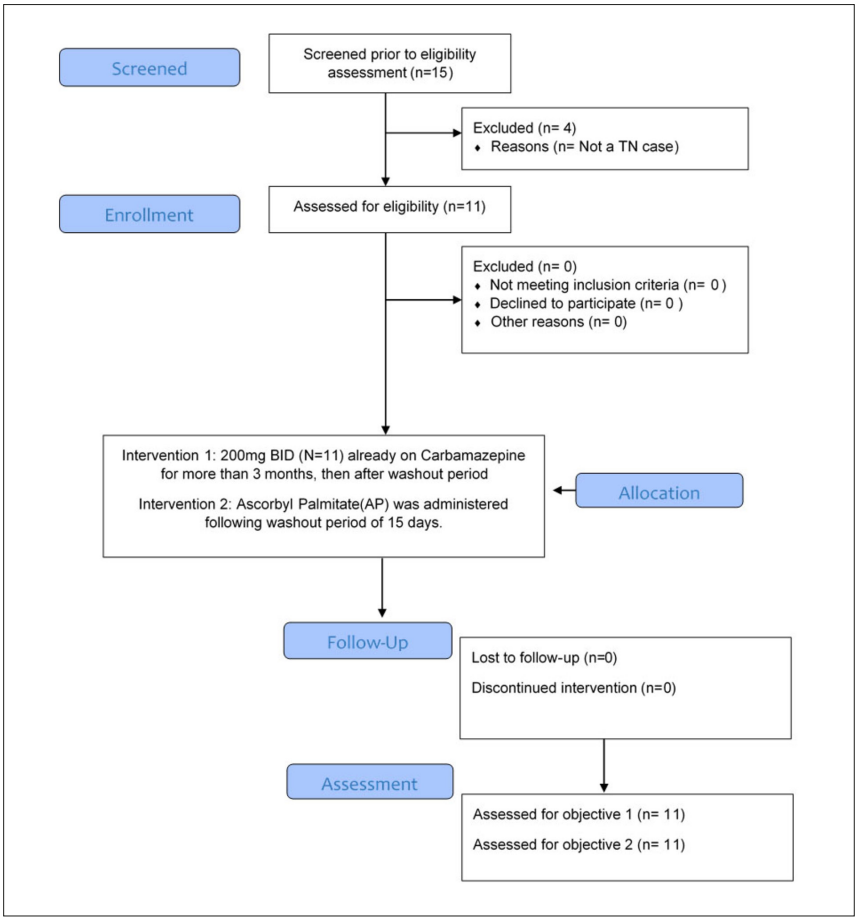

Figure 1. Flow chart illustrating the flow of inclusion of patients randomised to each intervention.

with no carbamazepine. In case where we failed to recruit TN cases without carbamazepine, we recruited patients who were already on carbamazepine for a minimum duration of 3 months. Later after the washout period, they were administered with AP. During this method, randomisation and crossing between treatments after washout period were challenging.

Pain levels were measured by using numerical rating scale (NRS; scale 0-10; 0 = no pain, 10 = worst pain), an established tool for measuring pain severity. In addition, Brief Pain Inventory Questionnaire was also used. The pain scores were recorded pre-intervention and then post-intervention for 30 minutes, 90 minutes and 48 hours and followed-up for three months. Subjects were asked to mark the descriptive scale i.e., markedly better, moderately better, unchanged, or worse to grade the PROM's outcome. The primary endpoint was changed in numerical rating scale (NRS), pain scores at various time intervals and secondary endpoints was Brief Pain Inventory Questionnaire following the initiation of therapy.

Baseline Subject Information

A patient-reported outcomes measures (PROMs) questionnaire was used for assessing the impact on day-to-day life and to determine quality of life following therapeutic intervention. Numerical rating scale (NRS) was used for measurement of pain in subjects before and after therapeutic intervention.

The inclusion criteria for selecting classic TN were based on the definition of the International Headache Classification: paroxysmal unilateral pain triggered in the anatomical region of the trigeminal nerve, without any sensory or motor focal symptoms in this region. Eligible patients had the most severe TN pain in the oral cavity or pain on touching trigger zones, aged 20 years or older, were capable of proper assessment of the severity of pain and their condition, and had experienced multiple episodes of intraoral pain for at least 3 months with a pain intensity of more than 4 points on the numerical rating scale (NRS; scale 0-10; 0 = no pain, 10 = worst pain). The Brief Pain Questionnaire was also used[13].

