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[Intervention Review]

Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation

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ABSTRACT

Background

Cognitive deficits are common in people who have received cranial irradiation and have a serious impact on daily functioning and quality of life. The benefit of pharmacological and non-pharmacological treatment of cognitive deficits in this population is unclear.

Objectives

To assess the effectiveness of interventions for preventing or ameliorating cognitive deficits in adult patients treated with cranial irradiation.

Search methods

In August 2014, we searched the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and PsycINFO and checked the reference lists of included studies. We also searched for ongoing trials via ClinicalTrials.gov, the Physicians Data Query and the Meta Register of Controlled Trials.

Selection criteria

We included randomised controlled trials (RCTs) that evaluated pharmacological or non-pharmacological interventions in cranial irradiated adults, with objective cognitive functioning as a primary or secondary outcome measure.

Data collection and analysis

Two review authors (JD, KZ) independently extracted data from selected studies and carried out a 'Risk of bias' assessment. Cognitive function, fatigue and mood outcomes were reported. No data were pooled.

Main results

Sixteen studies were identified for possible inclusion in the review, six of which were included. Three studies investigated prevention and three studies investigated amelioration. Due to differences between studies in the interventions being evaluated, a meta-analysis was not possible. Two studies investigated a pharmacological intervention for the prevention of cognitive deficits; memantine compared with placebo, and d-threo-methylphenidate HCL compared with placebo. In the first study the primary cognitive outcome of memory at six months did not reach significance, but there was significant improvement in overall cognitive function compared to placebo, with similar adverse events across groups. The second study found no statistically significant difference between arms, with few adverse events. The

third study investigated a rehabilitation program for the prevention of cognitive deficits but did not carry out a statistical comparison of cognitive performance between groups.

Three studies investigated the use of a pharmacological intervention for the treatment of cognitive deficits; methylphenidate compared with modafinil, two different doses of modafinil, and donepezil compared with placebo. The first study found improvements in cognitive function in both the methylphenidate and modafinil arms; few adverse events were reported. The second study combined treatment arms and found improvements across all cognitive tests, however, a number of adverse events were reported. Both studies were limited by a small sample size. The third study did not find an improvement in the primary cognitive outcome of overall performance, but did find improvement in an individual test of memory, compared to placebo; adverse events were not reported. No non-pharmacological studies for the amelioration of cognitive deficits were eligible. There were a number of limitations across studies but few without high risks of bias.

Authors' conclusions

There is supportive evidence that memantine may help prevent cognitive deficits for adults with brain metastases receiving cranial irradiation. There is supportive evidence that donepezil may have a role in treating cognitive deficits in adults with primary or metastatic brain tumours who have been treated with cranial irradiation. Patient withdrawal affected the statistical power of both studies. Further research that tries to minimise the withdrawal of consent, and subsequently reduce the requirement for imputation procedures, may offer a higher quality of evidence.

There is no strong evidence to support any non-pharmacological interventions (medical or cognitive/behavioural) in the prevention or amelioration of cognitive deficits. Non-randomised studies appear promising but are as yet to be conclusive via translation into high quality evidence. Further research is required.

PLAIN LANGUAGE SUMMARY

Interventions for preventing and ameliorating cognitive deficits in adults treated with cranial irradiation

Background

Problems with mental activities (cognitive deficits) are common in patients who have received radiation to the brain for a primary or secondary (metastatic) brain tumour, or to help prevent a tumour spreading to the brain from elsewhere in the body. This toxic side effect of brain radiation may be acute (during treatment) or early after treatment (one to six months) and may be reversible. However, late toxicities may occur many months or years later and are generally irreversible and are slowly progressive. Late cognitive deficits, such as memory loss, problems planning tasks or behavioural changes, can have a serious impact on quality of life and the ability to carrying out activities normally. Interventions to help prevent or treat these late radiation toxicities may improve a patient's well-being.

Study Characteristics

In August 2014 we searched four literature databases. Six randomised controlled trials (RCTs), in which patients were randomly assigned to the intervention or a comparison group (control group), were eligible for inclusion. Each trial assessed different interventions, so results were not combined. The largest trial investigated the medical drug memantine in 508 patients with a metastatic brain tumour. Another trial investigated donepezil in 198 patients with a primary or secondary brain tumour. The other trials were smaller and investigated modafinil and methylphenidate. We found one psychological intervention for preventing cognitive deficits during brain radiation. There is one ongoing medical drug trial recruiting participants. There were many non-randomised and non-controlled trials that offer promising results for further exploration using an RCT method.

Key findings

Findings into the efficacy of memantine offer supportive evidence for preventing cognitive deficits in patients with a secondary brain tumour receiving brain irradiation. Findings into the efficacy of donepezil offer some support for its use in the amelioration of cognitive deficits in patients with a primary or secondary tumour previously treated with radiation. The remaining studies did not have a sufficient number of participants to provide reliable results. The drugs used had few side effects (adverse events), although these were not reported well. Recruitment and retention of trial participants for these medical drug studies is difficult.

Quality of the evidence

We found limitations in the evidence across studies, most medical drug randomised controlled trials had a low risk of bias, whereas the psychological interventions were at a high risk of bias.