A summary of some of the recently published, seminal papers in neuroscience

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At 34 institutions in North America, patients with 1–3 brain metastases were randomized to receive stereotactic radiosurgery (SRS) or SRS plus whole brain radiation therapy (WBRT). The WBRT dose schedule was 30 Gy in 12 fractions; the SRS dose was 18–22 Gy in the SRS plus WBRT group and 20–24 Gy for SRS alone group. There were 213 randomized participants (SRS alone, n = 111; SRS plus WBRT, n = 102) with a mean age of 60 years. There was less cognitive deterioration at 3 months after SRS alone (63.5%) than when combined with WBRT (91.7%). The quality of life was higher at 3 months with SRS alone, including the overall quality of life. However, the time to intracranial failure was significantly shorter for SRS alone compared with SRS combined with WBRT (P < 0.001). There was no significant difference in functional independence at 3 months between the treatment groups. Median overall survival was 10.4 months for SRS alone and 7.4 months for SRS plus WBRT (P = 0.92). For long-term survivors, the incidence of cognitive deterioration was less after SRS alone at 3 months and 12 months. The authors concluded that, among patients with 1–3 brain metastases, the use of SRS alone compared with SRS combined with WBRT resulted in less cognitive deterioration at 3 months.

Contributed by Dr. Mazda K. Turel


The authors analyzed evidence regarding predictors that might affect biochemical remission and recurrence after transsphenoidal surgery (TSS), radiosurgery (RS), and radiotherapy (RT) in Cushing disease. First-line TSS was associated with high remission (76%) and low recurrence rates (10%). Remission after TSS was higher in patients with...
microadenomas or positive adrenocorticotropic hormone tumor histology. RT was not only associated with a high remission rate (RS, 68%; RT, 66%) but also with a high recurrence rate (RS, 32%; RT, 26%). Remission after RS was higher at short-term follow-up (≤2 years) and with high-dose radiation, whereas recurrence was higher in women and with low-dose radiation. The limitation of the study was that there was heterogeneity in the criteria and cutoff points used to define biochemical remission and recurrence.

**Contributed by Dr. Mazda K. Turel**


This phase II trial evaluated the efficacy of everolimus plus bevacizumab in patients with a recurrent, progressive meningioma, after treatment with surgical resection and local radiotherapy when appropriate. Patients with a recurrent meningioma following standard treatments with surgical resection and radiotherapy received bevacizumab and everolimus. The primary endpoint was progression-free survival (PFS). Secondary endpoints included response rate, as well as overall survival and safety. Seventeen patients with a median age of 59 years (29–84) received study treatment. World Health Organization (WHO) grades at the study entry included: I, 5 (29%); II, 7 (41%); III, 4 (24%); unknown, 1 (6%). Patients received a median of 8 cycles (1–37). The best response of a stable disease (SD) was observed in 15 patients (88%), and 6 patients had a SD for >12 months. Overall, median PFS was 22 months which was greater for patients with WHO grades II and III compared to grade I tumors (22.0 months vs 17.5 months). The combination of everolimus and bevacizumab was well-tolerated, and produced a SD in 88% of the patients; the median duration of disease stabilization was 10 months (range: 2–29 months).

**Contributed by Dr. Mazda K. Turel**


The authors conducted this study to evaluate the intellectual functioning and implications of limiting radiation exposure in the four biologically distinct subgroups of medulloblastoma, namely, wingless (WNT), sonic hedgehog (SHH), Group 3, and Group 4. A total of 121 patients with medulloblastoma (n = 51, Group 4; n = 25, Group 3; n = 28, SHH; and n = 17, WNT) had intellectual assessments. Intellectual outcomes declined comparably in each subgroup except for the processing speed; the intellectual outcome in SHH declined less than in Group 3 (P = 0.04). SHH had the lowest incidence of cerebellar mutism and motor deficits. Treatment with reduced dose of craniospinal irradiation plus a tumor bed boost was associated with preserved intellectual functioning in the WNT and Group 4 patients considered together (i.e., subgroups containing patients who were candidates for therapy de-escalation), but not in Group 3 or SHH. Across all subgroups, patients in all the other treatment groups declined over time (all P < 0.05). SHH patients appear to have the most distinct functional (i.e., motor deficits and mutism) outcomes and a unique processing speed trajectory. Only WNT and Group 4 patients seem to benefit from limiting radiation exposure. The authors concluded that their findings highlight the value of conducting subgroup-specific analyses. They can, therefore, be used to establish novel biological treatment protocols for patients with a medulloblastoma.

