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Research Submissions

Trigeminal Neuralgia Crisis – Intravenous Phenytoin as Acute Rescue Treatment

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Objective.—The aim of this retrospective cohort study was to analyze responses to intravenous (IV) phenytoin (PHT) for trigeminal neuralgia (TN) crisis in a group of patients treated at our institution.

Background.—TN is one of the most common causes of facial pain. Its treatment relies on preventive therapy with either carbamazepine or oxcarbazepine. During severe pain episodes, patients may be unable to eat, drink, or even swallow oral medication, requiring in-hospital treatment. There is scarce evidence to support IV medication use for TN, making management of this condition difficult.

Methods.—We reviewed clinical records of patients with TN crisis consulting the emergency department at a tertiary neurological referral center in Buenos Aires, Argentina, treated with IV PHT as analgesic strategy, and with at least 1-month posttreatment follow-up. Demographic features, magnetic resonance imaging findings, and therapeutic management were analyzed.

Results.—Thirty-nine patients with TN were included, 18 (46.2%) receiving IV PHT more than once (total number of infusions administered, 65). Immediate pain relief was observed in 89.2% (58/65) and 15.4% (10/65) presented side effects.

Conclusions.—We recommend IV PHT as acute rescue treatment in TN crisis.

Key words: trigeminal neuralgia, facial pain, trigeminal neuralgia crisis, phenytoin

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INTRODUCTION

Trigeminal neuralgia (TN) is considered as one of the most disabling facial pain conditions, with an estimated incidence of 4-13 cases per 100.000 individuals.[1-3] Usually triggered by innocuous stimuli, it is characterized by episodes of severe, brief, electric, recurrent, and in general unilateral pain, affecting one or more branches of the trigeminal nerve.[3] The 2018 International Classification of Headache Disorders, 3rd edition (ICHD-3) divided TN into 3 different subtypes: classical TN, in which no apparent cause other than neurovascular compression is present; secondary TN (occurring after stroke, multiple sclerosis, tumors or other conditions); and idiopathic TN, where no apparent cause is identified.[4] TN diagnosis is generally based on clinical history and pain features, complemented with magnetic resonance imaging (MRI) findings.[5,6]

Treatment is challenging, and pain control can be elusive in daily neurological practice. Currently,

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carbamazepine (CBZ) and oxcarbazepine (OXC) are used as the first-line treatment, but evidence is lacking on how to manage acute pain crisis, particularly when patients are unable to swallow oral medication.[6]

We hypothesized that use of intravenous (IV) medications such as phenytoin (PHT) may be effective during intense pain crisis when an oral agent cannot be administered.

The aim of this study was to examine adverse events and pain response in patients receiving IV PHT as rescue treatment for a TN crisis.

METHODS

A retrospective cohort study was conducted based on review of clinical records of adult patients diagnosed with TN, attending the emergency department (ED) at FLENI, a tertiary neurology referral center in Buenos Aires, Argentina, between June 2006 and June 2018.

Two members of the Neurology Department, under the supervision of 2 neurologists working in the Headache section, were assigned to review electronic patient records, and implement a search engine using the key words: "facial pain," "trigeminal neuralgia," and "neuralgia." Patients with facial pain, over 18 years of age, attending the ED within the time-frame mentioned were identified, and those meeting ICHD-3 diagnostic criteria for TN at time of diagnosis were selected for the study. This included patients receiving IV PHT for TN crisis management in the ED.

PHT was chosen as treatment, as fosphenytoin is not available in our country.

Data recorded included: patient variables (sex, age at TN onset); etiology and pain characteristics; duration of follow-up; preventive medication used at time of PHT infusion as well as changes made after ED visit; total number of PHT infusions (each separated by at least 24 hours); PHT dose and infusion rate; use of other pain medications before and/or after PHT infusion; and side effects during or after PHT infusion. Pain relief was selected as the primary outcome.

