

Study protocol

Early intervention for impairing post-concussion symptoms in adolescents and young adults: randomised trial

Changes to the initial study protocol:

The feasibility study phase resulted in the following important changes to the initial study protocol.

1. The number of participants was reduced to 120 (page 3) because a refined sample size calculation indicated that 60 patients in each treatment arm would be sufficient.
2. Inclusion criteria number 4 (page 4) regarding symptom severity measured by the Rivermead Post-concussion Symptom Questionnaire was changed to: "A score of 20 or more on the Rivermead Post Concussion Symptoms Questionnaire" based on data from the first 108 participants in the cohort study.
3. The following addition was made to the recruitment procedure (page 4): "In addition, general practitioners can refer patients to the study".
4. The structure of the newly developed intervention program was changed from group sessions only to a combination of group sessions and individual sessions based on experiences from the feasibility study (page 5). The content of the intervention remained the same.

The trial and the above changes to the protocol was registered in ClinicalTrials.gov (number NCT02337101) prior to inclusion of the first patient in the randomised trial.

Background

Concussion is an important public health concern.[1,2] In Denmark, approximately 25000 people are diagnosed with concussion each year.[3] Although complete resolution normally occur within the first days or weeks after a concussion, up to 15 % of patients continue to experience symptoms longer than 3 months post-injury.[4] These patients are at risk of long-term sickness, reduced health-related quality of life as well as permanently reduced working ability,[5-8] which are particularly serious and problematic prospects for adolescents and young adults. Currently, no standardised treatment is available for patients with persistent post-concussion symptoms.[9]

The aetiology of persistent post-concussion symptoms is only partly elicited,[10,11] and no consensus exists whether post-concussion symptoms constitute a true syndrome linked to neurobiological disturbances caused by accident or head trauma.[6,10,12-14] Nevertheless, the term post-concussion syndrome (PCS) is widely used to describe a set of persistent somatic, cognitive and emotional symptoms often observed in concussed individuals.[6] In this protocol, we use the abbreviation 'PCS' as a purely descriptive term for post-concussion symptoms. Typical post-concussion symptoms are headaches, dizziness, fatigue and cognitive complaints.[3] Neuropsychological studies of cognitive functioning after concussion, using traditional cognitive assessment, have produced ambiguous results,[15] but nevertheless, patients frequently report concentration and memory problems as well as reduced executive functioning.[9,16]

The literature suggest, that PCS are best understood in a complex, multifactorial model, where both biological and psychological factors contribute to persistent symptoms and associated disability.[5,7,8,11-13,17-20] Moreover, PCS overlap considerably with symptoms of other trauma-related conditions such as whiplash-associated disorders and post-traumatic stress disorder.[7] On this background, a number of trials have tested the effect of various psychosocial interventions on persistent PCS.[9,18,21] Although preliminary, there are promising results showing that treatment based on cognitive-behavioural therapy (CBT)[5,22,23] may be effective in treating PCS and prevent permanent suffering and disability.[9,18]

Some of the cognitive - behavioural mechanisms that have been found to play an important role in the maintenance of PCS are unhelpful illness perceptions, maladaptive coping strategies and all-or-nothing behaviour.[5,17,24] The all-or-nothing behaviour refers to a behavioural response, where patients overdo things when they believe symptoms are abating and then spend prolonged periods recovering when symptoms reappear.[5] Other patients report a gradual restriction of activity over time, because they fear worsening of symptoms.[24] A promising avenue for treatment therefore seems to be focusing on making sustainable, gradual increases in levels of activity (in intensity and / or duration) over time, and to avoid extreme oscillations.[24] This is often referred to as Graded Exercise Therapy (GET), a treatment that can effectively reduce impairment and suffering in chronic fatigue[25,26] and persistent pain[27] and that can be provided by physiotherapists[28] and hence delivered in a primary care or municipality setting.

Currently, systematic studies of psychosocial interventions for patients with persistent PCS remain limited, and more rigorous, large-scale RCT trials evaluating the effectiveness are therefore needed.[18,29]

Based on previous findings it seems reasonable to develop an intervention programme for patients with PCS based on a combination of principles from both CBT and GET. To our knowledge, this has not previously been systematically investigated in a large-scale study.

Aim:

- 1) to develop an early intervention programme based on CBT and GET principles for young patients aged 15 – 30 years with PCS lasting more than three months, and
- 2) to evaluate the efficacy of this intervention programme on PCS in a randomised, controlled trial.

Hypotheses***Primary hypothesis***

Patients in the early intervention group will 6 months after randomisation report a statistically and clinically significantly greater reduction of PCS compared to patients who receive enhanced usual care.