**Contributed by Dr. Mazda K. Turel**


The coflex trial was a prospective, randomized investigational device exemption study conducted at 21 clinical sites in the United States. Composite clinical success at 36 months was achieved by 62.2% among 196 coflex interlaminar stabilization (CIS) patients and 48.9% among 94 fusion patients (P = 0.03). Substantial and comparable improvements were observed in both the groups for patient-reported outcomes, although the percentage with a clinically significant improvement (≥15) in the Oswestry Disability Index seemed larger for the CIS group relative to that for the fusion group (P = 0.008). Radiographic measurements maintained index level and adjacent level range of motion in CIS patients, although range of motion at the level superior to the fusion was significantly increased (P = 0.005). The authors concluded that CIS for stenosis has proven to be effective and durable at improving the overall composite clinical success without altering normal spinal kinematic motion at the index level of decompression or at adjacent levels.

**Contributed by Dr. Mazda K. Turel**

The aim of this international multicenter study was to analyze data from patients who died within 3 months or 2 years after surgery, to identify the preoperative factors associated with poor or good survival, and to avoid inappropriate selection of patients for surgery in the future. A total of 1266 patients underwent surgery for impending pathologic fractures and/or neurologic deficits and were prospectively observed. Outcomes were survival at 3 months and 2 years post-surgery. In univariable analysis, age, emergency surgery, Karnofsky performance score (KPS), quality of life [EuroQol five-dimensions questionnaire (EQ-5D)] American Society of Anesthesiologists advisory (ASA), Frankel, and Tokuhashi/Tomita scores were significantly associated with short survival. In multivariable analysis, KPS and age were significantly associated with short survival. Associated with long survival in univariable analyses were age, number of levels included in surgery, KPS, EQ-5D, Frankel, and Tokuhashi/Tomita scores. In multivariable analysis, the number of levels included in surgery and primary tumor type were significantly associated with long survival. The authors concluded that poor performance status at presentation is the strongest indicator of poor short-term survival, whereas low disease load and favorable tumor histology were associated with long-term survival.

Contributed by Dr. Mazda K. Turel


This was a multicentre, randomized, double blind, placebo-controlled trial of vertebroplasty at four hospitals in Sydney, Australia. Patients with one or two osteoporotic vertebral fractures of less than 6 weeks’ duration and Numeric Rated Scale (NRS) back pain greater than or equal to 7 out of 10 were recruited. Follow-up was for 6 months. The primary outcome was the proportion of patients with NRS pain below 4 out of 10 at 14 days (between-group difference 23 percentage points, P = 0.011). The authors concluded that vertebroplasty is superior to placebo intervention for pain reduction in patients with acute osteoporotic spinal fractures of less than 6-week duration. These findings will allow patients with acute painful fractures to have an additional means of pain management that is known to be effective.

Contributed by Dr. Mazda K. Turel


The objective of this multicenter, international, prospective cohort study was to compare outcomes of laminoplasty (LP; n = 100) versus laminectomy and fusion (LF; n = 166) in patients undergoing posterior decompression for degenerative cervical myelopathy (DCM). Patients in both groups showed significant improvements in the mean Japanese Orthopedic Association (mJOA), Nurick grade, neck disability index (NDI), and short form (SF) 36v2 physical component (PCS) and mental health component (MCS) scores 24 months after surgery (P < 0.0001). At 24 months, mJOA scores improved by 3.4 in the LP group compared with 2.3 in the LF group (P = 0.006). Nurick grades improved by 1.5 in the LP group and 1.1 in the LF group (P = 0.07). There were no differences between the groups with respect to NDI and SF36v2 outcomes. After adjustment for preoperative characteristics, surgical factors, and geographical region, the differences in mJOA between surgical groups were no longer significant. The rate of treatment-related complications in the LF group was 21% compared with 28.31% in the LP group (P = 0.1). The authors concluded that both LP and LF are effective in improving clinical disease severity, functional status, and quality of life in patients with DCM.