Response to treatment was assessed once PHT infusion was complete. Patients were asked whether pain relief was 50% or greater during ED care (both in relation to number of episodes and intensity of pain), as a way of simplifying and unifying criteria among practitioners, and bearing in mind that for pain reduction to be considered meaningful, 50% reduction must be experienced.[7,8]

Only patients with at least 1-month follow-up after IV PHT administration were included in this study. No patients received oral PHT as preventive treatment before or after the infusion.

Brain MRI (1.5 or 3T scanner) was used to evaluate all patients. Cranial MRI angiography, T2-weighted axial images centered on the fifth cranial nerve, and volumetric contrasted-enhanced sequences were obtained.[9]

PHT loading dose was decided by the attending ED neurologist, as no current guidelines exist regarding the use of IV PHT for TN crisis management. Prior to IV treatment, electrocardiography and blood tests results were obtained to rule out potential cardiovascular contraindications. PHT was administered using a semi-automatized infusion pump, with continuous patient blood pressure, heart rate, and electrocardiogramme monitoring.

Complete data sets were available for all included patients.

Subjects were selected based on data collected and inclusion criteria detailed above. Statistical power calculations were not conducted prior to the study, which was approved by our Institutional Ethics Committee. No informed consent was required by the committee as this was a retrospective analysis. Patients did, however, sign a waiver authorizing publication of anonymized data for research purposes.

Statistical Analysis.—This work represents a descriptive analysis of our sample. Normally distributed variables were presented as mean ± standard deviation. Non-normally distributed variables were reported as median and ranges. Categorical variables were presented using absolute frequencies and their respective proportions. Data were analyzed using the Python programming language, and the open-source libraries Pandas, Statsmodels, and SciPy.

RESULTS

Patient Characteristics.—During the specified timeframe, 257 patients with facial pain consulted the ED at FLENI. Based on the flowchart describing patient selection criteria shown in Figure 1, 39 patients were included.

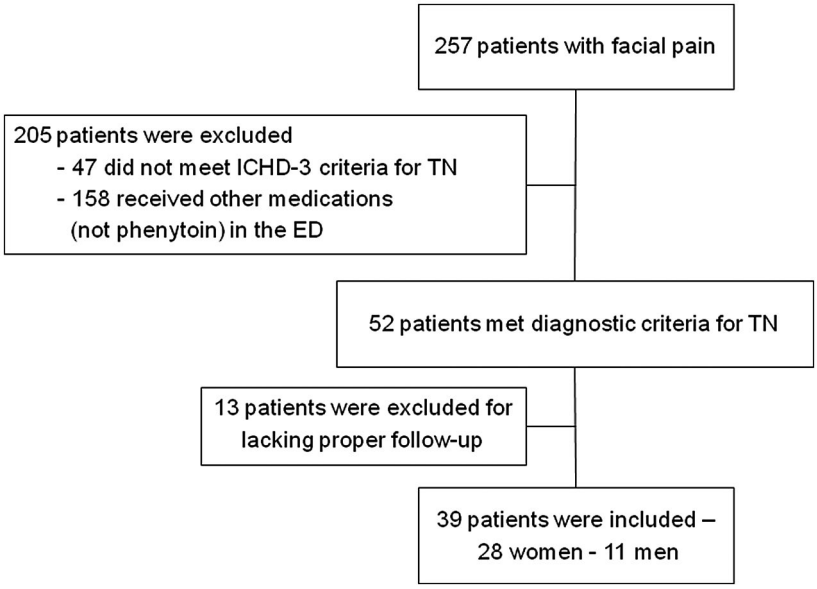

Fig. 1.—Flowchart. Emergency department (ED), trigeminal neuralgia (TN).

Table 1.—Patient Characteristics at Baseline

Female, n (%)	28 (71.8)
Age at beginning of TN, median (IQR)	49 (37-58.5)
Age at time of first PHT infusion, median (IQR)	53 (42-66)
Etiology	
Idiopathic TN, n (%)	18 (46.2)
Classical TN, n (%)	14 (35.9)
Secondary TN, n (%)	7 (17.9)
MS, n (%)	4 (10.2)
Tumor, n (%)	3 (7.7)
Clinical presentation	
Pure paroxysmal pain, n (%)	37 (94.8)
Concomitant continuous pain, n (%)	2 (5.2)

IQR = interquartile range; MS = multiple sclerosis; PHT = phenytoin; TN = trigeminal neuralgia.