Subjects with neurological diseases other than TN, severe psychological diseases, serious chronic diseases, such as ischemic heart disease, pulmonary emphysema, and those with a history of severe drug allergy and pregnancy, were excluded from the study. Subjects treated with oral anaesthetics and those with an allergy to vitamin C or on vitamin C were also excluded.

Statistical Analysis

A difference of at least 3 points in NRS score is considered clinically significant. For a power of 0.8 and significance level p=0.05, an allocation ratio of 1, a sample size was determined to be N=10 subjects. Subjects were investigated under observational design conditions.

The assessment of pre-NRS score and post-NRS score difference was calculated by using Wilcoxon signed-rank test. The difference in scores between the standard care arm and the AP group was assessed by Mann–Whitney U-test (since the sample size is small, this non-parametric test was employed). To compare differences between the two treatments, outcomes were categorised into three groups: excellent response, moderately better outcome and subjects with no or worse outcomes. The significance between the effective group (pain-free), less pain and not-effective (no change or worse pain) was done by using chi-square and Fishers exact *t*-test.

Safety Measurements and Adverse Events

AP is used as a chemical preservative in food for human consumption and it is generally recognized as safe when used in accordance with good manufacturing practices.

All patients were monitored for general health and for serious adverse events related to interventions. General and oral assessment including weight, blood pressure, pulse rate, skin, lymph node size, and thyroid palpation was recorded.

Results

Subject demographics and case details are provided in Table I, pain characteristics in Table II, and investigations used in the study are listed in Table III. Details of pre- and post-intervention of AP or carbamazepine are provided in Table IV and V. A total of N=11 subjects were recruited. There were N=7 males and N=4 females with an average mean age of 55.36±10.67 years (range 39-74 years) (Table I). Two patients were not available to record the patient reported outcome measures (PROM's).

The mean preoperative pain Interference score (using Brief Pain Inventory Scale) for AP was 7.32±2.64 (95% CI: 5.11, 9.53) and post-intervention pain inference score for AP was 3.73±2.45 (95% CI: 1.68, 5.78). The mean pre-operative pain severity score was 8.50±1.68 (95% CI: 7.09, 9.91) (p<0.001) and mean post-intervention pain severity score was 4.71±1.70 (95% CI: 3.28, 6.13) (p<0.001).

NRS Pain Scores pre- and post-intervention for carbamazepine and AP were illustrated in Table IV with the time duration from <30 mins to 3 months. There is a significant difference in the reduction of pain with AP (p<0.001) (Table V, Table VI). The patient reported outcome measures (PROM's) were mild to moderately better after AP intervention (Table VII). Changes in NRS pain scores are shown in Figure 2. Patients did not experience any adverse events or side effects due to AP administration. No adverse events were seen.

Discussion

This study included ten subjects with TN and found that AP can be helpful in reducing and prevent the recurrence of pain for a longer duration as hypostasized. Based on post-intervention evaluation, subjects reported being more satisfied and feeling better after using AP in performing routine activities compared to carbamazepine. Of note, most included subjects were already receiving carbamazepine and had experienced a recurrence of symptoms. According to MRI images, the compression of the nerve was the most frequent cause of TN[14]. The literature also reveals that trigeminal neuralgia syndrome[15] appears to be primarily caused by structural changes to the trigeminal nerve and its accompanying anatomical components, particularly by compression. Trigeminal neuralgia has several genetic and molecular targets linked to diverse pathophysiology's[16].

In the literature, various pharmacological, non-pharmacological and surgical/non-surgical therapies have been proposed for TN. The prescription of carbamazepine and oxcarbazepine is considered as the gold standard for management. The evidence on the effectiveness of interventions in TN pain was lacking. But recently, a network meta-analysis (NMA) on the efficacy and acceptability of different interventions have

Table I. Demographics and patient details.