Contributed by Dr. Mazda K. Turel


In this study, the authors prospectively examined the 7 and 10-year outcomes of cervical arthroplasty and compared them with the outcomes of anterior cervical discectomy and fusion (ACDF). As part of a Food and Drug Administration
investigational device exemption trial, a single center collected prospective outcomes data from 47 patients randomized in a 1:1 ratio to ACDF or arthroplasty. Success of both surgical interventions remained high at the 10-year interval. Both arthrodesis and arthroplasty demonstrated statistically significant improvements in the neck disability index (NDI), visual analogue (VAS) neck, and arm pain scores at all intervals including the 7 and 10-year periods. Arthroplasty demonstrated an advantage in comparison to arthrodesis, as measured by the final 10-year NDI score (8 vs 16, *P* = 0.0485). Patients requiring re-operation were higher in number in the arthrodesis cohort (32%) in comparison to the arthroplasty one [9%] (*P* = 0.055). The authors concluded that at 7 and 10 years, cervical arthroplasty compares favorably to ACDF, as defined by the standard outcomes scores in a highly selected population with radiculopathy.

**Contributed by Dr. Mazda K. Turel**


The authors conducted this study to better characterize the risks associated with cerebrovascular surgery. A total of 1141 cases were analyzed. The rate of complications was nearly twice that of previous estimates. Almost one-third of patients (30.9%) experienced at least one complication, which was significantly associated with 30-day mortality (odds ratio, 7.76; *P* < 0.001). Emergency surgery was associated with higher mortality rates (15.1%) than nonemergency procedures (2.3%). Significant predictors of complications included preoperative ventilator dependence, emergency surgery, bleeding disorders, diabetes mellitus, and alcohol abuse. Significant predictors of mortality included postoperative coma >24 hours, preoperative or postoperative ventilator dependence, black or Asian race, and stroke. The most common complications were ventilator dependence (64.5% in patients ventilated preoperatively, 8.4% in patients not ventilated preoperatively), bleeding requiring transfusion (10.2%), reoperation within 30 days (9.6%), pneumonia (7.3%), and stroke (7.3%).

**Contributed by Dr. Mazda K. Turel**

O’Donnell JM, et al. The risk of seizure after surgery for unruptured intracranial aneurysms (UIA). A total of 726 cases of UIA (excluding cases proximal to the superior cerebellar artery on the vertebrobasilar system) were identified and analyzed. Preoperative seizure history and complications of aneurysm repair were the only risk factors found to be significant. The risk of first seizure after discharge from the hospital following surgery for patients with neither preoperative seizure, treated middle cerebral artery aneurysm, nor postoperative complications (leading to a modified Rankin Scale score >1) was <0.1% and 1.1% at 12 months and 7 years, respectively. The risk for those with preoperative seizures was 17.3% and 66% at 12 months and 7 years, respectively. The risk of seizures with either complication (leading to a modified Rankin Scale score >1) from surgery or treated middle cerebral artery aneurysm was 1.4% and 6.8% at 12 months and 7 years, respectively. These differences in the 3 Kaplan-Meier curves were significant (log-rank *P* < 0.001). The authors concluded that the risk of seizures after discharge from hospital following surgery for UIA is very low when there is no preexisting history of seizures. If this result can be supported by other series, guidelines that restrict returning to driving because of the risk of postoperative seizures should be reconsidered.

**Contributed by Dr. Mazda K. Turel**


Gamma knife radiosurgery (GKRS) is one of the alternatives for the treatment of classical trigeminal neuralgia (TN). The authors conducted this study to retrospectively analyze long-term outcomes for TN using GKRS. One hundred and seventeen patients with medically refractory TN were treated with a mean maximum dose of 86.5 Gy (range: 80–90 Gy; median: 90 Gy). Clinical response was defined based on the Burchiel classification. They considered classes I and II as a complete response. For toxicity, they used the Barrow Neurological Institute facial numbness scale. The mean duration of follow-up was 66 months. Complete response at the last follow-up was observed in 81% patients, with an excellent response while off medication was seen in 52% patients. Pain-free rates without medication (class I) were 85% at 3 years, 81% at 5 years, and 76% at 7 years. Complete response rates (classes I–II) were 91% at 3 years, 86% at 5 years, and 82% at 7 years. Poor treatment response rates differed significantly between patients who had undergone previous surgery and were refractory to management with medication prior to GKRS. New or worsening facial numbness
was reported in 32.5% (30% score II and 2.5% score III). No anesthesia dolorosa was reported. Permanent recurrence pain rate was 12%. The authors concluded that GKRS achieved favorable outcomes compared with surgery in terms of pain relief and complication rates, notwithstanding decreasing pain-free survival rates over time. They consider GKRS to be an initial treatment in the management of medically intractable TN in selected patients.

