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Neurosurgery Concepts

Neurosurgery Concepts: Key perspectives on Traumatic Brain Injury, New Treatments for Glioblastoma, Hemicraniectomy for Extensive Middle-Cerebral-Artery Stroke, Minimally Invasive Spine Surgery and Lumbar Epidural Injections for Radiculopathy

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NEUROCOGNITION IN THE EMERGENCY DEPARTMENT AFTER A MILD TRAUMATIC BRAIN INJURY IN YOUTH[1]

Study Question: Does mild traumatic brain injury affect neurocognitive function in youths?

The authors used a computerized neurocognitive assessment tool (CNS Vital Sign, CNSVS) in a pediatric trauma patient in the emergency department to examine neurocognitive functioning in children and adolescents. They compared a mild traumatic brain injury (mTBI) group with orthopedic injury controls (OICs). CNSVS was developed to rapidly screen cognitive abilities and has high adequate concurrent validity. It is composed of several cognitive function tests including a verbal memory test and Stroop task. Each test score is computed and summarized in domain scores. The CNSVS comprises three domain scores: Verbal memory, cognitive flexibility, and reaction time.

The demographic data and head injury severity of two groups were not statistically different. There was no significant difference between the mTBI and OIC groups on the verbal memory domain score, which indicates that there was no significant difference for accuracy on immediate memory, delayed memory, or measures of attention and executive functioning. However, there was a significant difference in both the cognitive flexibility and reaction time domain scores. This demonstrates that the mTBI group performed significantly worse than the OIC group on psychomotor speed and reaction time tasks, despite having a Glasgow coma scale score of 15 and normal neuroimaging findings. In this study, the author shows that youthful mTBI patients preserved their accuracy on cognitive measures, but show slower psychomotor speeds and longer reaction times.

Perspective: One of the concerns of mTBI patients is neurocognitive dysfunction after trauma, which is subject to ongoing debate. Many current management guidelines for mTBI recommend neuropsychological testing as an objective marker of cerebral dysfunction that can be useful in assessing injury severity and recovery parameters. In this study, the authors show that children and adolescents

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with mTBI were suffering measurable neurocognitive dysfunction, especially in their psychomotor speed and reaction time, through a computerized screening battery. However, the actual clinical relevance of this study should be confirmed. Despite an increase in controlled clinical trials for neurocognitive dysfunction after mTBI, there is no consensus for its treatment. Further, the link between the early and late occurrence of cognitive dysfunction has not been established. Further studies exploring any potential link will be important to develop an appropriate management strategy for mTBI. Although some debates continue, a quick and easy screening tool could be useful for detecting acute neurocognitive deficits after mTBI, especially in children and adolescents.

Summary Written by Dr. Jin Mo Cho

THE COMBINATION OF CARMUSTINE WAFERS AND FOTEMUSTINE IN RECURRENT GLIOBLASTOMA PATIENTS: A MONOINSTITUTIONAL EXPERIENCE[7]

Study Question: In *recurrent glioblastoma treatment*, second surgery plus carmustine wafers, does the addition of intravenous fotemustine provide benefit?

To date, there is no standard treatment for recurrent glioblastoma (GBM). We analyzed the feasibility of second surgery plus carmustine wafers followed by intravenous fotemustine. Retrospectively, we analyzed patients with recurrent GBM treated with this multimodal strategy. Twenty-four patients were analyzed. The median age was 53.6 years; all patients had KPS between 90 and 100; 19 patients (79%) performed a gross total resection >98% and 5 (21%) a gross total resection >90%. The median progression-free survival from second surgery was 6 months (95% confidence interval [CI] 3.9–8.05) and the median OS was 14 months (95% CI 11.1–16.8 months). Toxicity was predominantly hematological: Five patients (21%) experienced grade 3–4 thrombocytopenia and three patients (12%) grade 3–4 leukopenia. This multimodal strategy may be feasible in patients with recurrent GBM, in particular, for patients in good clinical conditions.

Perspective: Surgery and chemotherapy remains the mainstay of treatment of patients with recurrent GBM. Standard therapy for newly diagnosed GBM includes surgical resection when feasible, radiotherapy, and temozolomide or carmustine wafer.[12,13] *In recurrent GBM, standard therapy lacks*. In the last years, there was interest in the role of bevacizumab, alone or in combination with cytotoxic drugs, but the results were conflicting.[10,11]

A recent study concluded that recurrent GBM patients in good clinical condition should be treated with second surgery.[9] Use of the carmustine wafer has demonstrated an overall survival benefit both in newly diagnosed and recurrent GBM.[2,3,13]

Lombardi suggests that it is the first study analyzing the multimodal strategy with resection plus carmustine wafers plus systemic therapy with fotemustine in patients with recurrent GBM. They demonstrated an interesting benefit of this multimodal treatment with a median PFS of 6 months and a median OS of 14 months. Toxicity was slightly higher than expected. The most common toxicity was hematological. In recurrent GBM patients that already have such a limited outcome, given these side effects, use of adjunctive intravenous fotemustine in recurrent GBM must undergo further study.

