RANDOMIZED PROSPECTIVE CONTROLLED STUDY ON THE IMPACT OF A PROGRAMME OF NEUROCOGNITIVE TELEREHABILITATION ON THE QUALITY OF LIFE AND THE COGNITION OF PATIENTS OPERATED FOR PRIMARY BRAIN TUMOUR

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1. Project summary

1.1. OBJECTIVES OF THE PROJECT

Main objective:

- Assess the effectiveness of neurocognitive rehabilitation in terms of improvement of the cognitive function and quality of life of patients operated for primary brain tumour, through a programme of cognitive telerehabilitation.

Secondary objectives:

- Determine the factors having an influence on achieving the best benefits of the cognitive rehabilitation programme in patients with primary brain tumour and thus to be able to decide in the future which patients should really be assessed for a cognitive rehabilitation treatment and which patients would most benefit from the usual treatment.

- Make a register of intracranial neoplasias and functional deficit.

- Try to better adapt the cognitive telerehabilitation system (PREVIRNERC), initially developed for patients with brain injury secondary to head injury or ictus, to patients operated for primary brain tumour.

1.2. DESIGN

Controlled, randomized, prospective, double-blind clinical trial to assess the effectiveness of a rehabilitation programme in the cognition and quality of life of a group of patients with primary brain tumour in comparison with a control group that received the usual treatment.

Selection of patients:

All the patients diagnosed with primary brain tumour in our hospital (Hospital Germans Trias i Pujol) having undergone surgery (biopsy, partial or complete resection of the tumour) were randomized to an experimental group that received cognitive rehabilitation or to a control group that followed the usual medical treatment and that were offered the possibility to receive the cognitive rehabilitation treatment after the completion of the study (control group on the waiting list).

Criteria for inclusion:

- Age between 18 and 70.
- Histological confirmation of primary brain tumour.
- KPS > 60.
- Having a computer at home.
- Having internet connection at home.
- Acceptance of participating in the cognitive rehabilitation programme.
- Signature of informed consent.

Criteria for exclusion:

- Difficulty in understanding Catalan or Spanish.
- Severe mental disorder.
- Any established neurological deficit that hinders the neuropsychological assessment and/or neuropsychological treatment.
- Illiteracy.
- Refusal to participate in the study.

1.3. PROCEDURE

Intervention:

The experimental group took part in a computerised cognitive rehabilitation programme with a duration of 12 weeks (1 hour per day, 4-5 days per week). First, an initial neuropsychological examination was carried out in order to detect the patient's cognitive alterations, which served as the basis for designing a weekly therapeutic programme with exercises addressing the cognitive alterations of each of the patients. The difficulty level of the tasks was set according to a therapeutic margin so that they were neither too complex nor too easy, thus avoiding feelings of frustration and lack of motivation. The computerised system automatically adjusted the difficulty level of the tasks based on the percentage of correct answers achieved in the same session. Weekly face-to-face sessions were also carried out to work on the strategies to mitigate the impact of cognitive impairment on daily activities and to provide guidelines allowing to generalise the skills learnt through the computer tasks and apply them to daily situations. The control group received the usual medical treatment and were offered the possibility to take part in the neurocognitive rehabilitation programme once the study was completed (control group on the waiting list).

Clinical and neuropsychological evaluation:

All the patients completed a clinical interview and a neuropsychological examination with a duration of three hours in two days before the start of the intervention (baseline), upon completion of the 12-week treatment programme, and 3 months after the end of this programme. The neuropsychologist who performed the neuropsychological evaluation did not take part in the cognitive rehabilitation sessions and was blind as to the type of intervention received by the patients.

Before the start of the treatment, three months after it, and again six months after it, the patients were examined by the neurosurgeon, who gathered a series of demographic and clinical variables detailed below, and by a rehabilitation practitioner, who gathered data on their functional capacity and the neurological sequelae using the Barthel, FIM, Lawton and Brody, and NIHSS scales.

1.4. METHODOLOGY

Clinical measures:

- Demographic variables: sex and age.
- Clinical variables: medical history, clinical presentation of the tumour, signs and symptoms, location of the tumour and size according to MR, KPS, surgery complications, average survival rate, epileptic crisis, psychopharmacological treatment and oncologic treatment (radiotherapy and/or chemotherapy).

Neuropsychological measures:

In order to assess the cognitive functions of each patient, they were administered specific neuropsychological tests focusing on assessing the most affected cognitive functions in cases of brain tumour, such as attention, speed, memory and executive functions. They were also administered specific scales to assess the quality of life of patients with brain tumour, fatigue and complaints on perceived cognitive alterations.