Secondary hypotheses

1. Patients in the early intervention group will 6 months after randomisation report a statistically and clinically significantly higher health related quality of life, everyday executive functioning and overall daily functioning compared to patients who receive enhanced usual care.
2. Negative illness perceptions and illness behaviours will be associated with a higher PCS score at baseline in both groups; compared to patients receiving enhanced usual care, patients in the early intervention group will show significant positive changes on illness perceptions and illness behaviours at end of treatment and 6 months after randomisation

Material and methods***Design and setting***

The present study is part of a intersectoral project in Central Denmark Region led by Hammel Neurorehabilitation and Research Centre (“Bristede drømme – nyt håb”),[30] which focus on strengthening the treatment options for adolescents and young adults with acquired brain injury or concussion.

The early intervention programme will take place in a secondary care setting at Aarhus University Hospital and will be tested in a randomized controlled trail (RCT). The RCT is embedded in a larger study investigating the epidemiology, aetiology, natural course, and consequences of PCS in the population.

Participants

180 patients aged 15 – 30 years diagnosed with concussion at hospitals in Central Denmark Region.

Inclusion criteria

1. Concussion caused by a head trauma according to the diagnostic criteria recommended by the Danish Consensus Report on Commotio Cerebri [3] within the last 2 - 3 months. The criteria are based recommendations by the WHO Task Force [1], but with the amendment, that there must have been a direct contact between the head and an object in order to rule out acceleration – deceleration traumas.

2. Age 15 to 30 years at the time of the head trauma.
3. Able to understand, speak and read Danish.
4. At least three items on the Rivermead Post Concussion Symptoms Questionnaire (RPQ)[31,32] rated as moderate or severe problem. The cut-off is currently evaluated in a pilot study prior to the RCT. RPQ symptoms have to be subjectively rated as causing substantial impairment in daily life.

Exclusion criteria

1. Objective neurological findings from neurological examination and / or acute trauma CT scan, indicating neurological disease or brain damage.
2. Previous concussion leading to persistent PCS within the last two years.
3. Severe misuse of alcohol, prescription drugs and / or illegal drugs.
4. Psychiatric morbidity or severe neurological disease that impedes participation in the treatment, i.e. Bipolar Disorder, autism, psychotic disorder (life time), multiple sclerosis etc..

Patients who are excluded from the project are offered enhanced usual care and will be referred for other relevant treatments, if available.

Randomisation

Participants will be randomised by means of a computer algorithm with predefined concealed random numbers. Randomisation will be done after the patient has signed informed consent to participate and after the clinical assessment. The procedure will be managed by an independent statistician.

Procedure

Recruitment

Patients with persistent PCS will be recruited from a larger epidemiological study (N=2000) based on a symptom screening performed from October 2014 until September 2016. Approx. 2 months after concussion, patients will receive a standardised and validated battery of self-report questionnaires measuring PCS and daily functioning. 240 patients from the epidemiological study, considered likely to meet inclusion criteria, will be invited to undergo further clinical assessment.

Clinical assessment:

The clinical assessment consists of a neurological examination and a short standard psychiatric interview to determine eligibility.

Treatments

Enhanced usual care:

All patients will after the initial clinical assessment be informed about typical PCS and the typical recovery process as well as given reassurance about the prognosis. The neurologist will provide advice about the use of pain medication.

Early intervention programme:

Besides the elements described above, patients in the early intervention programme will receive 8 group-based treatment sessions of 2 hours duration based on psycho education and principles from CBT and GET. Intervention will start approx. 3 months after the concussion. Treatment is

interdisciplinary and will mainly be provided by an occupational therapist and a physiotherapist under the supervision of a neuropsychologist. A treatment manual has been developed and is currently evaluated in a pilot study.

Outcome measures

Primary

- Post-concussion symptoms rated with Rivermead Post-Concussion Symptoms Questionnaire (RPQ).[31-33]

Secondary

- Self-reported executive functioning (BRIEF),[34] Quality of life and functioning (QOLBRI, SF-36),[35-37] subjective improvement (PGIC),[38] health anxiety (Whiteley-7),[39] depression (SCL-8),[40] and tendency towards somatisation (BDS-checklist).[41]
- Process measures are changes in illness related cognitions (B-IPQ),[42] and illness-related behaviours (BRIQ), [43]. Consumption of health care will be extracted from the following registers: The National Patient Register (Landspatientregistret), The Central Psychiatric Register (Det Psykiatriske Centralregister), The National Health Service Register (Sygesikringsregisteret), and The Danish Medicine Agency (Lægemiddelstyrelsen).

Questionnaires will be filled in immediately before randomisation (T0 = baseline, approximately 3 months after concussion), at the end of treatment (T1 = 3 months after randomisation), and at 6 (T2) and 15 (T3) months after randomisation. (See flowchart attached in “additional application material”).