ID	Gender	Age	Occupation	Education	Socio-economic status	Systemic disease	Family history of TN	Brain tumours	Personal history	Drug history	Allergy	Stress
1	M	72	Businessman	Primary school	BPL	No	No	No	No	Carbamazepine 200 mg in the last 6 months BD	No	-ve
2	M	50	Optometrist	University	ABL	No	No	No	No	Carbamazepine 200 mg Since 3 yrs TID and 400 mg since 2 months	Skin rashes recently after intake of carbamazepine	+ve
3	F	60	Housewife	Primary	BPL	No	No	No	No	Carbamazepine 200 mg BD dose in the last 6 months	No	+ve
4	F	55	Housewife	Illiterate	BPL	No	No	No	No	Oxcarbazepine BD dose in the last 1 year	No	-ve
5	M	60	Businessman	Pre-university	BPL	Hypertensive under treatment 10 years	No	H/o fall during childhood	Alcohol intake- 120 ml/ day 30 years, smoking 5-10cigarettes / day 35 years	Flexon MR, Zeptol 200 mg 2 months, Amlong 50 mg	No	+ve
6	F	49	Housewife	Primary	BPL	Hypertensive	No	No	No	Flexon MR, Zeptol 200 mg 2 months, Amlong 50 mg	Rashes on skin since 3 months	+ve
7	M	45	Driver	Primary	BPL	Hypertensive	No	No	Occasional Areca Nut chewing	Carbamazepine 200 mg 2 times/ day past 15 days	No	-ve
8	M	74	Retired	Secondary	ABL	No	No	No	No	Carbamazepine 100 mg BD past 15 days	No	
9	M	39	Driver	Degree	BPL	NA	No	No	Smoking 30 per day	Carbamazepine 200 mg BD for 2 weeks	No	+ve
10	M	55	Farmer/ Labour	Degree	BPL	NA	No	No	Tobacco Chewing 2 sachets and for 5-6 months	Carbamazepine 200 mg BD for 3 Months	No	-Ve

M: male; F: female; ABL: Above poverty line; BPL: Below poverty line; NA: Not Available; BD: 2 times daily; +ve: Positive; -ve: Negative; ID: Identification of patient as number.

Table II. Characteristics of pain amongst subjects.

ID	Type of Pain	Duration (Months)	Frequency of Pain (Per day)	Time of Event	Site of Pain	Side of Pain	Trigger points	Medications for Relief	Severity of Pain (VAS Scale)
1	Tingling and Burning Sensation	6	2-4	Any time during the day	Mandibular Premolar and Molar Region	Right	Intra-orally on the ridge	Carbamazepine	10
2	Lancinating	36	7-8	Chewing and talking	Maxilla	Right	Ala of nose & cheek region	Carbamazepine	10
3	Sharp, Lancinating and Electric Shock type pain	12	5-6	Chewing and speaking	Mandible molar ramus region	Left	In vestibule wrt 36.37 region	Carbamazepine	6
4	Shock type pain	24	All time during the day	Chewing and speaking	Maxilla	Right	Ala of nose & Upper Lip	Carbamazepine	10
5	Sharp, shooting	12	4-5	Early morning, during eating	Body of mandible	Left	Extra-orally lower third of face	Carbamazepine	10
6	Lancinating	48	7-8	Any time	Mandible	Right	Mandibular Ridge	Carbamazepine	8
7	Lancinating	15	6-7	Washing and Brushing	Maxilla	Left	Maxilla below eye, ala, temple region	Carbamazepine	10
8	Shocking	15	6-7	Washing Face	Maxilla	Left	Maxilla below eye, forehead	Carbamazepine	10
9	Sharp Shooting	1	2-3	Eating	Mental foramen	Both	Upper and Lower teeth	Carbamazepine	7
10	Sharp Shooting	3	2-3	Morning and Evening and elicits after sleep	Right side of face	Right	Nil	Carbamazepine	7

Table III. Investigation findings.

