



Protocol Full Title Retrospective Trial:

Post-traumatic neuropathy of the trigeminal nerve: a retrospective analysis.

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Analysis of PTTN

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Table of Contents

1.	Background and rationale	4
2.	Trial objectives and Design.....	4
2.1	Trial objectives	4
2.2	Primary endpoints.....	6
2.3	Secondary endpoints	6
6.	Selection and withdrawal of subjects	8
a.	Inclusion criteria.....	8
b.	Exclusion criteria	8
7.	Direct access to source data and documents.....	9
8.	Data Handling	10
9.	Data Management.....	10
10.	Analysis of Healthcare Costs, Productivity Loss, Medication Use	11
11.	Publication Policy	11
12.	Financial Aspects	12
13.	References.....	12
	Addendum 1: Castor CRF.....	13
	Addendum 2: brief Michiel Callens	13
	Addendum 3: artikel 26 van het KB nr. 35 van 20/07/67	13

1. Background and rationale

Trigeminal nerve injuries can be caused by dental or oro-maxillofacial procedures and are increasingly common with growing demand for dental work. In a previous study among 8845 patients seen at the department of Oral & Maxillo-Facial Surgery of Leuven in 2013–2014, we identified 53 cases of iatrogenic nerve damage. (1) Patient ages ranged from 15–80 years (mean age, 42 years), and two-thirds were females. The average referral delay was 10 months, with a range of 1 day to 6.5 years. The most common damage site was the inferior alveolar nerve (IAN) (28 cases), followed by the lingual nerve (LN) (21 cases). Most nerve injuries were caused during third molar removal (24 cases), followed by implant placement (9 cases) and local anaesthesia injuries (9 cases). Endodontics-related injuries occurred in 3 cases. Pain symptoms were experienced by 54% of patients suffering IAN injury, compared to 10% of patients with LN injury. Persistent neurosensory disturbances (NSD) were identified in 60% of patients. While prevention remains the key issue, timely referral seems to be a critical factor. Moreover, research on burden of disease indicates a significant, and still underestimated, impact on QoL. (2-4)

Fundamental information on clinical presentation, symptoms, value of parameters measured during the clinical exam, investigations and use of medications or surgical repair have never been reported on a large number of patients. Most of the treatments are expert opinion based.

Currently, little or no research is published on Quality of Life (QoL), costs, productivity loss and medication use in patients with post-traumatic trigeminal neuropathy (PTN). We presume the impact of PTN on patients and society is underestimated and should be further studied and objectified.

2. Trial objectives and Design

2.1 Trial objectives

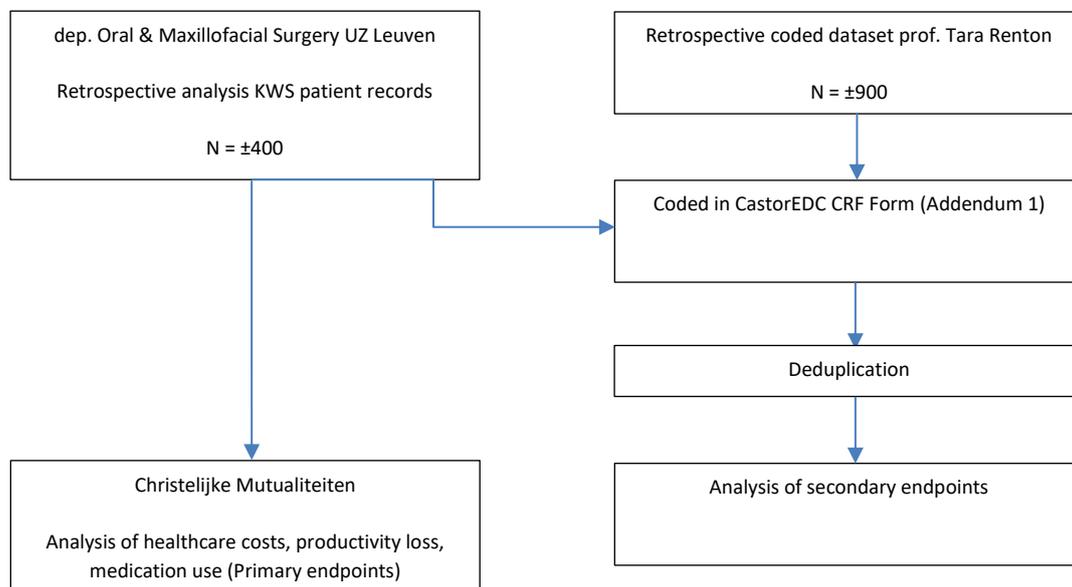
We aim to gain insights in the “burden of disease” of post-traumatic trigeminal neuropathy by performing a retrospective study analyzing patient records of all cases of post- traumatic, including iatrogenic, injury to branches of the trigeminal nerve seen at our department of Oral & Maxillofacial Surgery at UZ Leuven between January 2010 and October 2018 and possible subsequent post-traumatic neuropathy (PTN). The main endpoints are depicted underneath and focus on impact of the cause of injury, the injured branch of the nerve and the outcome (permanent versus temporary neurosensory disturbances) on healthcare costs, QoL, productivity loss and medication use.