Size of the sample:

When the project was designed, we based it on the only published randomized study (Gehring et al., 2009), and estimated a sample size of 64 individuals in each group. Later, taking into account a new study (Zuchella et al., 2013), we estimated (according to Cohen's guidelines) a sample size per group of 36 individuals in order to detect

significant differences with a type-I error probability of 5% and a statistical power of 80%.

Limitations of the study:

One of the main limitations of the study was the variability in type, size and location of brain tumours, the medical treatment received and the secondary effects of these treatments, many of which affect cognitive skills.

2. Results

The process of including patients in the study started on 2 June 2012 and finished on 1 June 2015. During this period, 250 patients were operated for brain tumours at the Hospital Germans Trias i Pujol. Only 86 patients met the inclusion criteria (164 were excluded), of whom 2 were lost before the randomization. Finally 84 patients were randomized, 42 in each group (control and experimental group). During the study, 12 patients were lost (10 within the control group and only 2 within the experimental group). There were no statistically significant basal differences between the two groups in relation to socio-demographic characteristics, basal characteristics of the disease, cognitive impairment or quality of life. In longitudinal analyses focusing on the main variable, the cognitive impairment (impairment index) showed that there were statistically significant differences between the two groups after 3 months ($p=0.02$) and after 6 months ($p=0.03$). That is, the experimental group showed better cognitive performance in general after 3 and 6 months.

The experimental group showed statistically higher performance after 3 months in attention ($p=0.02$) and executive functions ($p=0.04$). After 6 months, the difference was still present in attention and showed a statistical trend in language-related tasks ($p=0.08$). These differences were observed in the cognitive FIM assessment, which also detected significant differences with better scores for the experimental group compared to the control group after 3 months ($p=0.003$) and after 6 months only a statistical trend ($p=0.08$).

In order to control the possible effect of adverse neurological events and the progression of the disease on cognitive performance, the analyses were repeated with

adjustments for these factors. After adjusting the adverse neurological event and progression, significant differences were still present in cognition in general after 3 months (p=0.03) and after 6 months (p=0.04), and in attention (p=0.01) and cognitive FIM (p=0.003) after 3 months. The trends remained in executive functions after 3 months (p=0.08) and in language-related functions after six months (p=0.07). As regards the quality of life, a trend was detected towards improved results in the experimental result compared to the control group (scale FACT-G) (p=0.08) after 3 months. At the functional subscale, these differences were statistically significant (p=0.05) after 3 months.

3. Relevance and possible implications

The final results obtained from our project show that cognitive rehabilitation treatment is effective to improve the cognitive function of patients with brain tumours 3 months after the operation and that these improvements remain during the 3 following months.

These conclusions are very powerful, given that the results have been obtained from a very heterogeneous and relatively small population. It is worth noting that these results have been directly obtained from usual medical practice and are therefore easily reproducible. The cognitive deficits of patients with brain tumour may be caused by different reasons, such as the tumour itself (location, size, progression and growth), the treatment (surgery or surgery and chemo/radiotherapy), epilepsy secondary to brain tumour, depression or the pharmacological treatment received by the patient such as corticoids, anticonvulsants, antidepressants etc. or by a combination of any of these factors (Taphoorn and Klein, Schiff, Lee et al., 2015). With the information obtained from this study we will be able to research in derivative studies the influence that each of these factors may have on cognitive deficit and thus design strategies to mitigate their impact. In turn, we have planned to identify the patients that may obtain a greater benefit from this treatment and exclude those who do not obtain any benefit (secondary objective of the study).

It is worth noting that attention is one of the most altered functions in patients with brain tumour and it is the basis for the rest of the cognitive functions and the capacity

to manage daily activities autonomously. The neurocognitive rehabilitation treatment determines a relevant improvement in this area which is so special for higher functions. The better results of the cognitive FIM in the experimental group are a measure that confirms the improvement in cognition as an objective proof from the point of view of a blind evaluator.

One of the main limitations of the study of Zuchella (Zuchella, Capone et al., 2013) was that it did not assess the quality of life of this type of patient. Currently the concept of quality of life provides additional value to the usually known clinical data. It serves as a severity index for the disease or for the results of the treatment at a specific time such post-surgery. Our results show a statistical trend that treatment of cognitive rehabilitation improves the quality of life of patients operated for brain tumour.