**Contributed by Dr. Mazda K. Turel**


The authors compared the effects of hemicraniectomy on death and disability with conservative treatment in patients with large hemispheric infarctions from 7 randomized trials. The primary endpoint was a favorable outcome defined by modified Rankin Scale grades of 0–3 at 6–12 months post randomization. Of the 341 total randomized participants, the proportion of participants who achieved a favorable outcome was significantly greater among those randomized to hemicraniectomy (OR 2.04, \( P = 0.04 \)). Survival was also significantly greater among those randomized to hemicraniectomy (OR 5.56, \( P < 0.001 \)). There was a trend toward higher odds of a favorable outcome among those randomized to hemicraniectomy than among those randomized to conservative treatment in trials that permitted recruitment of patients aged 60 years or older (303 participants analyzed; OR 1.87, \( P = 0.09 \)). The authors concluded that compared with conservative treatment, the odds of achieving a favorable outcome at 6 months is approximately two-folds higher with hemicraniectomy in patients with large hemispheric infarctions.

**Contributed by Dr. Mazda K. Turel**


No evidence is available on the benefits of preventive suboccipital decompressive craniectomy (SDC) for patients with cerebellar infarction. The purpose of this matched case–control study was to investigate whether preventive SDC was associated with good clinical outcomes in patients with cerebellar infarction and to evaluate the predisposing factors leading to the infarction. Between March 2007 and September 2015, 28 patients underwent preventive SDC. The authors performed propensity score matching to establish a proper control group among 721 patients with cerebellar infarction during the same period. Group A (n = 28) consisted of those who underwent a preventive SDC, and group B (n = 56) consisted of those who did not undergo a preventive SDC. Clinical outcomes were better in group A than in group B at discharge (\( P = 0.048 \)) and at a 12-month follow-up (\( P = 0.030 \)). Group B had more deaths within 12 months than group A (log-rank, \( P < 0.05 \)). Logistic regression analysis showed that preventive SDC (odds ratio, 4.815; \( P = 0.009 \)) and the absence of brain stem infarction (odds ratio, 2.862; \( P = 0.033 \)) were independently associated with a favorable outcome (modified Rankin Scale score of 0–2) at a 12-month follow-up. The authors concluded that favorable clinical outcomes, including overall survival, could be expected after preventive SDC in patients with a volume ratio between 0.25 and 0.33 and the absence of brainstem infarction. Among these patients, preventive SDC might be better than the best medical treatment alone.

**Contributed by Dr. Mazda K. Turel**


Neurologic impairment after spinal cord injury (SCI) is usually measured and classified by functional examination. The purpose of this study was to determine how well inflammatory and structural proteins within the cerebrospinal fluid (CSF) of acute traumatic SCI patients predicted American Spinal Injury Association Impairment Scale (AIS) grade conversion and motor score improvement over 6 months. Fifty acute SCI patients (29 AIS A, 9 AIS B, 12 AIS C; 32 cervical, 18 thoracic) were enrolled and CSF was obtained through a lumbar intrathecal catheter to analyze interleukin (IL)-6, IL-8, monocyte chemotactic protein (MCP)-1, tau, S100β, and glial fibrillary acidic protein (GFAP) at 24 h post-injury. The levels of IL-6, tau, S100β, and GFAP were significantly different among patients with baseline AIS grades of A, B, or C. The levels of all proteins (IL-6, IL-8, MCP-1, tau, S100β, and GFAP) were significantly different between those who improved an AIS grade over 6 months and those who did not improve. Linear discriminant analysis modeling was 83% accurate in predicting AIS conversion. For AIS A patients, the concentrations of proteins such as IL-6 and S100β correlated with conversion to AIS B or C. Motor score improvement also strongly correlated with the 24-h post-injury CSF levels of...
all six biomarkers. The analysis of CSF can provide valuable biological information regarding the injury severity and the recovery potential after acute SCI.

