Statistical Analysis Plan

Post-traumatic stress – does it affect outcomes of a multimodal physiotherapy intervention for patients with chronic neck pain

Broholm, Daniel; Andersen, Tonny Elmose; Boyle, Eleanor; Ris Hansen, Inge

Publication date:
2018

Document version:
Final published version

Statistical Analysis Plan

Post-traumatic stress – does it affect outcomes of a multimodal physiotherapy intervention for patients with chronic neck pain

Daniel Broholm[1], Tonny E. Andersen[2], Eleanor Boyle[1, 3], Inge Ris[1]

[1] University of Southern Denmark, Faculty of Health Sciences, Department of Sports Science and Clinical Biomechanics, Research Unit for Musculoskeletal Function and Physiotherapy, Campusvej 55, 5230 Odense M, Denmark

[2] University of Southern Denmark, Faculty of Health Sciences, Department of Psychology, Campusvej 55, 5230 Odense M, Denmark

[3] Division of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Health Science Building, 155 College Street, Toronto, ON, M5T 3M7, Canada

Correspondence:

Daniel Broholm

University of Southern Denmark, Campusvej 55, 5230 Odense M, DK

Email: dabro16@student.sdu.dk or danielbroholm@hotmail.com

Table of contents

Aim and hypotheses

The aim of this study is to explore the influence of post-traumatic stress symptoms (PTSS) on effect of a multimodal physiotherapy intervention for persons with chronic neck pain.
The objectives are first, to explore if traumatic chronic neck pain patients with high levels of PTSS differ from those with low levels of PTSS and non-traumatic chronic neck pain patients on self-reported outcomes and clinical tests. Secondly, to determine if the level of PTSS modify the treatment effect, e.g. the groups responds differently to a multimodal intervention from baseline to 12 months on self-reported outcomes and from baseline to four months follow-up for the clinical tests.

Two specific hypotheses are proposed based on previous research (Campbell et al., 2015, Ravn et al., 2018, Vaegter et al., 2017).
1st hypotheses: patients with high levels of PTSS differ significantly from those with low levels of PTSS and non-traumatic neck pain patients, with worse scores on physical and mental quality-of-life, depression, neck-related disability, kinesiophobia, pressure pain threshold and cervical neck muscle endurance (H1).
2nd: traumatic neck pain patients with high levels of PTSS will improve significantly less from a multimodal intervention program compared to those with low levels of PTSS and non-traumatic neck pain patients (H2)

Defining exposure group

A three-level exposure variable will be defined as trauma-high PTSS, trauma-low PTSS and non-trauma. The traumatic neck pain patients will be divided into high or low levels of PTSS based on their scores from the *The Impact of Event Scale* (IES) (Horowitz et al., 1979), which was administered at baseline. Using the cutpoint of 26, those who scored 26 and more will be defined as trauma-high PTSS and those whose scored below 26 will be defined as trauma-low PTSS (figure 1) (Sterling, 2008). The non-traumatic neck pain patients will be kept in a separate category.
The classification of being "traumatic" or "non-traumatic" was based upon the participants' self-reported cause for their neck pain at the baseline measurement in the study. At baseline, 120 participants reported traumatic onset and 80 participants reported non-traumatic onset of their neck pain.

Figure 1 show a flowchart of participants in the study.

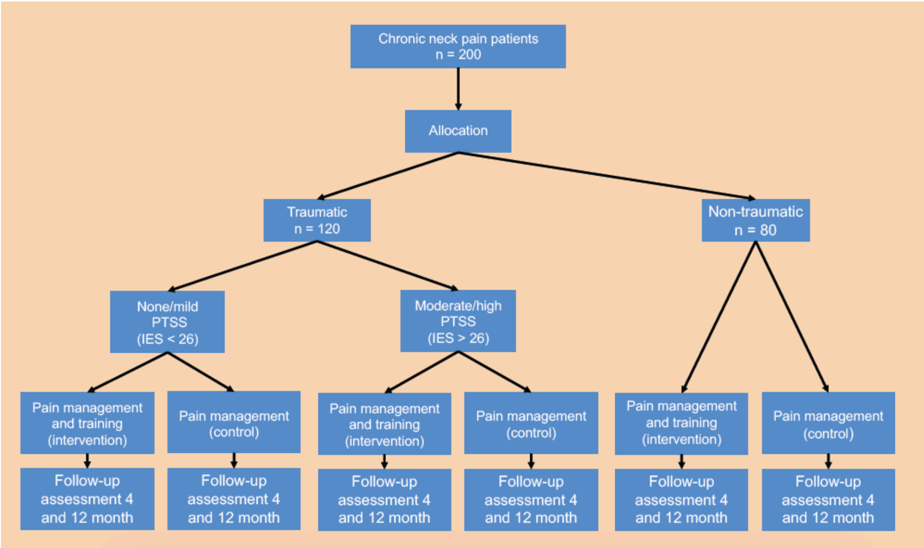

Figure 1 Flowchart of the study.