ID	MRI	Blood	BMI
1	No significant pathology	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal; Creatinine-1.58 mg/dl, Hb-12.4 gm/dl, RBC 4.26/microlitre, ESR 5 mm/hour; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	31.3
2	Indentation of trigeminal nerve by the superior cerebellar artery	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal; ESR 14 mm/hour, other NA; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	24.2
3	Superior cerebellar artery is close and abuts the left trigeminal nerve	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal; ESR 38 mm/hour, other L-17%; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	26.7
4	Neurovascular compression by superior cerebellar artery along the Trigeminal nerve	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal; Creatinine 0.4 mg/dl, Eosinophils 18%, Ab lymphocyte-3.5/micorlitre, ESR 32mm/hour; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	24.0
5	No vascular or neural compression noted on bilateral trigeminal nerve, Hypertensive ischemic changes bilaterally, in periventricular regions	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal; Hsc reactive protein-14.4 mg/ltr MCV-97.4 fl, lymphocytes-13%, Ab neutrophil count 8.2/microliter; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	19.8
6	The superior cerebellar artery is seen to abut the cisternal segment of trigeminal nerve likely suggestive of Trigeminal neuralgia	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal; Hb- 11.4 gm/dl, ESR 17 mm/hour; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	28.9
7	No significant pathology	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal; Eosinophils 8%, Ab Eosinophil count 0.7/microlitre, ESR 15mm/hour; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	29.8
8	Superior cerebellar artery is close and abuts the left trigeminal nerve	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal; Neutrophils-81%, Lymphocytes-14%, ESR-17 mm/hour, Uric acid-2.7 mg/dl; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	19.0
9	Left Superior Cerebellar traversing in close relation to entry zone of left trigeminal nerve	Serum Folate: Normal; Vitamin B12: Normal; Ferritin: Normal, Zinc: Normal;	19.3
10	Vascular Loop in the exit zone of right trigeminal nerve	Serum Folate: Normal; Vitamin B12: 122.0; Ferritin: Normal, Zinc: Normal; CRP: < 0.5; Glycated Hb: 4.7%; Estimated average glucose: 91.06 mg/dl; Iron: 249 ug/dl; Blood Urea: 20.2 mg/dl; TSH: 1.86 ulU/mL; Creatinine: 0.55 mg/dl; Ferritin: 137.6 ng/ml; Antibody screening extractable nuclear antigen (ENA) and Anti-Nuclear Antibodies (ANA)	15.1

ID: Identification of patient as number; MRI: magnetic resonance imaging; BMI: body mass index.

Table IV. NRS Pain Scores pre- and post-intervention for carbamazepine and ascorbyl palmitate.

ID	Carbamazepine						Ascorbyl palmitate					
	Pre-Intervention NRS (1-10)	Post-Intervention NR (1-10)					Pre-Intervention NRS (1-10)	Post-Intervention NRS (1-10)				
		< 30 mi	> 90 mi	48 h	1 mo	3 mo		< 30 mi	> 90 mi	48 h	1 mo	3 mo
1	10	9	8	6	9	7	10	7	7	7	5	0
2	7	7	6	6	7	9	10	9	9	9	5	2
3	10	9	8	5	8	6	6	6	6	6	5	5
4	10	9	8	7	8	9	10	9	9	9	8	9
5	8	8	8	6	7	8	10	9	9	9	8	9
6	10	10	9	8	8	7	8	7	7	7	4	2
7	10	10	9	8	8	8	10	8	8	8	6	6
8	10	10	9	8	8	7	10	7	7	7	6	4
9	10	10	9	8	8	8	7	8	8	8	4	2

Mi: minutes; h: hours; mo: months; ID: Identification of patient as number.

Table V. Descriptive Statistics.

Treatment	Duration	N	Mean ± SD	SE	95% confidence Interval
Carbamazepine	Pre	10	9.5 ± 1.08	0.34	8.72, 10.27
	< 30 mi	10	9.2 ± 1.03	0.32	8.46, 9.93
	> 90 mi	10	8.3 ± 0.94	0.3	7.62, 8.97
	48 h	10	7.0 ± 1.15	0.36	6.17, 7.82
	1 mo	10	7.9 ±0.56	0.17	7.49, 8.30
	3 mo	10	7.7 ± 1.00	0.34	7.63, 8.98
Ascorbyl palmitate	Pre	10	7.8 ± 1.03	0.32	7.06, 8.53
	< 30 mi	10	7.8 ± 1.03	0.32	7.06, 8.53
	> 90 mi	10	7.8 ± 1.03	0.32	7.06, 8.53
	48 h	10	7.8 ±1.03	0.32	7.06, 8.53
	1 mo	10	5.5 ± 1.50	0.47	4.42, 6.57
	3 mo	10	4.1 ± 3.10	0.98	1.87, 6.32

SD: standard deviation; SE: standard error; mi: minutes; h: hours; mo: months.

been conducted. Based on 13 clinical studies, 672 TN patients' data and 14 interventions, lidocaine, botulinum toxin and combined continuous and pulsed radiofrequency thermo-coagulation were significant in reducing pain[5,6]. These interventions have been found to be effective in short term with increased cost of treatment. The major event addressed was a psychological and mood disturbance.