**Contributed by Dr. Mazda K. Turel**


There has been increased interest in the potential importance of biochemical parameters as predictors of outcome in severe traumatic brain injury (sTBI). Of 107 patients with sTBI (age 18–65 years, with a Glasgow Coma Scale score of 4–8, presenting within 8 hours after injury) who were randomized for a placebo-controlled Phase II trial of progesterone with or without hypothermia, the authors serially analyzed serum biomarkers [S100-B, glial fibrillary acidic protein (GFAP), neuron-specific enolase (NSE), tumor necrosis factor-α, interleukin-6 (IL-6), estrogen (Eg), and progesterone (Pg)]. This analysis was performed using the sandwich enzyme-linked immunosorbent assay technique at admission and 7 days later for 86 patients, irrespective of their assigned group. A favorable Glasgow Outcome Scale (GOS) score (4–5) at 1 year was predicted by higher admission IL-6 and Day 7 Pg levels. An unfavorable GOS score (1–3) at 1 year was predicted by higher Day 7 GFAP levels. Survivors at 1 year had significantly higher Day 7 Pg levels. Nonsurvivors at 1 year had significantly higher Day 7 GFAP serum levels and Day 7 IL-6 serum levels. In the multivariate logistic regression analysis, independent predictors of outcome at 1 year were serum levels of Day 7 Pg (favorable GOS-OR 3.24, P = 0.003; and favorable survival-OR 2, P = 0.01); admission IL-6 (favorable GOS-OR 1.04, P = 0.04); and, Day 7 GFAP (unfavorable GOS-OR 0.79, P = 0.01; and unfavorable survival-OR 0.80, P = 0.01). The authors concluded that serial Pg, GFAP, and IL-6 monitoring could aid in prognosticating outcomes in patients with acute sTBI.

**Contributed by Dr. Mazda K. Turel**


The authors examined 5554 patients from the vagal nerve stimulation (VNS) therapy Patient Outcome Registry, and performed a systematic review of the literature that included 2869 patients across 78 studies.

The registry data revealed a progressive increase over time in seizure freedom after VNS therapy. Overall, 49% of patients responded to VNS therapy 0 to 4 months after implantation (≥50% reduction seizure frequency), with 5.1% of the patients becoming seizure-free, whereas 63% of patients were responders at 24 to 48 months, with 8.2% achieving seizure freedom. On multivariate analysis, seizure freedom was predicted by age of epilepsy onset >12 years [odds ratio (OR), 1.89], and predominantly generalized seizure type (OR, 1.36), whereas overall response to VNS was predicted by nonlesional epilepsy (OR, 1.38). Systematic literature review results were consistent with the registry analysis. At 0 to 4 months, 40.0% of patients had responded to VNS, with 2.6% becoming seizure-free, whereas at the last follow-up, 60.1% of individuals were responders, with 8.0% having achieved seizure freedom. The authors concluded that response and seizure freedom rates increase over time with VNS therapy, although complete seizure freedom is achieved in a small percentage of patients. VNS is a useful procedure in patients who are not good candidates for resective surgery.

**Contributed by Dr. Mazda K. Turel**


The authors investigated the safety and potential effectiveness of deep brain stimulation (DBS) for individuals with chronic, disabling traumatic brain injury (TBI) and problems of behavioral and emotional self-regulation in a prospective design with serial assessments of behavioral outcomes and positron emission tomography 2 years after the DBS implantation. Four participants 6 to 21 years after severe TBIs from automobile crashes were included. Although alert and volitional, all experienced significant executive impairments, including either impulsivity or reduced initiation. DBS implants were placed bilaterally in the nucleus accumbens and anterior limb of the internal capsule to modulate the prefrontal cortex. The procedure was safe, and all participants had improved functional outcomes. Two years after implantation, 3 met a *priori* criteria for improvement on the Mayo-Portland Adaptability Inventory-4. Improvement was due largely to better emotional adjustment, although 1 participant showed marked increases in multiple domains. DBS for severe TBI may be safely conducted and may be potentially effective in improving functions years after injury.