To improve statistical power, the coded dataset from a retrospective study by prof. Tara Renton, co-investigator, will be provided to the principal investigator of the current study (dr. Frédéric Van der Cruyssen) and merged with the dataset acquired in this study to further analyze presentation, symptoms, clinical exam, radiographic evaluation, treatments and outcome parameters. The dataset provided by prof. Tara Renton was build by using the same inclusion

and exclusion criteria between January 2010 and October 2018. This should allow for a justified merging of both datasets. Statistical analysis will determine correlation of data.

Only looking at our own records of the department of Oral & Maxillofacial Surgery, UZ Leuven (thus not including the data from prof. Tara Renton) we will evaluate healthcare costs, medication use and productivity loss in relation to the injury and Quality of Life (QoL) measured using the EQ5D survey. This survey has been used by several other authors investigating impact of orofacial pain and in studies evaluating burden of disease in relation to healthcare costs. (5-7) To achieve this goal, we will cooperate with the National Christian Sickness Fund (Christelijke Mutualiteiten, CM hereafter), see underneath for all details.

In summary:



2.2 Primary endpoints

1. What is the difference in total healthcare costs per patient and in total in patients with iatrogenic trigeminal nerve injury seen in our department according to cause of injury, injured nerve and outcome (temporary or permanent injury)?
 - A temporary injury will be defined as an injury that completely recovered with no more symptoms and clinical exam parameters within the normal limits during one of the consultations during the follow up period.
 - Permanent injury will be defined as an injury where no significant improvement in symptoms or clinical exam parameters was seen during one of the consultations during the follow up period.
2. What is the average productivity loss in days in patients with iatrogenic trigeminal nerve injury seen in our department according to cause of injury, injured nerve and outcome (temporary or permanent injury)?
3. Amount of medication use per medication class per patient in patients with iatrogenic trigeminal nerve injury seen in our department according to cause of injury, injured nerve and outcome (temporary or permanent injury)?

2.3 Secondary endpoints

1. Are symptoms or clinical exam parameters (2 point discrimination, directional sense, light touch, percentage of dermatome affected, pinprick threshold), MRCS classification and Sunderland classification predictive of a temporary or permanent injury? If so, which parameters can be withheld?
2. When an injury is present we will evaluate following parameters according to cause of injury, injured nerve branch and between temporary or permanent injury
 - Demographic data: age, gender
 - Symptoms, pain descriptors, interference with lifestyle
 - Clinical exam parameters (quantitative sensory testing)
 - Outcome & Follow-up: IHS criteria, surgical repair, use of medication
 - Social reimbursement rate and professional status
3. If data is present in the patient file regarding legal action taken by the patient against the caregiver who caused the injury this will be registered. We will evaluate how many patients undertook legal action and if they received compensation.
4. If sufficient follow up data is present, we will evaluate how long symptoms are present in case of a temporary injury and evaluate evolution of symptoms in relation to time.
5. Was imaging performed in light of the injury? If yes, what imaging modality was used (conebeam CT, CT, MRI, orthopantomogram) and did this influence treatment decisions?