AP is a greasy lipid-soluble powder and is taken orally stirred into yogurt or spread on buttered toast. AP should be considered in view of its demonstrated anti-inflammatory and antibiotic properties[2]. A daily intake of 2.4 g was determined as sufficient based on the information of this product. Within a few hours of taking AP, the sensation of numbness was reduced to near zero with generally successful eradication of pain[7]. AP mechanism of action was demonstrated by using gap-junctional intercellular communication model (GJIC). AP protects the gap-junctional intercellular communication[8].

Table VI. Post-hoc analysis.

Intervention		Comparison of pain scores by Duration (Scheffe)				
		0	30	48	90	720
Carbamazepine	< 30 min	-0.6 0.80	-	-	-	-
	> 90 min	-1.5 0.023	-0.9 0.407	1.3 0.072	-	-
	48 h	-2.8 0.000	-2.2 0.000	-	-	-
	1 mo	-1.9 0.001	-1.3 0.072	0.9 0.407	-0.4 0.95	-
	3 mo	-2.1 0.000	-1.5 0.023	0.7 0.68	-0.6 0.80	-0.2 0.99
Ascorbyl palmitate	< 30 min	0 1.000	-	-	-	-
	> 90 min	0 1.000	0 1.000	0 1.000	-	-
	48 h	0 1.000	0 1.000	-	-	-
	1 mo	-2.3 0.100	-2.3 0.100	-2.3 0.100	-2.3 0.100	-
	3 mo	-3.7 0.001	-3.7 0.001	-3.7 0.001	-3.7 0.001	-1.4 0.60

Mi: minutes; h: hours; mo: months.

Table VII. Patient Reported Outcome Measures (PROM's).

Pain severity	Daily activity	Drinking cold	Social activity	Others
Markedly better	Markedly better	Moderately better	Markedly better	Feeling happy and painless for 6 months
Moderately better	Moderately better	Moderately better	Moderately better	-
Mildly better	Mildly better	Unchanged	Unchanged	-
Mildly better	Mildly better	-	Unchanged	-
Mildly better	Mildly better	Mildly better	Unchanged	-
Markedly better	Markedly better	Markedly better	Markedly better	Happy and relieved
Mildly better	Unchanged	Mildly better	Unchanged	-
Mildly better	Unchanged	Mildly better	Unchanged	-
Markedly better	Markedly better	Moderately better	Markedly better	Feeling happy as there was no pain and was pain free for 6 months

Recently, Royal College of Surgeons in England developed clinical guidelines for the management of trigeminal neuralgia[17]. The guidelines were developed to formulate a well-defined care pathway for managing both acute and chronic TN using a multidisciplinary approach to treat, in order to address the need for better TN patient care nationwide. The evidence was collected from previous well-established guidelines worldwide, systematic reviews and meta-analyses which would give a perspective about different interventions as compared to control or placebo. Since there are many non-pharmacological and pharmacological interventions, a clinician must make a choice keeping in mind harmful and side effects. It is also reasonable that guidelines and recommendations are developed considering network meta-analysis reports[3,4,18-21]. In addition, in terms of gene association, the following genes are suggested to be potential contributors to the development of TN based on the human research that is now available: CACNA1A, CACNA1H, CACNA1F, KCNK1, TRAK1, SCN9A, SCN8A, SCN3A, SCN10A, SCN5A, NTRK1, GABRG1, MPZ gene, MAOA gene, and SLC6A4[19].

