Commentary

Would decompressive craniectomy really bring the hope to severe traumatic brain injury?

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In September of this year, the results of the Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp) trial—an international multicenter randomized control trial (RCT) by Hutchinson and colleagues was reported in the *New England Journal of Medicine* (1). This study was organized as a collaboration between the University of Cambridge Departments of Neurosurgery/Neuro-intensive Care and the European Brain Injury Consortium, and enrolled 409 patients with medically refractory intracranial hypertension after traumatic brain injury (TBI) from 52 centers in 20 countries. Undoubtedly, it is one of the most encouraging clinical researches in the field of TBI in the past five years. The results showed that, in contrast to medical care, decompressive craniectomy (DC) in patients with TBI and refractory intracranial hypertension can not only immediately and constantly reduce intracranial pressure (ICP) but, even more importantly, result in a nearly 20 percent reduction in mortality at 6 and 12 months. Unfortunately, DC also caused higher rates of vegetative state, lower severe disability, and upper severe disability than medical care. Therefore, the long-awaited large study will again provoke some new thoughts about the role of DC in the management of refractory hypertension after TBI.

DC is a straightforward procedure that for more than a century has been widely used to treat medically refractory intracranial hypertension of patients with severe TBI (2). Although a series of clinical studies demonstrated that DC is the most effective treatment in reducing ICP, the effect on outcome of severe TBI has yet to be clearly established (3,4). In the 4th edition guidelines of management of severe TBI that just emerged on September of this year, DC as a new topic was included for the first time (5). Base on the results of the Decompressive Craniectomy in Patients with Severe Traumatic Brain Injury (DECRA) study which is the first and previously only RCT to compare DC to medical management in severe TBI patients (6), new guidelines present the level IIA recommendation for the debates surrounding the relative merits of these two treatment strategies (5). Although the DECRA study indicated that DC may be associated with a worse functional outcome in patients with diffuse TBI, the trial results have been widely criticized and some commentators stated that "no conclusions regarding management of the use of DC in patients with TBI should be drawn from this trial and clinical practice should not be changed on the basis of these results" (7,8). Therefore, the guidelines also show the expectation on the results of the RESCUEicp trial.

As with the DECRA study, the latest RESCUEicp study was also well planned and of high quality RCT that compared DC with standard medical management. However, there were some inherent differences between these two studies. First, enrolled population. In contrast to the DECRA study, the patients enrolled in the RESCUEicp study had the wider range of Glasgow Coma Scale (GCS) scores (3–15 versus 3–8) and more commonly encountered types of patients with TBI (diffuse TBI or traumatic intracranial mass lesion versus diffuse TBI only). Second, timing of DC. In the RESCUEicp study, DC was undertaken as last-tier (life-saving) therapy when all medical therapy failed to reduce ICP, so more rigorous criteria about threshold for ICP (25 mmHg at least 1 hour) was set. While, In the DECRA study, DC was performed as a second-tier (early) therapy (neuro-protective) in

patients with relatively transient and mild increase in ICP (>20 mmHg for 15 minutes). Third, DC procedure. The RESCUEicp study used more reasonable surgical options according to tomographic imaging and at the discretion of the surgeon (bifrontal DC or hemi-craniectomy versus bifrontal DC alone). Fourth, medical management. At last stage of the protocol of the RESCUEicp trial, patients in medical management group received continued medical therapy with the option of adding barbiturates to reduce the ICP. While, the DECRA study did not adopt barbiturates. Therefore, all above differences might be the main reasons of different conclusions in these two studies. In addition, the main similarity between the results of these two studies was that DC reduced ICP effectively but increase larger proportion of survivors in the vegetative state and severe disability significantly. Therefore, we have to ask ourselves: "dose a therapy which can not improve life quality worth popularization?". We will further discuss the uncertainty of the effect of DC on TBI patients through above four questions.

First, suitable population for DC. GCS scores of enrolled patients in the RESCUEicp study were on a broad range from 3 to 15. The scoring range can be used as a reference indicator for the severity of TBI (extremely severe: 3–5; severe: 6–8; moderate: 9–12; mild: 13–15) (9,10). Whether DC is too radical for mild TBI patients or has been already powerless for extremely severe TBI deserves further investigation by subgroup analysis. In addition, besides diffuse TBI patients, although the RESCUEicp trial recruited patients with cerebral mass lesion who were in a minority (about 20%), the study still cannot be generalized to all patients with severe TBI. Therefore, Prospective randomized evaluation of therapeutic DC in severe TBI with mass lesions (PRECIS) study (11) and Randomized Evaluation of Surgery with Craniectomy for patients Undergoing Evacuation of Acute Subdural Haematoma (RESCUE-ASDH) study (12) hope to investigate whether DC can benefit TBI patients with mass lesion.

Second, the optimal timing of DC. The DECRA study established that relatively mild transient intracranial hypertension might not benefit from early DC, so the RESCUEicp trial set a higher threshold (25 mmHg at least 1 hour). Therefore, we believed that DC might be too invasive to benefit the patients with less pronounced elevation of ICP (e.g., 20 mmHg). In the RESCUEicp trial, although last-tier DC (ICP >25 mmHg) caused lower mortality, "produced" more vegetative state and severe disability. Is it because too "conservative" DC might cause irreversible brain damage? Therefore, maybe we should continue to explore a more "just right" threshold for ICP. The other question is what other indicators need established in order to evaluate DC timing. The RESCUEicp trial adopted high ICP as the main operation indication. However, some studies suggested that high ICP was not the most powerful predictor of neurological worsening, and models used to predict outcome adopted age, motor response in GCS, pupil reactivity and some characteristics of the initial computed tomography (CT) scan as input variables (13). In addition, evidences also suggest that low cerebral perfusion pressure (CPP) at levels below 50–55 mmHg is one of the major contributors to unfavourable clinical outcome, so modern intensive-care management of severe TBI can also base on CPP-driven therapeutic protocol (14,15). Therefore, whether we need to combine the ICP thresholds for defining medically refractory intracranial hypertension with other indicators warrants consideration.

Third, the proper method of DC. The RESCUEicp study allowed surgeons to choose the method of DC (bifrontal or unilateral approaches). However, to date adequately powered clinical studies testing the effect of these two DC methods on TBI patients are lacking.

Fourth, the barbiturate coma. At last stage of the protocol of the RESCUEicp trial, patients were randomly assigned to undergo DC with medical therapy or to receive continued medical therapy with the option of adding barbiturates to reduce the ICP. Although barbiturates are included in level II recommendations of TBI guideline (5), a Cochrane systematic review concluded that barbiturates may reduce ICP but do not reduce mortality or improve outcome in severe TBI survivors (16). In addition, its hypotension side effect might offset any ICP lowering effect on CPP.

In conclusion, aforementioned questions have yet to be addressed. For DC, we cannot give it up too early or cannot stick to it too blindly. Exploring the beneficiary patient population and operation timing remain the prime concerns.

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Footnote

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by Ming Zhong (Associate Professor, Department of Critical Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

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Comment on: Hutchinson PJ, Kolias AG, Timofeev IS, *et al.* Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. N Engl J Med 2016;375:1119-30.

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