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General review

Influence of cognitive impairment on the management of ischaemic stroke☆

Traitement de l'accident vasculaire cérébral ischémique : influence des troubles cognitifs préexistants

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ABSTRACT

Background. – Because of ageing of the population, it is more and more frequent to treat ischaemic stroke patients with pre-stroke cognitive impairment (PSCI). Currently, there is no specific recommendation on ischaemic stroke management in these patients, both at the acute stage and in secondary prevention. However, these patients are less likely to receive treatments proven effective in randomised controlled trials, even in the absence of contra-indication.
Objective. – To review the literature to assess efficacy and safety of validated therapies for acute ischaemic stroke and secondary prevention in PSCI patients.
Results. – Most randomised trials did not take into account the pre-stroke cognitive status. The few observational studies conducted at the acute stage or in secondary prevention, did not provide any information that the benefit could be either lost or replaced by harm in the presence of PSCI.
Conclusions. – There is no reason not to treat ischaemic stroke patients with PSCI according to the currently available recommendations for acute management and secondary prevention. Further observational studies are needed and pre-stroke cognition should be taken into account in future stroke trials.

RÉSUMÉ

Introduction. – En raison du vieillissement de la population il est fréquent de prendre en charge pour une ischémie cérébrale des patients ayant un déclin cognitif préalable, déjà exploré ou pas. Il n'y a pas de recommandation particulière concernant la prise en charge de ces patients en phase aiguë ou en prévention secondaire. Il semble toutefois qu'ils aient un

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accès plus limité que les autres aux traitements validés par des essais cliniques, même lorsqu'ils n'ont pas de contre-indication.
Objectif. – Évaluer par une revue de la littérature concernant l'efficacité et les risques des traitements validés dans la prise en charge de l'ischémie cérébrale, en présence d'un déclin cognitif préalable.
Résultats. – La plupart des essais randomisés n'ont pas pris en compte l'état cognitif du patient. Quelques études observationnelles ont évalué les bénéfices et les risques des traitements chez les patients ayant un déclin cognitif préalable. Leurs résultats n'apportent pas d'arguments laissant penser que le bénéfice disparaîtrait ou serait remplacé par un effet délétère en présence d'un déclin cognitif préalable.
Conclusion. – Il n'y a actuellement aucun argument dans la littérature pour ne pas prendre en charge de la même façon une ischémie cérébrale, selon que le patient ait ou pas un déclin cognitif préalable. Des études observationnelles complémentaires sont nécessaires dans cette population, et il est important dans les essais futurs d'évaluer l'état cognitif préalable.

1. Introduction

About 10% of stroke patients were already demented when they have a first-ever stroke and 10% will develop new onset dementia after stroke. Stroke patients with pre-stroke cognitive impairment (PSCI) have more severe strokes [1] more complications [2,3], and worse early and long-term outcomes [4–6]. There is no clear indication of stroke management for patients with PSCI, but in practice they are less likely to have access to recommended treatments, especially stroke unit (SU) care, thrombolysis [7], antiplatelet therapy and oral anticoagulation [8–11]. Clinicians will face more and more frequently stroke patients with PSCI in the future because of aging population [12–14]. Therefore, we need more information on the efficacy and safety profiles in patients with PSCI, for treatments recommended in ischaemic stroke patients. The aim of this narrative review was to search for evidence whether the presence of PSCI influences or not the efficacy and safety of treatments validated in ischaemic stroke.

2. Acute stroke therapies

2.1. *Stroke unit care*

Although SU care is highly recommended for all stroke patients [15], patients with PSCI tend to be less frequently admitted to SU [1]. Cognition was not evaluated in stroke unit trials, and some of them even excluded patients with dementia. As there is no publication on the benefit/risk for an admission in SU of patients with PSCI, we consider there is no rationale to exclude them from SU care. However, we can also estimate that the extra-cost of SU care is not acceptable for patients highly dependent who are at the end-stage of dementia, and considered in palliative care.

2.2. *Recanalisation*

2.2.1. *Intravenous recombinant tissue plasminogen activator*

The license of intravenous (i.v.) recombinant tissue plasminogen activator (rt-PA) in the European Union is currently restricted to patients aged 80 years or less. According to the results from the 3rd International Stroke Trial (IST-3) [16] and the updated meta-analysis [17] that proved the efficacy of rt-PA in patients aged 80 years or more, the use of rt-PA for elderly patients in clinical practice will increase. Therefore, more ischaemic stroke patients with PSCI will be eligible for thrombolysis [18]. However, the safety and the efficacy of rt-PA for the patients with PSCI are controversial. PSCI mainly includes vascular dementia (VD) or Alzheimer's disease (AD) or a mix of them. Stroke patients with VD or AD often have underlying brain pathology, such as leukoaraiosis, brain microbleeds and multiple micro-infarcts as the consequence of cerebral amyloid angiopathy (CAA) [19] or lipohyalinosis [20,21]. Leukoaraiosis could be a risk factor of intracerebral haemorrhage (ICH) after rt-PA [22–26]. Cerebral microbleeds might slightly increased the risk of haemorrhagic transformation but overall the benefit of rtPA is not outweighed [27,28]. However, no study took into account the location and numbers (i.e. association with underlying vessel disease such as CAA) of cerebral microbleeds [29]. Small-vessel disease may be also a marker of increased risks for haemorrhagic transformation [23,30]. Hence, patients with PSCI may have a high risk of symptomatic intracerebral haemorrhage (sICH) after rt-PA. Furthermore, they may also have higher sensitivity to the toxic effect of rt-PA because of the dysfunction of the blood brain barrier [31–35] and lower capacity to recover from brain injury [36]. Despite these theoretical reasons for having less efficacy of rt-PA and worse safety profiles, no observational study found an increased rate of sICH after i.v. rt-PA in patients with PSCI [7,37,38]. In one of these studies, preexisting dementia was associated with a non-specific increase in in-hospital mortality that was not the consequence of sICH, and in the other towards less so-called ''favourable outcomes'' [38], which is not specific of patients treated with rt-PA. In two other studies, outcomes did not significantly differ from those of non-demented patients [7,37]. There were many limitations in these studies, including a small sample size, lack of systematic search for PSCI including not only dementia, but also cognitive impairment no-dementia (CIND), lack of important predictors of outcome in the analysis, and lack of evaluation of efficacy criteria such as having a modified Rankin scale (mRS) score 0–1 or 0–2 at 3 months. We recently