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LETTER TO THE EDITOR

Corticosteroid therapy for acute spinal cord injury: The NASCIS controversy☆

Uso de corticoides tras la lesión medular aguda: la controversia NASCIS

Dear Sir,

In the May 2013 issue of the journal *Spine*,[1] Druschel et al. published a survey which reflected how 55.4% of centers in Germany still used high doses of corticoids in the treatment of acute spinal cord injury. We recently carried out the same survey among a group of traumatologists and neurosurgeons from different Spanish regions, all of them belonging to services which treated acute spinal cord injury, and found that 75% of them used high doses of corticoids at their centers. Of these, 50% followed the NASCIS II protocol, 25% the NASCIS III and 17% another protocol. Only 17% of respondents believed in the neuroprotective effect of the treatment, 42% administered it because this was the common practice at their center and 25% because they thought that it was a legal requirement.

The use of corticoids following acute spinal cord injury is a controversial topic. Their administration at high doses, mainly with methylprednisolone, is justified by the work conducted by Bracken MB in the past 2 decades with the *National Acute Spinal Cord Injury Studies* (NASCIS), which were reflected in the NASCIS I, II and III trials.

Some publications with considerable social impact in the USA, such as the *New York Times*, *Chicago Tribune* and *Science News*, published promising news regarding the use of corticoids for the treatment of spinal cord injuries between March and April 1990. After these news appeared in the media, on 13th April 1990, the US *National Institute of Health* (NIH) sent a fax to all A&E services in the country, recommending the use of high doses of methylprednisolone as a treatment for acute spinal cord injury, despite the skepticism of various specialists due to the lack of clinical evidence.[2] The NASCIS II trial, the first to reveal a possible clinical benefit, was published weeks later, on 17th May 1990. A similar governmental recommendation was issued once more through the web page of the *National Institute of Neurological Disorders and Stroke* on 27th May 1997 following the publication of the NASCIS III trial in the *Journal of the American Medical Association*, which recommended the use of high doses of corticoids for 48 h.

The methodological quality of the NASCIS work has been extensively criticized in the literature. Moreover, we find a potential conflict of interests between the author and the pharmaceutical industry, specifically with the Pfizer division ''Pharmacia & Upjohn Company'', which sponsored the trials. We should point out that, according to the conflict of interests declaration of those works, Bracken MB occasionally acted as a paid consultant, and that, at that time, Pfizer held the USA patent for the drug for intravenous use at high doses with methylprednisolone as an active ingredient (Solu-Medrol®).

Furthermore, it is interesting to know that, according to the biography published in the web page of Yale University, many of the studies conducted by Bracken MB were financed by the NIH, and that he also took part in the founding of *Cochrane Collaboration International*, which published the 3 existing systematic reviews on the use of corticoids following spinal cord injury (in 2000, 2002 and 2012), whose single author was Bracken MB himself, in all cases.

The journal *Neurosurgery* has recently published new clinical practice guidelines (CPG) for the management of spinal cord trauma. The section on drug treatment[3] advises against the use of corticoids following spinal cord injury, highlighting that the indication has not been approved by the *Food and Drug Administration* (FDA) and that there is currently no existing evidence of level I or II regarding its clinical benefit. On the other hand, there is level I, II and III evidence for its possible association with secondary effects, including death. The mentioned guidelines also recommend categorizing the NASCIS trials as studies with evidence level III (instead of level I), arguing that the conclusions regarding the clinical benefit of high dose corticoid therapy were derived from the results of an *a posteriori* analysis (*post hoc*), and that none of the clinical trials had been originally designed to support the conclusion, which would classify the trials as retrospective studies.

The most relevant work to date showing the damage caused by high doses of corticoids in trauma patients is the *Corticosteroid Randomization After Significant Head injury* (CRASH)[4] multicenter trial conducted at 239 hospitals in

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49 countries. Although it was initially designed for calculating a necessary sample size of 20,000 patients in order to obtain differences of 3% in mortality between treatments, it had to be interrupted after analyzing the first 10,008 patients because the mortality in the group of patients treated with high doses of corticoids was 3.4% higher. Other secondary effects which were more frequent among patients treated with high doses of corticoids included gastrointestinal hemorrhage, surgical wound infection and pulmonary embolism.

It is interesting to highlight that if we use the results of the CRASH study to calculate the number needed to harm (NNH), we find that treating 30 patients with high doses of corticoids, 1 of them will die due to the corticoids (NNH = 30; 95% CI: 19.6–58.7).

In conclusion, we wish to highlight that, although high doses of corticoids have been used to treat spinal cord injuries for over 20 years, it seems increasingly clear that their generalized use should not be recommended. Based on the survey we conducted, we believe that knowledge and application of the most recent guidelines and recommendations on drug treatment for acute spinal cord injury are not widely extended among centers in our country, particularly among professionals involved in the care of multiple trauma patients with spinal cord lesions (emergencies in and out of the hospital, neurosurgeons, traumatologists and orthopedic surgeons...).

We believe that further studies may be required which allow us to identify those patients in whom the neuroprotective effect of corticoids (experimental, to date) could be indicated, or that, alternatively, the time has come to leave aside this indication and focus research efforts on new treatments which improve the prognosis of spinal cord injuries.

Conflict of interests

The authors have no conflict of interests to declare.

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