Intracerebral hemorrhage as a manifestation of cerebral hyperperfusion syndrome after carotid revascularization: Systematic review and meta-analysis

Authors:

Pedro Abreu[1]

Jerina Nogueira[1]

Filipe Brogueira Rodrigues[2,3,4]

Ana Nascimento[5]

Mariana Carvalho[5]

Ana Marreiros[1]

Hipólito Nzwalo[1]

[1]Department of Biomedical Sciences and Medicine, University of Algarve, Portugal

[2]Clinical Pharmacology Unit, Instituto de Medicina Molecular, Lisboa, Portugal

[3]Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, University of Lisbon, Lisbon, Portugal

[4]Huntington's Disease Centre, Institute of Neurology, University College London, London, United Kingdom

[5]Department of Neurology, Centro Hospitalar do Algarve, Portugal

Correspondig Author :

Hipólito Nzwalo, MD, MSc

Departement of Biomedical Sciences and Medicine,

University of Algarve, Campus da Penha, 8005-139 Faro, Portugal.

E-mail address: nzwalo@gmail.com

Abstract

Background: Intracerebral hemorrhage (ICH) in the context of cerebral hyperperfusion syndrome (CHS) is an uncommon but potentially lethal complication after carotid revascularization for carotid occlusive disease. Information about its incidence, risk factors and fatality is scarce. Therefore, we aimed to perform a systematic review and meta-analysis focusing on the incidence, risk factors and outcomes of ICH in the context of CHS after carotid revascularization.

Methods: We searched on PubMed and EBSCO host for all studies published in English about CHS in the context of carotid revascularization. Two reviewers independently assessed each study for eligibility based on predefined criteria. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed and PROSPERO register was made (register number: CRD42016033190), including the pre-specified protocol.

Results: Forty-one studies involving 28956 participants were deemed eligible and included in our analysis. The overall quality of the included studies was fair. The pooled frequency of ICH in the context of CHS was 38% (95% CI: 26% to 51%, I2=84%, 24 studies) and the pooled case-fatality of ICH after CHS was 51% (95% CI: 32% to 71%, I2=77%, 17 studies). When comparing carotid angioplasty with stenting (CAS) with carotid endarterectomy (CEA), post-procedural ICH in the context of CHS was less frequent in CEA. ICH following CHS occurred less often in large series and was rare in asymptomatic patients. The most common risk factors were periprocedural hypertension and ipsilateral severe stenosis.

Conclusions: ICH as a manifestation of CHS is rare, more frequent after CAS, and associated with poor prognosis. Periprocedural control of hypertension can reduce its occurrence.

Keywords

“cerebral hyperperfusion syndrome”, “intracerebral hemorrhage”, “carotid endarterectomy”, “carotid angioplasty”, “carotid revascularization”

1-Introduction

Ischemic strokes is a major cause of morbidity and mortality worldwide. (12, 33, 53) Carotid artery disease contributes to 18-29% of all cases.(59, 66) Carotid invasive interventions such as carotid endarterectomy (CEA) and carotid angioplasty with stenting (CAS) are widely used to treat carotid artery disease.(6, 26, 62) One potentially severe complication is intracerebral hemorrhage (ICH) in the context of cerebral hyperperfusion syndrome (CHS).(37) Clinical manifestations of CHS are diverse and include symptoms such as throbbing headaches, confusion, focal neurological deficits, partial or generalized seizures, among others.(25, 27, 60) Diagnostic exams such computerized tomography scan (CT), magnetic resonance imaging (MRI), transcranial Doppler (TCD), single-photon emission computerized tomography (SPECT) and positron emission tomography (PET) can be used to confirm or exclude this diagnosis.(3, 11, 24, 60) The pathophysiology behind CHS is still poorly understood.(41) Three mechanisms have been associated with the syndrome: failure of brain vessels' auto-regulatory mechanisms to adapt to the sudden and deregulated increase in cerebral blood flow after carotid revascularization in long standing hypoperfused brains due to severe stenosis/obstruction(2, 36, 48, 54, 60); baroreflex disturbances secondary to carotid revascularization (58); disturbances in the trigeminovascular reflex.(35, 60) Despite its severity, the knowledge about the frequency, risk factors and prognosis of ICH in the context of CHS is scarce. Previous reviews did not specifically addressed the occurrence of ICH in the context of CHS .(32, 41) Therefore, we set up to perform a systematic review of the existent studies and meta-analytically estimate the frequency of ICH after CHS and its case-fatality.