**Contributed by Dr. Mazda K. Turel**

Nonarguably, diagnosis of a brainstem metastasis (BSM) is a warranted death declaration for any patient, with very limited options of palliative treatment. In the present times, metastatic brainstem lesions pose challenging scenarios for the clinicians. Traditionally, whole brain radiotherapy (WBRT) is the only available palliative treatment option available for BSM. Radiosurgery is rapidly emerging as an additional treatment option supplementary to WBRT for effective local control. There is a dearth of well-designed trials to evaluate combination radiosurgery (WBRT plus SRS) and isolated SRS. In this multicentric trial from North America, Trifiletti et al., have attempted to define the response and toxicity following SRS of BSM. SRS for BSM traditionally exceeds dose tolerance limits even at the level of tumor margin; and, radiation induced injuries at this location can lead to severe and potentially life threatening complications. Traditionally, 12 Gy is considered to be the tolerance dose for the brainstem. The adjoining brainstem parenchyma receives a higher dose than the tolerance limit, and logically the radiation toxicity must be high. As such, there is no specific dose-defined criteria for BSM; however, this article shows that, with a 20 Gy marginal dose, the 12-month local control rate of 82% is achieved with SRS, with induced radiation toxicity in the range of 7.4%. The adverse risk factors were prior administration of WBRT, a large lesion size, and multiple metastases. Well-designed multicentric randomized trials are needed to further substantiate this report for a disease, which is gradually becoming a major health burden.

Contributed by Dr. Manjul Tripathi


Man cannot discover new oceans unless he has the courage to lose sight of the shore (Andre Gide). However, in present times, even a common man is a global citizen with the numbers of international travelers exceeding 1.2 billion in 2015 itself. In words of Freya Stark, “To awaken alone in a strange town is one of the pleasantest sensations in the world.” However, travel exposes the traveler to multiple health hazards, and adequate medical considerations before any travel are a necessity. Though there are various guidelines available on the Internet before travelling to some specific nations, a gross overview is still lacking. In this comprehensive review, Freedman and colleagues have nicely reviewed and summarized the available guidelines to travel in any part of the world. This article acts as a quick resource for a medical professional to guide the traveler. It not only covers the guidelines for vaccination, infectious, and noninfectious diseases but also for people with special needs such as children, pregnant women, and geriatric patients, as well as for people with high-risk behavior. These guidelines are needed to encourage disease-free travel and for prevention of new diseases in nonendemic areas.

Contributed by Dr. Manjul Tripathi


The human cerebral cortex is the most beautiful but the most complex structure ever created by nature. All the available atlases remain restricted in their description by complying to any set pattern of underlying criteria such as anatomy or functionality. In this article, researchers from “Human Connectome Project” provided an updated atlas of human cerebral cortex based on multimodal magnetic resonance imaging (MRI) images such as task based functional MRI (fMRI), resting state fMRI, myelin density measurement, and its integration with classical neuroanatomical images in a large number of participants. The team has delineated 360 different cortical areas, which are based on an automatic integrative algorithm and not on limited defining criteria. For example, fMRI evaluates the changes in blood flow, which is a proxy marker for neuronal activity, rather than an actual measurement. A computational integrative analysis of various modalities over the same subject increases the confidence that anatomical boundaries are reflecting the functional and biological reality rather than measurement biases. This advanced map provides new opportunities to the researchers to better delineate the disease and function-related information for individual and average brain.

Contributed by Dr. Manjul Tripathi


A healthy care provider is the building block of the health of a nation. In this thought provoking review, Colin P West and his team have analyzed the issue of physician burnout, its causes, and its effects on medical education, resident teaching program, patient care, judgmental ability, professionalism, and overall impact on health care delivery. In the available
literature from the west (principally USA), physician burnout leads to increased errors, depersonalization, emotional exhaustion, and suicidal tendencies in extreme cases. Alarmingly, physician burnout has already reached epidemic levels with the prevalence rate reaching up to 50% in USA. The causes are multifactorial such as long working hours, peer criticism, medicolegal concerns, discordance in family, financial obligations, and negative self-criticism. Various interventions on individual, institutional, or organizational level have brought about an improvement in the emotional exhaustion, depersonalization, and depression. The article does not detail any specific intervention in any particular branch of medicine. Such studies are also needed from the developing world, as only a “healthy” care provider can ensure the health of his patients.