- When looking at questionnaires applied in our department: are the results from the questionnaires comparable between the different causes of nerve injury, different affected branches? Are results comparable between patients suffering from a temporary or permanent injury? Following internationally validated questionnaires are part of routine examination of pain patients in our department and may be present in the patient KWS record:
 - McGill Pain Questionnaire
 - CPAQ-A
 - Brief Pain Inventory
 - EQ-5D
 - GAD-7
 - GCPS,
 - IES-DVL
 - OHIP-49
 - PainDetect
 - PHQ-9
 - PHQ-15
 - PSEQ
 - CPSI
 - IES
 - West Have-Yale Multidimensional Pain Questionnaire
 - Central sensitization inventory
- Is there a correlation between quality of life measured with EQ5D questionnaire and cause of injury, temporary versus permanent injuries, healthcare costs, productivity loss or medication use?

3. Selection and withdrawal of subjects

Using underneath criteria patients will be included or excluded from this retrospective study. We estimate a sample size of 400 subjects within our department (UZ Leuven). Another 900 subjects are estimated to be included from the retrospective dataset provided by prof. Tara Renton (King's College).

3.1 Inclusion criteria

- Presentation with post traumatic, iatrogenic, injury of the trigeminal nerve or its branches (eg. inferior alveolar nerve, lingual nerve)
- Iatrogenic nerve injury caused by M3 removal, implant placement, orthognathic surgery, endodontic therapy, non-M3 removal, local anesthesia injection, trauma.
- Clinical diagnosis of neurosensory deficit in the distribution of the trigeminal nerve caused by a previous dental or maxillofacial procedure in the vicinity of the affected branch.

3.2 Exclusion criteria

- Neuropathic pain in another region than the trigeminal nerve
- Neuropathic pain not caused by iatrogenic injury

4. Direct access to source data and documents

The selected CRF platform, CastorEDC (www.castoredc.com), permits trial-related monitoring, audit and EC review or regulatory inspection. Source data will be directly accessible to the rightful instance or person on request.

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to the Ethics Committee.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. All medical data, the data collected in the course of the study is treated with the utmost confidentiality. The medical secrecy, the international guidelines (ICH-GCP) and the Belgian legislation are complied with. The investigators undertake to respect the conditions in the European General Data Protection Regulation (2016/679 Europese Algemene Verordening Gegevensbescherming, AVG/GDPR) and the Belgian legislation on the protection of natural persons with regard to the processing of personal data.

5. Data Handling

Data will be analyzed by Steffen Fieuids, statistician at Leuven Biostatistiek en Statistische Bioinformatica Centrum. Following statistical methods will be applied.

Non-parametric analyses (Mann-Whitney U tests, Kruskal-Wallis tests, Spearman correlations, Fisher exact tests) will be used to compare in a univariable setting the primary and secondary endpoints between groups (e.g. type of nerve) and to evaluate relations between continuous and/or ordinal variables.

(Multivariable) Linear models will be used to evaluate the relations with healthcare costs. In case the period referring to the calculation of the cost differs between subjects, a weighted version of the proposed model will be considered (with the weight being a function of the length of the period. The productivity loss (number of days) will be evaluated with (multivariable) models for count data (e.g. negative-binomial) will be used (with an offset term in case the periods differ between subjects).

(Multivariable) logistic regression will be used for the permanent/temporary classification of the injury. In all multivariable models, multiple imputation methods based on the fully conditional specification (FCS) approach (8) will be considered to handle the presence of missing data. In models applied on aggregated data from Belgium and UK, center will be added as a fixed effect and it will be verified if the relations are country dependent.

P-values smaller than 0.05 will be considered significant. Given the multitude of planned analyses, a single significant p-value will be interpreted with caution.

6. Data Management

All medical data, the data collected in the course of the study is treated with the utmost confidentiality. The medical secrecy, the international guidelines (ICH-GCP) and the Belgian legislation are complied with. The investigators undertake to respect the conditions in the European General Data Protection Regulation (Europese Algemene Verordening Gegevensbescherming, AVG) and the Belgian legislation on the protection of natural persons with regard to the processing of personal data.