Statistical analysis

All statistical analyses will be performed as a per protocol analyses on participants with follow up at 12 month. Missing data will be examined with Little's "Completely Missing At Random" test (Li, 2013) and missing data will be imputed with the Expectation Maximization method.

Dropouts in the study will be examined across groups and compared on their baseline demographic variables and outcome measures to explore the possibility of attrition bias (Table 1).

For all three exposure groups, baseline data on demographics, test results and patient reported outcomes will be summarized using either mean or median with 95% confidence intervals or frequencies (see table 2-4).

All data will, before analyses, be visually inspected for normality by histograms and residual plots. For the continuous variables at baseline, analysis of variance (ANOVA) or Kruskal Wallis will be conducted to determine if at least one of the means/medians is different from the others. If found significant, then we will calculate Dunnett's C post hoc test to determine if the non-traumatic and the traumatic low PTSS groups differ from the traumatic high PTSS

group if the assumption of homogeneity of the variances holds, or perform post hoc comparisons of traumatic high PTSS versus traumatic low PTSS and traumatic high PTSS versus non-traumatic will be conducted using Wilcoxon's Sign Rank test.
Effect sizes of the difference in outcome measures between group will be calculated based on eta-squared (effect sizes are regarded as small η^2=0.01, medium η^2=0.06, large η^2=0.14 (Portney and Watkins, 2014)).

For the categorical variables, chi-square or Fisher's exact test will be conducted determine if one of the proportions is different across groups. Fisher's exact test will be conducted over chi-square test if any of the expected values in a cell is less than five (Portney and Watkins, 2014). If significance is found, the planned post hoc comparisons of traumatic high PTSS versus traumatic low PTSS and traumatic high PTSS versus non-traumatic will be conducted using chi-square or Fisher's exact test in separate 2x2 tables. Effect sizes on differences on proportions between groups will be calculated based on Cramer's V (effect sizes are regarded as small V = 0.10, medium V=0.30, large V=0.50 (Portney and Watkins, 2014)).
In order to reduce the risk of Type I errors, the level of significance will be corrected by the Bonferroni procedure.

In evaluation of the treatment effect of the intervention, the primary outcome is the mean group change in the Short Form 36 Physical Component Summary Scores (SF-36 PCS) from baseline to 12 month follow-up. The secondary outcomes are the between group differences in mental QoL, depression, self-reported neck function, kinesiophobia (from baseline to 12 months; table 5) and clinical tests of pressure pain threshold and physical measures of neck flexion and extension endurance (table 6) from baseline to four months.

For the continuous data from the questionnaires, multilevel modelling will be performed to control for the autocorrelation that would be occurring as the result of multiple time points (baseline; four and 12 months). For the continuous data from the clinical test of pressure pain threshold, multiple regression modeling will be performed. The models will be adjusted for baseline variables that is found to be unbalanced between groups (Table 5 and 6). Ordinal regression analyses will be performed for the ordinal variables (Cranio Cervical Flexion Test, Cervical Extensor Endurance Test) (Table 6).

A per protocol analysis will be performed on the participants with 'good' (75%) adherence to pain education and the exercise regime, equivalent to participating in three out of four pain education sessions and participating in six out of eight exercise sessions.

All statistical analysis will be conducted in StataIC (Version 15.1, StataCorp, Texas, USA).

Table 1

Dropouts in the study will be compared in numbers and by their baseline characteristics according to their exposure group.

Variable	Description	Statistical test
Dropouts n (%)	The rate of dropouts according to their exposure group.	Chi-square

Abbreviation: n = number

Table 2

Demographic data of all participants

Variable	Description	Statistical test
Intervention (%)	Count (%)	Chi-square
Sex (f/m) (%)	Count (%)	Chi-square
Age	Mean age in years (95% C.I.)	ANOVA / Kruskal Wallis
Duration of pain	Mean duration in month (95% C.I.)	ANOVA / Kruskal Wallis
Education level n (%)	Academic/skilled/unskilled in %	Chi-square
Working situation n (%)	Unemployed, working full-time, working part-time, retired, early retirement, sick leave, student	Chi-square / Fisher's exact
Sleep disturbances	Sleep undisturbed, disturbed ≤ 3 times/night, disturbed > 3 times/night	Chi-square
Pain distribution (%)	Percentage coverage of pain distribution painted on a bodychart (95% C.I.)	ANOVA / Kruskal Wallis

Abbreviation: n = number; f/m = female/male; 95% C.I = 95% Confidence Interval. SF-36 = Medical Short Form 36 questionnaire