**Contributed by Dr. Manjul Tripathi**

**Aulakh R. Mandatory publication in India: Setting quotas for research output could encourage scientific fraud. BMJ 2016 Sep 15. doi: 10.1136/bmj.i5002**

The recent reports of poor publication rate and no research outcome of the majority of medical colleges from India has propelled Medical Council of India (MCI) to revise its guidelines for teaching faculty appointment and promotion to higher ranks. The intention of this initiative is to encourage research potential, scientific learning, development of the skill set, and capacity building for training of junior faculty and medical students. Though proposed with a good intent, an unsupervised, incentive-based forced research has the potential to corrupt the world literature. This initiative of MCI should be welcomed but the bar has to be raised to maintain the quality and authenticity of the publications.

**Contributed by Dr. Manjul Tripathi**


To fuse or not to fuse a case of lumbar spinal stenosis (LSS) is a matter of heated debate. LSS is usually a result of degenerative changes at facet joint arthrosis, which causes neurogenic claudication and radicular pain. Fusion in cases of LSS with degenerative spondylolisthesis has seen a remarkable increase over the last decade due to the unknown fear of future worsening, as well as industry-guided misleading results and lack of level one evidence in literature for simple decompression. In the April issue of New England Journal of Medicine, studies by Forsth et al., and Ghogawala et al., have challenged the prevailing custom of fusion in degenerative lumbar spine disorders. The arguments in support of the combination procedure are the incipient risk of progressive instability and weakness of posterior tension bands. However, the combination procedure also exposes the patients to an increased risk of surgical complications, perioperative cardiovascular events, and health care costs. In cases of “degenerative spondylolisthesis without overt instability,” the neural elements gradually adjust to the changed pathophysiology and the goal of improving walking distance and nerve root decompression can be achieved solely by decompression. Instrumentation in such cases does not provide any added advantage. Both the studies show no clinical benefit of the added instrumentation in terms of relief of back pain, performance improvement on walking test, and an improvement in the Oswestry Disability Index score.

**Contributed by Dr. Manjul Tripathi**


This article helps to understand the possibilities for a researcher when the primary outcome of a randomized controlled trial (RCT) fails. A set of ten questions is proposed by the authors that can help us to better understand negative results in an RCT. In spite of the failure of the primary outcome, there can be certain situations where the result could be positive. The researcher may plan the next trial based on the useful information that emerges from a particular trial. This article is a useful to understand the nuances of failed trials.

**Contributed by Dr. Ravi Yadav**


This trial addresses a long pending important issue of the role of thymectomy in non thymomatous myasthenia gravis. The authors conducted a multicenter, randomized trial comparing thymectomy plus prednisone with prednisone alone in patients with myasthenia in the age group of 18–65 years with a disease duration of less than 5 years. The primary outcomes were the time-weighted average Quantitative Myasthenia Gravis score over a 3-year period, as assessed by blinded rating, and the time-weighted average required dose of prednisone over a 3-year period. A total of 126 patients underwent randomization at 36 sites during a 6-year period from 2006 to 2012. The patients who underwent a thymectomy had a lower 3-year time weighted...
average Quantitative Myasthenia Gravis Score than those who received prednisone alone. Patients in the thymectomy group also had a lower requirement of alternative day therapy with prednisone. This trial concluded that thymectomy improved clinical outcomes in patients with nonthymomatous myasthenia gravis over a 3-year period.

Contributed by Dr. Ravi Yadav


This trial was conducted to address a very challenging question that is faced by physicians regarding the management of blood pressure in patients with an intracranial hemorrhage. In this acute intra-cerebral haemorrhage-2 (ATACH-2) trial, the investigators randomized eligible patients with an intracerebral hemorrhage (volume <60 ml) and Glasgow coma scale of 5 or more to a systolic blood pressure target of 110–139 mmHg in the intensive treatment group versus a target of 140–179 mmHg in the standard treatment group. This was done to test the superiority of reduced blood pressure in the intensive group versus the standard treatment group. The blood pressure was reduced by using intravenous nicardipine, which was administered within 4.5 hours of the onset of intracerebral hemorrhage. The primary outcome was death or disability (Modified Rankin Scale of 4 to 6). The enrolment was stopped due to the futility of the prespecified interim analysis where it was found that there was no reduction in death or disability at 3 months in patients who underwent an intensive blood pressure reduction versus those who were given standard therapy. The negative results of this trial in a large sample of 1000 patients has to some extent addressed the issue that an acute reduction in blood pressure in patients with intracranial hemorrhage is not very useful in preventing morbidity.