2-Material and Methods

2.1-Protocol and registration

This systematic review was registered at PROSPERO database (CRD42016033190) and written in accordance with PRISMA guidelines.(31)

2.2-Eligibility criteria

Primary studies involving patients submitted to carotid revascularization (CAS or CEA) due to carotid occlusive disease were included. Studies with CEA/CAS preformed for other specific conditions, case reports and animal studies; and studies in which the definition and frequency of ICH related CHS was not described were excluded.

2.3-Information sources

The search process was performed using the search engines PubMed and EBSCOHost (1986 to January 2016). Databases accessed via EBSCOhost include MEDLINE, sciencedirect, academic one file, J-stage, general one file, OAlster, expanded academic ASAP, China/Asia on demand, SciELO, Scitech conect, MedicLatina and Korean studies information study system. Only full-text English-written publications were included.

2.4-Search strategy and study selection

The Mesh terms "cerebral hyperperfusion syndrome", "complications", "carotid revascularization", "endarterectomy" and "carotid angioplasty" were used to retrieve relevant literature. Studies were selected by two independent investigators. A consensus between the authors was used to resolve any disagreements about the inclusion of specific studies.

2.6-Data collection process

Studies were analysed by two independent investigators. A consensus between the authors was used to resolve any disagreements about the inclusion of specific studies.

2.7-Data items

The following items were extracted: type surgical procedure; frequency of CHS with ICH; associated risk factors, outcome (case-fatality, morbidity rates).

2.8-Studies Risk of bias

The National institutes of Health (NIH) tools were used (15) for quality assessment (supplement). Two reviewers performed the assessment independently. Discrepancies in the classifications were discussed and agreement achieved.

2.11-Planned methods of analysis

Qualitative analysis with quantitative description including all selected studies was performed whenever applicable. To address the risk factors; and for the meta-analysis of frequency and case-fatality of ICH after CHS, only large studies (≥ 100 patients) were considered. This arbitrary threshold was selected to minimize the effects of substantial variability in the diagnostic criteria, time of evaluation and populations included in our study. We used Stata/SE 14.0 software for conducting the analysis and to derive forest plots. Random-effects meta-analysis weighted by the inverse-variance method was performed to estimate pooled frequency and 95% confidence intervals (CI). Heterogeneity was assessed with the I2 test. We used a random-effects model as substantial heterogeneity between studies results was expected. The limit for statistical significance was established at 0.05.

3-Results

3.1-Study selection

Initial search yielded a total of 545 manuscripts (423 publications at EBSCOhost and 122 publications at PubMed) (Figure 1). After extraction removal of duplicates and studies not fulfilling our eligibility criteria, 41 studies were included in the final analysis (Figure 1). Reasons for study exclusions were documented at supplement - 1.

3.2-Study characteristics

A total of 28.956 participants were included, with studies sample sizes ranging from 26 to 4.494 participants (Table 1). Eighteen studies (44%) defined both CHS and ICH at methods section. (1, 2, 7-9, 16, 19, 20, 22, 24, 29, 34, 42, 44, 46, 47, 61, 65) The frequency of ICH after carotid intervention in studies with less than 100 participants ranged from 0% to 4.44%.(4, 8, 14, 17, 18, 21, 22, 24, 40, 46, 48, 64) In studies with 101 to 1000 participants the range was from 0% to 2.21%.(1, 2, 5, 7, 9, 10, 13, 19, 20, 23, 29, 30, 34, 39, 42, 43, 51, 55, 57, 65) In studies that included 1001 or more participants a range from 0.09% to 0.6% was found.(16, 44, 45, 47, 49, 50, 52, 61, 63) With regard to the quality evaluation, the majority were rated as "good" (1, 2, 5, 7, 8, 18, 22, 29, 30, 34, 50, 65) or fair (4, 9, 10, 13, 16, 17, 19-21, 23, 24, 39, 40, 42-49, 51, 55-57, 63, 64), and three were "poor".(14, 52, 61) The risk of bias was considerable in most studies (Supplement 2).(4, 9, 10, 13, 16, 17, 19-21, 23, 24, 39, 42-45, 47, 49, 55, 64) The pooled frequency of ICH in the context of CHS was 38% (95% CI: 26% to 51%, I2=84%) (Figure 2)