The CastorEDC (www.castoredc.com) platform will be used to ensure a systematic approach towards entering datapoints after accessing the patient record in KWS. After reading the patient record in KWS, all data will be coded immediately in the CastorEDC database by creating a new and unique identifier, the study ID. A separate patient ID Log file will be kept on a secured UZ Leuven server containing the study ID and patient EAD. After completion of patient inclusion all data entered in CastorEDC will be exported to a coded SPSS database for further statistical analysis without names, initials, date of births, EAD or EMD numbers. The dataset will be password protected and stored on the UZ Leuven server while the study is in progress. Afterwards the study will be deleted from the Castor platform. The password protected SPSS dataset will be stored on the UZ Leuven server for

future research purposes or audits for the next 20 years. The database with research results does not relate to elements such as names, initials, and complete date of birth (dd /mm/yyyy).

Data from the already conducted retrospective study by prof. Tara Renton, will be delivered in a secured and coded SPSS dataset without names, initials, or dates of birth and will be manually imported in the CastorEDC platform using separate study specific ID's to allow data merging in 1 CRF platform: CastorEDC. This will allow to conduct retrospective analysis on a larger sample size.

7. Analysis of Healthcare Costs, Productivity Loss, Medication Use

A separate and independent analysis will take place by the R&D department of the Christelijke Mutualiteiten (CM), to analyze health related costs, productivity loss and medication use for these patients. The followed procedure was discussed and agreed upon by all involved parties including the principal investigator, dr. Frédéric Van der Cruyssen, all co-investigators (prof. Dr. Constantinus Politis, Prof. Dr. Reinhilde Jacobs, Prof. Dr. Tara Renton), department of R&D of the CM (represented by dr. Michiel Callens and dr. Ing. Frank De Smet), CTC legal advisor (Jean-Jacques Dereze) and UZ Leuven Data Protection Officer (Griet Verhenneman). Data collected from KWS records will be used to identify CM members who met the inclusion criteria. An official request by dr. Michiel Callens, advising physician, (Addendum 2) according to article 26 of KB nr 35 of 20/07/67 (Addendum 3) will ask for additional information on CM-members seen at our department suffering from PTN to further analyze above mentioned endpoints involving injury related costs, productivity loss and medication use within the records of the CM.

Data gathering will include:

The data will be collected by a CM data team using their own records and will be stored in a coded database on their servers. The data results from the CM will be shared with the principal investigator on a secured medium only containing coded results. The followed procedure and legal basis is similar to a previously conducted study by Beutels et al. (9) The database from the CM contains all resource use information of members of the largest sickness fund in Belgium. The membership population of CM corresponds to 43.7% of the total Belgian population. There is a slight bias in favour of the older age groups, but this should not grossly distort the estimates based on this sickness funds. In terms of socio-economic characteristics, the unemployed are slightly underrepresented (40.6% of the unemployed are members), but, again, the overall difference is relatively limited (i.e. 43.7% versus 40.6%), cited from Beutels et al. We estimate 200 records from our department will be eligible for further analysis by the CM.

8. Publication Policy

This retrospective study will be sent for publications in a journal concordant with the subject and after careful considerations with the whole team.

9. Financial Aspects

No external funds are necessary.

10. References

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Addendum 1: Castor CRF

See separate file named "Addendum 1 CRF v2 23-01-2019.pdf"

Addendum 2: brief adviserend geneesheer Christelijke Mutualiteiten dr. Michiel Callens

See separate file named "Addendum 2 Brief CM.pdf"

Addendum 3: artikel 26 van het KB nr. 35 van 20/07/67

Bij het vervullen van zijn opdracht houdt de adviserend geneesheer verbinding met de behandelend geneesheer. Samen met hem onderzoekt hij de mogelijkheden om de diagnose nauwkeuriger te stellen en de therapie te verbeteren en om desgevallend de kosten der behandeling te verminderen, zonder de doelmatigheid van de behandeling ook maar enigszins te schaden. De adviserend geneesheer is verplicht te antwoorden op elk verzoek om inlichtingen uitgaande van de behandelend geneesheer, naar aanleiding van een beslissing die hij heeft genomen. Hij mag de geneeskundige sanitaire en medisch-sociale instanties alle statistische gegevens verstrekken die bij de uitvoering van hun opdracht nuttig kunnen zijn. Hij helpt de verzekerde en de behandelend geneesheer om voor de verzekerde elke door hem verantwoord geachte bemoeiing van een medische of sociale instelling te verkrijgen.