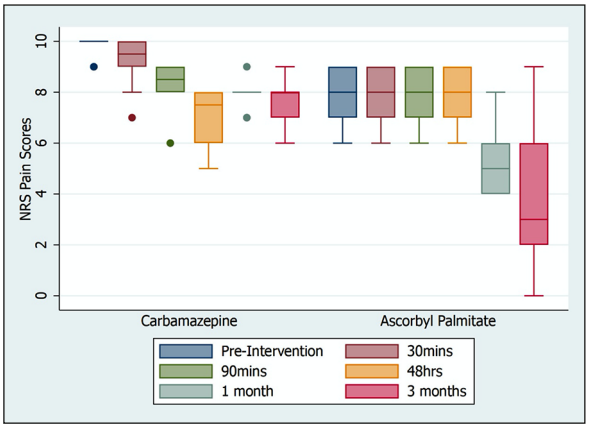

Figure 2. Whiskers and Box plot showing the NRS Pain Scores.

A new sodium channel blocker (CNV1014802) that blocks specifically the Na v1.7 sodium channel and injections of botulinum neurotoxin type A are both used. Non-pharmacological methods for treatment include non-invasive electrical stimulation using either transcranial direct-current stimulation or repetitive transcranial magnetic stimulation, both of which need to be further assessed for their relevance. Surgical treatment was suggested if none of these treatment modalities demonstrated worse clinical outcomes[22]. Various reports were published on informal trial basis relying on consultant diagnosis and patient self-reporting of outcomes[23-26]. In this work, regression analysis illustrates that AP is 1.5 times more effective and prevent the recurrence of pain in the long-term than carbamazepine (Table VIII).

The clinical trial described in the present study is a logical next step to validating and adopting AP as an appropriate treatment strategy. TN is generally assumed to be the result of inflammation causing pressure on the trigeminal root within the foramen and the successful use of an anti-inflammatory drugs in treatment supports this view[1].

Limitations of the study include the small number of subjects recruited. In this regard it is noteworthy that, as TN is a rare condition that has many instances of incorrect diagnosis, it is challenging to identify true positive cases for inclusion in the trial. This was overcome by using

Table VIII. Regression analysis.

Pain scores	Regression coefficient	Standard error	*t*-value	*p*-value	95% CI	
Age	-0.01	0.012	-1.14	0.25	-0.03	0.01
Intervention						
Ascorbyl Palmitate	-1.51	0.26	-5.63	0.00	-2.05	-0.98
Duration (hrs)						
30 min	-0.3	0.46	-0.64	0.52	-1.22	0.62
48 h	-1.4	0.46	-3.0	0.003	-2.32	-0.47
90 min	-0.75	0.46	-1.61	0.11	-1.67	0.17
1 mo	-2.1	0.46	-4.50	0.00	-3.02	-1.17
3 mo	-2.9	0.46	-6.21	0.00	-3.82	-1.97

Mi: minutes; h: hours; mo: months.

standard criteria of diagnosis as described in the inclusion criteria. This study can also be viewed as a proof-of-concept study, suggesting that further well-designed cross over RCT's is required for further evaluation of AP in the management of TN.

Conclusions

According to the results, AP can be an adjunct to the standard gold treatment and can effectively decrease the symptoms and frequency of pain in TN cases. Based on PROM's, the patient's quality of life also improved. More randomised clinical trials are needed to confirm this statement for adding evidence and helping clinicians to determine the benefits of this intervention as first line of approach while planning a management strategy for TN patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval and Consent to Participate

The ethical approval was taken from Central Ethics Committee, Nitte (Deemed to be University) Mangalore India with the ref: NU/CEC/2018/0198 and informed consent was obtained for all patients before participation.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article. Trial registration: CTRI/2018/07/015021. Registered 28 July 2018, (http://ctri.nic.in/Clinicaltrials/advsearch.php).

Consent for Publication

Not applicable as the manuscript do not contain individual details, images, or videos.

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Authors' Contribution

S.K., Z.N., A.C., S.M.S., A.B., A.D.C., M.G., M.P., M.R., F.G., C.M., M.D.F., and C.C. conceived and designed the analysis. All the authors contributed on analysis and interpretation of data for the work. All authors revised the work critically for intellectual content. Integrity of the work was appropriately investigated and resolved by all authors. All authors contributed and approved equally to the final version of the manuscript.

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