Summary Written by Dr. Chaim B. Colen

BEVACIZUMAB PLUS RADIOTHERAPY–TEMOZOLOMIDE FOR NEWLY DIAGNOSED GLIOBLASTOMA.A RANDOMIZED TRIAL OF BEVACIZUMAB FOR NEWLY DIAGNOSED GLIOBLASTOMA[4]

Study Question: Is the addition of bevacizumab to temozolomide and radiotherapy followed by maintenance temozolomide in the treatment of newly diagnosed GBM beneficial?

Two randomized, double-blinded, placebo-controlled trials in newly diagnosed GBM adult patients were performed and published concomitantly in the *New England Journal of Medicine*.

The first study NCT00943826 randomized newly diagnosed supratentorial GBM patients to either placebo or bevacizumab plus 6 weeks standard radiotherapy and temozolomide. After a 28-day treatment break, maintenance bevacizumab every 2 weeks or placebo, plus temozolomide, was continued for six 4-week cycles, followed by bevacizumab monotherapy every 3 weeks or placebo until the disease progressed or unacceptable toxic effects developed. The coprimary end points were investigator-assessed progression-free survival and overall survival.

A total of 458 patients were assigned to the bevacizumab group, and 463 patients to the placebo group. The median progression-free survival was 10.6 months in the bevacizumab group and 6.2 months in the placebo group (stratified hazard ratio for progression or death, 0.64; 95% CI, 0.55–0.74; $P < 0.001$). There was, however, no difference in overall survival between the two groups (stratified hazard ratio for death, 0.88; 95% CI, 0.76–1.02; $P = 0.10$). The respective overall survival rates with bevacizumab and placebo were 72.4% and 66.3% at 1 year ($P = 0.049$) and 33.9% and 30.1% at 2 years ($P = 0.24$). Baseline health-related quality of life and performance status were maintained longer in the bevacizumab group, and the glucocorticoid requirement was lower. More patients in the bevacizumab group than in the placebo group had grade 3 or higher adverse events (AEs) (66.8% vs. 51.3%) and grade 3 or higher AEs often associated with bevacizumab (32.5% vs. 15.8%).

The second study NCT0088471 was also a randomized, double-blind, placebo-controlled trial of adult GBM patients treated with standard radiotherapy (60 Gy) and daily temozolomide. Patients were randomized to receive bevacizumab or placebo during week 4 of radiotherapy and were continued for up to 12 cycles of maintenance chemotherapy. At disease progression, the assigned treatment was revealed, and bevacizumab therapy could be started or continued. The coprimary end points were reduction in the risk of death and reduction in the risk of progression or death.

Of the 978 registered patients, 637underwent randomization. There was no significant difference in overall survival between the bevacizumab group and the placebo group (median, 15.7 and 16.1 months, respectively; hazard ratio for death in the bevacizumab group, 1.13). Progression-free survival was longer in the bevacizumab group (10.7 months vs. 7.3 months; hazard ratio for progression or death, 0.79). There were modest increases in rates of hypertension, thromboembolic events, intestinal perforation, and neutropenia in the bevacizumab group. Over time, an increased symptom burden, a worse quality of life, and a decline in neurocognitive function were more frequent in the bevacizumab group.

Perspectives: Bevacizumab is a recombinant humanized monoclonal antibody that inhibits vascular endothelial growth factor A (VEGF-A). By inhibiting VEGF-A, the drug therefore interferes with angiogenesis. Bevacizumab has been Food and Drug Administration (FDA) approved in the treatment of recurrent GBM. These two studies asked the question, should we add bevacizumab to standard of care for the treatment of newly diagnosed GBM.

The results of these two studies demonstrate that the addition of bevacizumab to radiotherapy–temozolomide did not improve survival in patients with newly diagnosed GBM. The addition of bevacizumab did improve progression-free survival, but patients who were randomized to the bevacizumab group had more AEs in both studies. In one study, the treatment group had improved maintenance of baseline quality of life and performance status but in the other study the bevacizumab group experienced a worse quality of life, and a decline in neurocognitive function.