3.3-Risk factors

Table 2 resumes the risk factors found in larger studies (≥ 100 patients). Table 1 shows that when comparing CEA and CAS, the frequency of ICH in the context of CHS in large studies was higher after CAS, ranging from 0.28% to 4.05%.(1, 7, 9, 19, 30, 39, 42, 47, 49, 55, 57, 65) In CEA varied from 0% to 2.15%.(2, 5, 9, 10, 13, 16, 18, 20, 23, 29, 34, 43-45, 47, 61) Also, 73% of the studies involving CAS had a frequency of ICH in the context of CHS above 0.5%.(1, 7, 9, 19, 30, 39, 42, 47, 49, 55, 57, 65) In CEA, these frequencies occurred in only 26% of the cases.(2, 5, 9, 10, 13, 16, 18, 20, 23, 29, 34, 43-45, 47, 61) The "ICH to CHS proportion" has higher after CAS in comparison to CES: 7 out of 11 CAS studies (63.6%) had 50% or more hemorrhagic CHS (range 0-100%).(2, 5, 9, 10, 13, 16, 18, 20, 23, 29, 34, 43-45, 47, 61) In CEA, 5 out of 12 studies (41.6%) had 50% or more cases of hemorrhagic CHS (range 0-80%).(2, 5, 9, 10, 13, 16, 18, 20, 23, 29, 34, 43-45, 47, 61) Post procedure ICH in asymptomatic patients was addressed in 9 large studies (1, 7, 10, 13, 47, 49, 55, 57, 61) and occurred in three.(47, 57, 61) Overall, periprocedural hypertension is the most frequent risk factor, being documented in 4 studies.(16, 20, 47, 50) Three studies mention ipsilateral severe stenosis as risk factor.(50, 51, 63) Younger age was considered a risk factor in 2 studies but denied as a risk factor in other 2 studies.(16, 47, 51, 63)

3.4-Outcomes

The mortality of ICH related to CHS ranged from 0% to 100%.(1, 8, 9, 16, 20, 21, 23, 30, 39, 40, 42, 45, 47, 49, 51, 55, 57, 61, 63-65). In large studies the mortality was ≥ 50% in more than half of the studies (range 0 to 100%).(1, 10, 17, 21, 24, 31, 39, 42, 45, 47, 49, 51, 55, 57, 61, 63, 65) The pooled case-fatality of ICH after CHS was 51% (95% CI: 32% to 71%, I2=77%) (Figure 3).

4-Discussion

This is the first systematic review and meta-analysis addressing the frequency, risk factors and outcome of ICH in the context of CHS. Despite being discussed since 1981(54), no consensual definition exists for CHS and its pathophysiology is still to be elucidated.(28, 60) We found a high variation in the frequency of ICH in the context of CHS, with a range of 0% to 4.44%.(1, 2, 4, 5, 7-10, 13, 14, 16-24, 29, 30, 34, 39, 40, 42-52, 55, 57, 61, 63-65) The overall case-fatality associated to ICH in the context of CHS was high.(1, 8, 10, 17, 21, 22, 24, 31, 39, 40, 42, 45, 47, 49, 51, 55, 57, 61, 63-65) Of notice, the two larger studies reported associated mortality varying from 25.93% to 57.14%(16, 47). Important variation exists regarding mortality rates when considering all studies information (0 to 100%). However, this may be explained by the inclusion of different studies designs, samples sizes and the classification criteria used for ICH in the context of CHS . In large studies, the frequency of ICH was higher after CAS in comparison to CEA and was rare after asymptomatic carotid disease. The higher "ICH to CHS proportion" post CAS CHS further supports the notion that patients with CHS after CAS are at increased risk of ICH.(38) The mandatory use of double antiplatelet therapy in CAS could contribute to this finding. Indeed, the use of antithrombotics was associated with the occurrence of post CAS ICH in two small studies and in one large study based on administrative data.(38) Periprocedural hypertension and ipsilateral severe stenosis where the commonest risk factors described.(16, 20, 47, 50, 51, 63) This data is relevant and stresses the importance of pre and post carotid revascularization blood pressure control, particularly in patients with severe stenosis. One frequent bias found in the included studies was the lack of definition for CHS with ICH. However, the requirement of brain imaging for ICH diagnosis may minimize the impact of this bias for the overall comparison. The use of different methodologies and size discrepancies between the studies can also explain the variation in the frequency of ICH in the context of CHS.(1, 2, 4, 5, 7-10, 13, 14, 16-24, 29, 30, 34, 39, 40, 42-52, 55, 57, 61, 63-65) The lack of information regarding associated factors such as use of antithrombotics, time interval from ischemic event to revascularization procedure, and presence of chronic with matter alterations represent a limitation when evaluating the occurrence of ICH in the context of CHS.

5-Conclusion

This systematic review and meta-analysis showed that ICH in the context of CHS is rare in large series, occurs more frequently after CHS secondary to CAS and than post CAS, and is generally associated with high case-fatality rate. The main risk factors are periprocedural hypertension and ipsilateral severe stenosis. Further studies to better describe the contribution of other risk factors are needed.

Funding - No funding was received for this research

Conflict of interest: FBR is supported by CHDI Foundation and by the EHDN. All authors certify that they are no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

This article does not contain any studies with human participants performed by any of the authors.

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