Primary data analysis showed median age at time of first PHT infusion was 53 years, and mean number of years between TN diagnosis and first infusion was 3 years. Eighteen patients presented idiopathic TN, 14 classical TN, and 7 secondary TN (tumor n = 3, multiple sclerosis n = 4) (Table 1).

Eighteen subjects received IV PHT for TN crisis on more than 1 occasion, separated by at least 24 hours. The total number of infusions administered to individuals in the study was 65 (Fig. 2).

Preventive treatment had been given to 56 patients on 65 occasions prior to PHT infusion.

Phenytoin Infusions.—In a secondary analysis of our data, we focused on individual infusion characteristics. Both dose and duration of IV PHT were prescribed

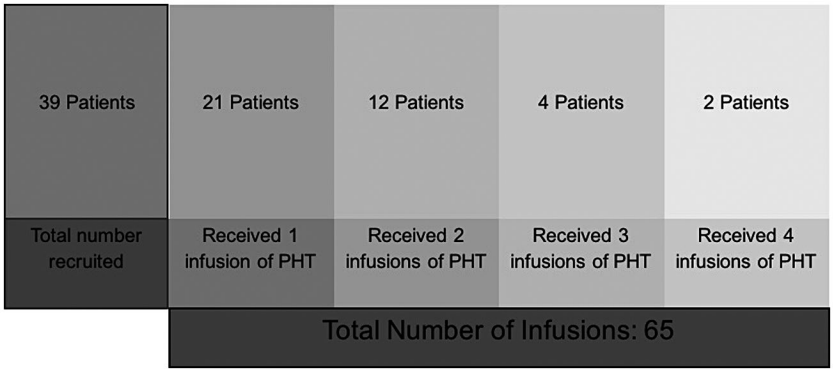

Fig. 2.—Number of infusions received per patient (each separated by at least 24 hours). Phenytoin (PHT).

Table 2.—Phenytoin Infusions (Total Number of Infusions: 65). Response to Treatment

	Number of Infusions	Response	No Response
Total number of infusions, n (%)	65 (100)	58 (89.2)	7 (10.8)
Etiology			
Idiopathic TN, number of infusions (%)	29 (44.6)	26 (89.7)	3 (10.3)
Classic TN, number of infusions (%)	26 (40)	22 (84.6)	4 (15.4)
Secondary TN, number of infusions (%)	10 (15.4)	10 (100)	0 (0)
PHT doses			
Number of infusions ≤10 mg/kg, (%)	54 (83.1)	48 (88.9)	6 (11.1)
Number of infusions ≥15 mg/kg, (%)	11 (16.9)	10 (90.9)	1 (9.1)
Infusion duration			
Number of infusions lasting:			
60 minutes, (%)	50 (76.9)	45 (90)	5 (10)
31-59 minutes, (%)	3 (4.6)	3 (100)	0
30 minutes, number of infusions (%)	12 (18.5)	10 (83.3)	2 (16.7)

PHT = phenytoin; TN = trigeminal neuralgia.

by the ED neurologist evaluating the patient, based on their prior clinical experience. PHT doses selected were 10 mg/kg in 51 infusions, 15 mg/kg in 9, and 20 mg/kg in 2. On 3 occasions, PHT dose was not adjusted to body weight, as it was under 10 mg/kg (5-7.5 mg/kg).

The mean duration of infusion was 60 minutes. Twelve infusions were administered in less than 30 minutes, 3 took between 31 and 59 minutes to complete, and 50 infusions lasted 60 minutes or longer. The mean infusion rate was 10.67 mg/minute (range: 2.78-50 mg/minute). This information is summarized on Table 2.