Table 3

Clinical tests

Variable	Description	Statistical test
Pressure Pain Threshold (PPT) Tibialis anterior (L and R) Cervical Spine (L and R) Infraspinatus (L and R)	Mean or median value in Kgf (95% C.I.)	ANOVA / Kruskal Wallis
Cranio Cervical Flexion test pressure (CCFT)	Count of value in mmHg grouped in 20, 22, 24, 26, 28, 30mmHg.	Chi-square test / Fisher's Exact
Cervical Extensor Endurance Test (CE) (duration in seconds)	Count of time grouped in 0-10s; 11-38s; 39-119s; 120s (Ris et al., 2017)	Chi-square test / Fisher's Exact

Abbreviation: L = left; R = Right; Kgf = kilogram-force; 95% C.I. = 95% Confidence Interval; s = seconds

Table 4

Patient reported outcome measures

Variable	Description	Statistical test
SF36 Physical Component Score (SF36-PCS)	Mean (95% C.I.)	ANOVA
SF 36 Mental Component Score (SF36-MCS)	Mean (95% C.I.)	ANOVA
Beck Depression Inventory II (BDI-II)	Mean (95% C.I.)	ANOVA
Neck Disability Index (NDI)	Mean (95% C.I.)	ANOVA
Tampa Scale of Kinesiophobia (TSK)	Mean (95% C.I.)	ANOVA
Bodily Pain (BP)	Mean score on SF-36 Bodily Pain subscale (95% C.I.)	ANOVA

Abbreviation: 95% C.I. = 95% Confidence Interval

Table 5

Patient reported outcome measures

Variable	Description	Statistical test
SF36 Physical Component Summary (SF36-PCS)	Between group change at 4 and 12 month. Mean (95% C.I.)	Multilevel modelling
SF36 Mental Component Summary (SF-36-MCS)	Between group change at 4 and 12 month. Mean (95% C.I.)	Multilevel modelling
Beck Depression Inventory II (BDI-II)	Between group change at 4 and 12 month. Mean (95% C.I.)	Multilevel modelling
Neck Disability Index (NDI)	Between group change at 4 and 12 month. Mean (95% C.I.)	Multilevel modelling
Tampa Scale of Kinesiophobia (TSK)	Between group change at 4 and 12 month. Mean (95% C.I.)	Multilevel modelling

Abbreviation: 95% C.I. = 95% Confidence Interval

Table 6

Clinical tests

Variable	Description	Statistical test
Pressure Pain Threshold (PPT) Tibialis anterior (L and R) Cervical Spine (L and R) Infraspinatus (L and R)	Between group change from baseline to 4 month. Mean (95% C.I.)	Multiple linear regression
Cranio Cervical Flexion test pressure (CCF) (mmHg)	Between group change from baseline to 4 month. Mean (95% C.I.)	Ordinal regression
Cervical Extensor Endurance Test (CE) (duration)	Between group change from baseline to 4 month. Mean (95% C.I.)	Ordinal regression

Abbreviation: L = left; R = right; 95% C.I. = 95% Confidence Interval

References

CAMPBELL, L., KENARDY, J., ANDERSEN, T., MCGREGOR, L., MAUJEAN, A. & STERLING, M. 2015. Trauma-focused cognitive behaviour therapy and exercise for chronic whiplash: Protocol of a randomised, controlled trial. *Journal of Physiotherapy,* 61**,** 218.

HOROWITZ, M., WILNER, N. & ALVAREZ, W. 1979. Impact of Event Scale: a measure of subjective stress. *Psychosom Med,* 41**,** 209-18.

LI, C. 2013. Little's test of missing completely at random. *Stata Journal,* 13**,** 795-809.

PORTNEY, L. G. & WATKINS, M. P. 2014. *Foundations of Clinical Research : applications to practice,* Harlow, Pearson.

RAVN, S. L., VAEGTER, H. B., CARDEL, T. & ANDERSEN, T. E. 2018. The role of posttraumatic stress symptoms on chronic pain outcomes in chronic pain patients referred to rehabilitation. *J Pain Res,* 11**,** 527-536.

RIS, I., JUUL-KRISTENSEN, B., BOYLE, E., KONGSTED, A., MANNICHE, C. & SOGAARD, K. 2017. Chronic neck pain patients with traumatic or non-traumatic onset: Differences in characteristics. A cross-sectional study. *Scand J Pain,* 14**,** 1-8.

STERLING, M. 2008. The Impact of Event Scale (IES). *Aust J Physiother,* 54**,** 78.

VAEGTER, H. B., ANDERSEN, T. E., HARVOLD, M., ANDERSEN, P. G. & GRAVEN-NIELSEN, T. 2017. Increased Pain Sensitivity in Accident-related Chronic Pain Patients with Comorbid Posttraumatic Stress. *Clin J Pain*.