Statistical analysis

The efficacy of the early intervention program will be evaluated on an “intention-to-treat” basis by means of random effects model regression analysis adjusted for predefined prognostically important baseline characteristics. The main efficacy analysis will pertain to the data obtained 6 months after baseline. A statistician with expertise in the evaluation of RCTs is part of the research group.

Power calculation

A previous pilot study examining the treatment effect of CBT delivered to patients at risk of PCS, which has applied RPQ as an outcome measure, has been able to statistically detect a medium effect size [44] whereas results from other studies have been ambiguous.[18,45,46] As it is difficult to perform precise power calculations based on these different findings, we adhere in a first step to the principles for a design comparing two groups, applying the rule of thumb that at least 200 subjects (100 in each group, i.e. intervention and control group) offers sufficient stability for statistical analysis [47]. Based on this we plan to include 90 patients in each group to attain a medium effect size (Cohen’s $d=.50$) on our primary outcome with a power of 0.90. Subsequently in a next step, we will based on the data from the ongoing pilot study, where the newly developed Danish version of RPQ is applied, perform a more specific and detailed power calculation for the RCT.

Ethical considerations

The study is conducted in accordance with the Helsinki Declaration II. The RCT is approved by the Committee of Health Research Ethics of the Central Denmark Region (no. 1-10-72-79-14) and the Danish Data Protection Agency (no. 2007-58-0016).

Perspectives

We expect the early intervention programme to prevent cases of permanent PCS, thereby leading to an improved quality of life for a large number of young people and reduced societal costs. Following the PhD, additional analysis will be performed to investigate the long term effect of the treatment programme in terms of consumption of health care (based on register-data) and illness-related absence from school or work (based on both self-reported and register-based data). Furthermore, data from the study will be linked to data from a separate brain scan study and the larger epidemiological study in order to explore associations of persistent PCS with structural brain abnormalities, cognitive functioning and psychosocial factors and to compare trial outcomes to findings based on the natural illness course.

Time schedule

The project is designed as a PhD project for Neuropsychologist Mille Møller Thastum (MMT), who is planned to follow a PhD programme from October 2014 – October 2017.

- **Prior to PhD programme** (ongoing, completed October 2014): Development and pilot testing of the early intervention programme, including development of material for psycho education and manual for the physiotherapist and occupational therapist. Approvals and registration of the RCT. Registration of the RCT in ClinicalTrials.gov prior to inclusion of the first patient.
- **1st and 2nd year:** Patients are continuously recruited from the epidemiologic study for further assessment and subsequently included in the RCT. The treatment programme is carried out and data is collected. First analysis of baseline data.
- **3rd year:** Data analyses and publication. Dissemination of results.

Budget and economy

The major part of the study is financed through the regional project “Bristede Drømme - nyt håb”, which again is financed by budget funds earmarked for strengthening the treatment options for adolescents and young adults with acquired brain injury or concussion. The remaining part is sought externally financed through funds. The Research Clinic for Functional Disorders, Aarhus University Hospital, has agreed to cover expenses if this is unsuccessful.

Publication

Results will be published in international peer-reviewed journals in English with MMT as first author of the primary trial report. There will be additional authors from the project group dependent on contributions. Positive as well as negative or inconclusive results will be published. The following articles are expected:

1. “The effect of an early intervention programme for impairing post-concussional symptoms in adolescents and young adults: results from a randomised clinical trial.”
2. “Improvements in self-reported executive functioning in adolescents and young adults with impairing post-concussional symptoms as the result of an early intervention programme.”
3. “Feasibility of an early intervention programme for impairing post-concussion symptoms in adolescents and young adults: a pilot study.”

Project group

Collaborators in the concussion project (role in the project):

Mille Møller Thastum, neuropsychologist (PhD candidate)¹

Per Fink, head of department, professor, PhD, DMSc (main supervisor)¹
Andreas Schröder, consultant, PhD (co-supervisor)¹
Charlotte Rask, consultant, Associate professor, PhD (co-supervisor)¹
Susanne Wulff Svendsen, consultant, PhD (responsible for the epidemiological study)²
Erhard Trillingsgaard Næss-Schmidt, physiotherapist, MSc (treatment provider and PhD student on a separate brain scan study)²
Jørgen Feldbæk Nielsen, consultant, professor, DMSc (resource person, main supervisor on the brain scan study, representative from project "Bristede drømme – Nyt håb")²
Leif Østergaard, head of department, professor, DMSc (co-supervisor on the brain scan study)³
Nigel King, Consultant clinical neuropsychologist, senior research fellow, PhD (resource person)⁴

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