In 13 infusions, patients had initially received other pain-relieving medication (ketorolac, diclofenac, tramadol, and morphine) prior to PHT, but failed to obtain pain relief. No other medication was given during PHT infusions (total = 65).

Outcome (Response to Treatment).—In 58 of 65 infusions (58/65, 89.2%), good pain control was achieved. Seven patients (7/65, 10.8%) failed to respond to IV PHT, requiring in most cases opium derivatives and showing only moderate response.

Clinical characteristics of PHT responders and nonresponders are summarized on Table 2.

Table 3.—Phenytoin Infusion Side Effects

	Number of Infusions	Presented Side Effects
Total number of infusions, (%)	65 (100)	10 (15.4)
Number of infusions according to etiology		
Idiopathic TN, (%)	29 (44.6)	4 (13.8)
Classic TN, (%)	26 (40)	5 (19.2)
Secondary TN, (%)	10 (15.4)	1 (10)
Number of infusions according to PHT dose		
≤10 mg/kg (%)	54 (83.1)	7 (13)
≥15 mg/kg (%)	11 (16.9)	3 (27.3)
Duration of infusion		
60 minutes, (%)	50 (76.9)	5 (10)
31-59 minutes (%)	3 (4.6)	0
30 minutes (%)	12 (18.5)	5 (41.7)
Preventive medication at moment of infusion		
Carbamazepine, number of infusions (%)	41 (63.1)	4 (9.75)
≥1000 mg/day, number of infusions (%)	9 (13.8)	2 (22.2)
Oxcarbazepine, number	9 (13.8)	4 (44.4)
of infusions (%)	5 (7.7)	4 (80)
≥1200 mg/day, number of infusions (%)	15 (23.1)	1 (6.7)
Pregabalin, number of infusions (%)	5 (7.7)	0
Gabapentin, number of infusions (%)	8 (12.3)	3 (37.5)
Amitriptyline, number of infusions (%)	3 (4.6)	1 (33.3)
Baclofen, number of infusions (%)	1 (1.5)	0
Lamotrigine, number of infusions (%)	7 (10.8)	2 (28.6)
No preventive medication, number of infusions (%)		
Received IV PHT 48 hours prior to new administration, number of infusions (%)	10 (15.4)	4 (40)

PHT = phenytoin; TN = trigeminal neuralgia.

Side Effects.—Side effects, observed in 10/65 (15.4%) infusions, most frequently included nystagmus, dysarthria, ataxia, and hypotension. Other less common adverse reactions are listed in Table 3, all resolving after treatment. No life-threatening events were recorded. PHT-related side effects reported are the result of collected data, no external source was used.

Patients receiving 15 mg/kg of PHT or more presented somewhat higher incidence of side effects (see Table 4).

Infusion duration, however, did appear to be associated with adverse events. Patients receiving infusions

Table 4.—Phenytoin Side Effects (Observed in 10 Infusions)

Nystagmus, n (%)	5 (50)
Dysarthria, n (%)	3 (30)
Ataxia, n (%)	3 (30)
Hypotension, n (%)	2 (20)
Drowsiness, n (%)	2 (20)
Gait disturbance, n (%)	1 (10)
Palpitations, n (%)	1 (10)
Dizziness, n (%)	1 (10)
Diplopia, n (%)	1 (10)
Phlebitis, n (%)	1 (10)

Several patients presented more than one side effect.

lasting 30 minutes or less presented side effects more often (5/12, 41.7%) than those whose infusion duration was 60 minutes or longer (5/50, 10%).

Given that plasma elimination half-life of PHT is 30-100 hours,[10] cases treated twice in less than 4 days were reviewed. Patients retreated within 48 hours or less were more likely to present side effects (4/10, 40% of retreatment infusions caused adverse reactions).

Pharmacological interactions were also examined to see whether association between preventive medication dose and PHT side effects was present (see in Table 4). Preventive medication used by patients did not show strong link to infusion-related side effects, with the exception of OXC which was administered in 9 infusions. In 5 of these, the dose was 1200 mg or more per day. On 4 occasions in which adverse reactions were observed during infusion, OXC was used to treat them (4/9, 44.4%), 1200 mg or more per day (4 of 5 who received this dose of OXC, 80%).