Summary Written by Dr. Gordon Li

HEMICRANIECTOMY IN OLDER PATIENTS WITH EXTENSIVE MIDDLE CEREBRAL ARTERY STROKE[6]

Study Question: Does hemicranectomy improve the outcome of patients older than 60 years with extensive middle cerebral artery (MCA) stroke?

One hundred and twelve patients aged older than 60 years with extensive MCA stroke were randomized to undergo hemicraniectomy within 48 h of onset of symptoms or conservative treatment in intensive care unit. Primary outcome was survival without severe disability as defined by modified Rankin score (mRS) 0–4 at 6 months. Secondary outcome, all measured at 12 months, included mRS and survival, NIHSS score, level of activity of daily living (Barthel index), quality of life (as measured by SF36 and EQ-5D), depression (as measured by Hamilton Depression Rating scale), and AEs.

One hundred and twelve patients underwent randomization, with 49 patients assigned to the hemicraniectomy group and 63 patients assigned to the control group. At 6 months, 38% of hemicraniectomy group had a mRS of 4 or better versus 18% in the control group. Mortality rate was significant lower for the surgical group (33% vs. 70%). However, only 7% of patients of the hemicraniectomy group had a mRS 3 (moderate disability) or better versus 3% in the control. At 12 months, mortality of both group increased from the 6 month time point to 43% for the surgical group and 76% in the control group. Only 6% of patients in the hemicraniectomy and 5% in the control group had mRS of 3 or better at 12 months.

Perspective: Hemicraniectomy has been shown to significantly improve the outcome of young patients with malignant MCA stroke. Not only did surgery improve survival, it also significantly increased the chance of achieving the outcome of survival with only mild or moderate disability. Whether this benefit will also be translated into older patients is unknown, and this is what this trial set out to evaluate. Consistent with some retrospective series, this randomized trial also showed that while there is some benefit for hemicraniectomy in patients older than 60 with malignant MCA stroke, its benefit is less compared with patients aged under 60 years. In both cases, mortality was lower in patients undergoing hemicraniectomy, but very few patients aged over 60 years achieved survival with mild or moderate disability (7% vs. 43% in young patients). Moreover, comparing the 12 months outcome to 6 months outcome, mortality was increased and there was no evidence of delayed neurological recovery. This trial provided valuable information for clinicians, patients, and caregivers to consider when they have to make the difficult decision of whether to undergo a hemicraniectomy or not when sustaining a malignant MCA stroke.

Summary Written by Dr. Vincent Yat Wang

OUTCOMES AFTER DECOMPRESSIVE LAMINECTOMY FOR LUMBAR SPINAL STENOSIS: COMPARISON BETWEEN MINIMALLY INVASIVE UNILATERAL LAMINECTOMY FOR BILATERAL DECOMPRESSION AND OPEN LAMINECTOMY[8]

Study Question: Are the outcomes following minimally

invasive decompression for lumbar stenosis comparable to open decompression?

The authors conducted the first prospective randomized study comparing minimally invasive bilateral decompression through a unilateral laminectomy and open laminectomy for the treatment of lumbar stenosis. They enrolled 79 patients who were randomized into these two surgical procedures and were able to analyze 54 patients; 27 in each arm. The inclusion criteria were: Lower extremity radiculopathy, or neurogenic claudication, or urinary dysfunction that was due to one or two level lumbar central canal stenosis. They excluded patients with prior surgery, spondylolisthesis, or degenerative scoliosis. The outcome measures used were: Ostwestry disability index (ODI) scores, visual analogue scale (VAS) scores for leg pain, patient satisfaction index (PSI) scores, and 12-Item short Form Health Survey (SF-12) scores. Both groups had significant improvements postoperatively pertaining to ODI, PSI, SF-12, and VAS scores. The minimally invasively treated group had significantly better VAS scores compared with the open group. Moreover, the minimally invasively treated group had shorter hospital stay with 55.1 versus 100.8 h for the open group, which were more likely not to require opiates postoperatively, 51.9% versus 15.4% in the open group, and faster times to mobilization with 15.6 versus 33.3 h in the open group. The complication profile was similar in both groups with one intraoperative incidental durotomy that did not require further surgeries in each group. One patient who underwent an open decompression had a foot drop and one had a postoperative hematoma. The follow up was 44.3 months for the open group and 36.9 months in the minimally invasive group.

Perspective: The main premise of minimally invasive spinal surgery is to achieve the goals of any open spinal surgery with minimal collateral damage. The use of tubular retractors that obviate muscle dissection, soft tissue destruction, and damage have translated clinically into shorter hospital stays, less blood loss, less cerebrospinal fluid leaks, and faster recovery and that was not at the expense of long-term outcomes.

