We read with interest about the CRASH-3 trial[1] and congratulate the CRASH-3 trial collaborators for their outstanding work. On the basis of the results of a prespecified sensitivity subgroup analysis excluding patients who were predicted to have the worst outcome, the authors concluded that early administration of tranexamic acid within 3 h of traumatic brain injury reduces head injury-related death. However, the primary endpoint was 28-day mortality.

Functional outcome is just as relevant, if not more, than mortality in traumatic brain injury because of the high rate of disability in patients who survive. The main goal is to achieve survival with a so-called acceptable disability; therefore, it is surprising that the authors did not address the issue of neurological prognosis as a main outcome. It is difficult to study traumatic brain injury without a neurological functional endpoint, which is usually measured with the Glasgow Outcome Scale or its extended version.[2]

Guidelines focused on the treatment and on monitoring the management of traumatic brain injury emphasise the prevention of secondary injuries, which affect both mortality and neurological prognosis.[3-5] The CRASH-3 trial does not provide any information about initial management. However, the optimisation of cardiorespiratory parameters, control of intracranial pressure, maintenance of cerebral perfusion pressure, and the need for surgery, including decompressive craniectomy or cerebrospinal fluid drainage, can affect mortality and functional outcome.

Given the insufficiency of crucial data, even if the inclusion criteria were relevant for clinical practice, CRASH-3 conclusions should be interpreted with caution, considering that the results might be caused by statistical chance. Despite the authors' findings, we strongly believe that a change to medical practice on the basis of these results would be premature.

We declare no competing interests.

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Authors' reply

We thank the many correspondents for their comments about the CRASH-3 trial.[1]

Most treatments for traumatic brain injury are unproven. Evidence from randomised trials is scarce. Most of the time, doctors manage their patients' injuries through using pathophysiological theory and clinical experience. Some widely used treatments have done more harm than good.[2] Large randomised trials reduce therapeutic uncertainty, but to categorise their results as positive, neutral, or negative on the basis of arbitrary statistical rules that statisticians reject is unnecessary.[3]

The results of the CRASH-3 trial[1] should be considered in the context of the pathophysiology of traumatic intracranial bleeding, the mechanism of action of tranexamic acid, and the available evidence from other randomised trials.[4,5] Our scientific reasons for prespecifying head injury death as the primary outcome in the statistical analysis plan are presented in detail elsewhere.[6] Briefly, including outcomes that are unaffected by tranexamic acid (eg, organophosphorus poisoning or blood transfusion errors), which only vary randomly between groups, will dilute the treatment effect towards the null, obscuring the real treatment effects.

As noted by Davi Solla and colleagues, the mortality reduction with tranexamic acid was greater in less severe traumatic brain injury, possibly because intracranial bleeding accounts for a larger proportion of head injury deaths in patients with mild and moderate traumatic brain injury. However, we did not find strong evidence of heterogeneity and do not believe that the treatment of severe traumatic brain injury is futile.

We can reassure Charles Reynard and colleagues and Angelos Kolias and colleagues that the risk ratios for patients with mild, moderate, and severe traumatic brain injury were presented in the supplementary appendix of our Article,[1] but we would also like to remind them that only patients with mild traumatic brain injury with complications (ie, intracranial bleeding) were enrolled. Combining this group with the group of patients with a moderate traumatic brain injury for presentational purposes (having also presented these results for each group separately) does not turn a prespecified subgroup analysis into a post-hoc analysis.

We agree with Patrick Schober and colleagues that we cannot completely rule out the possibility of adverse effects, but the evidence from the CRASH-2 trial[5] and CRASH-3 trial[1] is reassuring. Future trials will further reduce uncertainty. The CRASH-4 trial will examine the effects of early (including before hospital admissions) intramuscular tranexamic acid in older adults (>70 years old) with mild traumatic brain injury.

We declare no competing interests.

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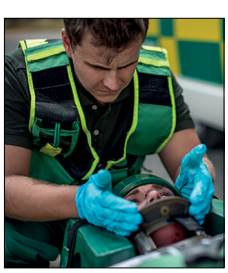
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See Online for appendix

Published Online
July 10, 2020
https://doi.org/10.1016/
S0140-6736(20)31525-7

Inflammatory olfactory neuropathy in two patients with COVID-19

We report two cases of olfactory neuropathy diagnosed at autopsy in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. One patient experienced anosmia. Information about anosmia was not available in the other patient.

Patient 1, a man aged 70 years, and patient 2, a man aged 79 years, both tested positive for SARS-CoV-2. Patient 1 was a renal transplant recipient with coronary artery disease and arterial hypertension. He developed progressive respiratory failure due to COVID-19 pneumonia and required mechanical ventilation. He was treated with hydroxychloroquine (total 1600 mg). Patient 2 was previously diagnosed with severe pulmonary hypertension and was admitted with fever, cough, and increasing dyspnoea as well as loss of taste and smell. He was also treated with hydroxychloroquine (total 1600 mg); however, he declined invasive treatment. Patient 1 died 8 days after hospital admission; patient 2 died 6 days after hospital admission.

Patient consent for research was obtained from both patients. Post-mortem histological analysis of the olfactory epithelium in both patients showed prominent leukocytic infiltrates in the lamina propria and focal atrophy of the mucosa. The histological analysis of olfactory epithelium from both patients is in the appendix. We found a slight predominance of CD3-positive T cells over CD20-positive B lymphocytes. Expectedly, olfactory nerve fibres in the lamina propria were negative for myelin basic protein. However, they showed so-called digestion chambers, which stained positive for CD68 on immunohistochemistry, suggestive of axonal damage. Scattered CD45-positive leukocytes were consistent with an inflammatory neuropathy; the infiltrates comprised both CD4-positive and CD8-positive T lymphocytes. CD20 staining was negative. In both patients, the olfactory tracts showed few isolated CD45-positive infiltrates; the olfactory striae were unremarkable. Both brains showed perivascular leukocytic infiltrates, predominantly in the basal ganglia and intravascular microthrombi.

Anosmia is a common symptom in patients with COVID-19.[1] Inflammation of the olfactory system and anosmia have been reported in other viral diseases,[2] as was age-related atrophy of the olfactory epithelium.[3] The observed neuritis is most likely associated with axonal damage, as olfactory fila lack myelin.[4] Consistent with previous reports, the olfactory tracts were largely unremarkable, except for a few endoneurial leukocytes in both patients.[5] SARS-CoV-2-induced damage might be mediated by viral entry through its receptor angiotensin converting enzyme 2 and the transmembrane serine protease 2, which are expressed in non-neural cells of the olfactory epithelium.[6] It is unclear whether the observed inflammatory neuropathy is a result of direct viral damage or is mediated by damage to supporting non-neural cells. Due to the rapidly evolving pandemic, unravelling the neuroinvasive properties of SARS-CoV-2 will have major implications for patients with COVID-19.

PS, AA, and KF contributed equally. SU reports grants from Swiss National Science Foundation, Zurich Lung, and Orpha Swiss; and personal fees from Actelion and MSD, outside of the submitted work. TH reports grants from aspuraclip, Sony, the Smell and Taste Lab, and Takasago, outside of the submitted work. All other authors declare no competing interests. We thank Daniela Meir and Fabian Baron for technical assistance.

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