DISCUSSION

Severe pain attacks in patients suffering from TN can be debilitating to the point that eating, drinking, or even swallowing oral medication is difficult, exposing patients to risk of dehydration, malnutrition, and treatment discontinuation.[11,12] Prompt pain relief is needed to administer preventive medication and eventually plan a neurosurgical intervention.[13] This goal is hard to reach with preventive medications alone, not only because oral administration is not possible, but also because rapid augmentation of CBZ or OXC often causes undesired side effects,[12] making IV treatment the best option. Improved understanding of infusion therapies for pain management when oral treatments fail is growing, but lack of consensus guidelines limits more widespread use.[14]

Poor response of TN to NSAIDs or opioids,[11,12,15,16] and lack of evidence on results after IV medication,[3,6] further complicate adequate management of TN crisis.

TN is believed to be a phenomenon similar to epilepsy, in which uninhibited paroxysmal neural discharges occur. If this is the underlying mechanism, it would explain the pain-relieving effects of drugs promoting neural membrane stability.[11]

Historically, PHT was the first effective treatment for TN.[11,15,17] PHT-induced sodium channel block on neuronal membranes, in this case of the trigeminal nerve, is capable of reducing electrical signal propagation,[15] hence stabilizing the membrane.[11,15-17] Factors influencing PHT as our choice for TN crisis treatment included its mechanism of action, the extensive evidence on its tolerability, and the rapid increase in plasma concentrations after IV administration.[12] The choice of PHT over fosphenytoin was due to lack of availability of the latter in our country. Fosphenytoin is a prodrug of PHT. One mg of PHT is equivalent to 1.5 mg of fosphenytoin (fosphenytoin infusion rates are expressed as PHT sodium equivalents, PE).[18]

Although IV administration of either PHT or fosphenytoin have already been proposed to treat acute exacerbations, only limited evidence from small case series (less than 20 patients), has been reported.[12,15,19,20] To the best of our knowledge, this is the first study with a large cohort, confirming the evidence in favor of use of PHT for TN crisis management. Our study also evaluated responses in different TN subtypes (classical, idiopathic, and secondary) showing no differences in this more numerous case series.

To date, no guidelines to indicate best dosing parameters exist, making application of treatment during a TN crisis problematic. In previously published data, levels ranged between 15 mg/kg (analogous to loading doses used in epilepsy)[16] and 100 mg PE (fosphenytoin) every 10 minutes.[12] In this study, different PHT doses were compared, generating a more evidence-based recommendation. Limitations to the study are the fact that it was a retrospective analysis and patient randomization was not applied. The 10 mg/kg dose showed a response rate of 88.9% (48/54) and side effects in

only 13% (7/54) of patients. Given that this is not a life-threatening emergency, infusion duration can be lengthened to 60 minutes (increasing tolerability).

No patient or disease characteristics were associated with better or worse response to PHT (probably because of an underpowered sample size). But higher doses of OXC were linked to higher risk of side effects (likely secondary to OXC-induced PHT level increase),[21] as was a prior PHT infusion (within 48 hours). Disease duration did not appear to affect response to IV PHT in this study.

This is a small, retrospective, single-center non-placebo-controlled study, a fundamental limitation when gathering data from charts, which can influence interpretation of the variables, with potential for information and selection bias.

A randomized, placebo-controlled trial is needed, not only to confirm IV PHT is an acceptable option to treat a TN crisis, but also to establish safe and effective dosing regimens.

CONCLUSION

Based on results from this study, we would recommend, as acute rescue treatment for a TN crisis, a 10 mg/kg PHT infusion lasting at least 60 minutes (equivalent to an infusion rate of 10-15 mg/minute), prior exclusion of electrocardiographic contraindications. Considering the variable etiology of TN cases presented here, and the minimum complexity required for administration, we would advocate its use in daily clinical practice.

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