One of the most commonly used minimally invasive spinal surgeries is minimally invasive decompression for patients with lumbar stenosis who suffer from radiculopathy and/or neurogenic claudication. While other multiple studies have demonstrated the advantages of minimally invasive unilateral laminectomy for bilateral decompression compared with open laminectomy, this was the first prospective and randomized study to reiterate these findings.

With soft tissue and posterior tension band preservation, minimally invasive spinal surgery is not as biomechanically destabilizing as its open counterparts. This also allows room for minimally invasive decompression for stenosis in the setting of degenerative spondylolisthesis in patients who primarily are suffering from neurogenic claudication. This, at least in theory, will obviate fusions in this subset of patients.

Summary Written by Dr. Nader Dahdaleh

A RANDOMIZED TRIAL OF EPIDURAL GLUCOCORTICOID INJECTIONS FOR SPINAL STENOSIS[5]

Study Question: Are lumbar epidural glucocorticoid injections, a common nonsurgical intervention for patients with neurogenic claudication and lumbar radiculopathy, effective in providing short-term symptomatic relief when compared with injection with lidocaine alone (randomized controlled, multisite trial: ClinicalTrials.gov: NCT01238536).

Four hundred patients with lumbar central stenosis and moderate-to-severe leg pain were enrolled in a double-blind, multisite trial. The enrolled subjects received one of two lumbar epidural treatments: Glucocorticoid plus lidocaine or lidocaine alone. The primary outcome measure was a score on the Roland–Morris Disability Questionaire (RMDQ), which has a range of 0–24 (higher scores for greater disability) and a 0–10 rating for leg pain intensity. The procedures were carried out by a total of 26 board-certified anesthesiologists, physiatrists, and radiologists at separate study sites. Injections were either interlaminar or transforaminal and carried out at one spinal level below the site of worst compression. Overall, 200 patients were assigned to each group and 193 completed both pretreatment at 6 week assessment in each treatment group.

The results from the treated patients demonstrated that the baseline RMDQ score in lidocaine treated patients was 15.7 ± 4.3 and the steroid–lidocaine treated patients was 16.1 ± 4.5. At 6-week follow-up, the lidocaine group had decreased to 12.5 ± 6.4 (change: –3.1 ± 5.3) and the steroid–lidocaine group had decreased to 11.8 ± 6.3 (change: –4.2 ± 5.8). Treatment comparison demonstrated an adjusted difference of –1.0 (–2.1 to 0.1, 95% CI) with a *P* value of 0.07. Numerical leg pain score changes were quite similar between each group at 6 week: Lidocaine only –2.6 ± 3.0 and Lidocaine + steroid -2.8 ± 3.1 ($P = 0.48$). At 3 weeks, the patients receiving steroid + lidocaine showed a small improvement in RMDQ or pain scores, but this improvement did not continue to 6 weeks. Total AEs (event rate) was 34/200 (17%) for patients with lidocaine and 43/200 (21.5%) for steroid–lidocaine ($P = 0.02$). The most common AEs were pain, headache, fever, and numbness.

Perspective: Lumbar epidural steroids are commonly offered as a first-line nonsurgical treatment for lumbar spinal stenosis and/or radiculopathy. In many circumstances, these injections are a requirement, for insurance authorization of decompressive surgery. Furthermore, it is commonly held and taught that best-practice decisions involve a serial escalation of care from epidural injections to steroids. These current practices assume that lumbar epidural steroid injections are both effective, durable, and cost-effective.

The current randomized controlled trial, published in the *New England Journal of Medicine*,[5] fails to show a significant difference in 6-week outcomes when comparing steroid and lidocaine to lidocaine alone. At the 3-week time period, there was a modest improvement in the steroid group. These results fail to substantiate the role of lumbar epidural steroids in this patient population. Further, without evidence of their efficacy, we need to question if this treatment only add extra cost and delays effective intervention. Spinal decompression is a well-established procedure that is both effective and durable.

The current study does have some shortcomings. There is no sham control group, and thus it is difficult to isolate a placebo effect. Further, there are many subtypes of spinal stenosis. The current study, groups together patients with both central and lateral recess stenosis. To many neurosurgeons, these patients have quite unique presentations and treatments.

Overall, this clinical trial must raise questions regarding our current practice patterns and the true benefits of epidural steroid injections. This intervention, if not effective, may delay relief of symptoms, add cost, and place patients at risk for AEs. Further, in light of this study, insurance companies will need to re-evaluate if these treatments are required for surgical authorization.

Summary Written by Dr. Zachary A. Smith.

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