Contributed by Dr. Ravi Yadav


Atrial fibrillation is an important cause of morbidity and mortality in the world. This study included cohort data from a prospective registry in 47 countries among patients who presented to a hospital emergency department with atrial fibrillation or flutter as the primary diagnosis. A total of 15400 patients were enrolled from various countries 1 year after attending the emergency department. Patients from North America, western Europe, and Australia were used as reference. Approximately 11% patients died in 1 year. Heart failure was the most common cause of death followed by stroke. Stroke was seen in 4% of 15361 patients. The highest number of strokes occurred in patients in Africa and China and the lowest occurred in India. In North America, western Europe, and Australia, 3% of the patients had a stroke. Thus, there was a very wide variation in the incidence of stroke and mortality among the different geographical regions. The authors suggested that the management of heart failure was a priority in this group of patients.

Contributed by Dr. Ravi Yadav


This study was done to determine whether glucocerebrosidase (GBA) gene mutations and the E326K polymorphism modify the symptom progression in Parkinson’s disease (PD). Patients were screened for the coding region of the entire GBA gene and E326K in 740 patients with PD who were enrolled at 7 sites. These patients were followed up with detailed longitudinal motor and cognitive assessments in the on state. Patients with combined GBA variants and E326K were associated with a faster progression in the postural instability and gait (PIGD) scores, but not in tremor scores. E326K carriers and GBA variant carriers progressed to mild cognitive impairment or dementia in more patients than in those without the mutations.

Contributed by Dr. Ravi Yadav


This study investigated the role of low calcium levels in hematoma volume expansion in patients with intracranial hemorrhage (ICH). Prospectively, 2123 patients were enrolled, and hypocalcemia was defined as a serum calcium level of <8.4 mg/dl. Baseline and follow-up hematoma volumes were measured. Hematoma expansion was defined as 30% increase in size or >6 ml increase in volume. Hypocalcemic patients had a higher median baseline hematoma volume than that of normocalcemic patients; and, low calcium levels were independently
associated with a higher baseline ICH volume. It was also found that higher the calcium level, lower was the risk of hematoma expansion. The authors concluded that lower calcium levels were associated with the risk of hematoma expansion possible due to subtle coagulopathy defects. These observations have important implications for therapy and would need a randomized control trial to unequivocally establish the veracity of these findings.

**Contributed by Dr. Ravi Yadav**


Although it is known that tau pathology frequently exists in patients with Parkinson’s disease (PD) and Diffuse Lewy Body (DLB) disease, there is less data on the extent of its presence as determined on in-vivo imaging. This study evaluated the contrast tau aggregation in DLB, cognitively impaired persons with PD (PD-impaired), cognitively normal individuals with PD (PD-normal), and healthy persons serving as control participants, and assessed the association between tau aggregation, amyloid deposition, and cognitive function. Using Pittsburgh compound B for the positron emission tomographic imaging, the authors identified tau deposition in the inferior temporal gyrus and precuneus in patients with DLB and PD who had associated impaired cognition. The findings support the existence of tau co-pathology in patients with PD and DLB.

**Contributed by Dr. Ravi Yadav**


It is known that persistent mild traumatic brain injuries can lead to a progressive neurodegenerative condition known as chronic traumatic encephalopathy. This study tried to determine whether persistent symptoms after mild traumatic brain injury are associated with brain injury as evaluated by cerebrospinal fluid biochemical markers for axonal damage and other aspects of central nervous system injury. The results showed that there was an increase in neurofilament light proteins and reduced amyloid beta peptides in patients with post-concussion syndrome. This suggested axonal injury, and the presence of amyloid deposition showed that these biomarkers may be measured and used as an objective tool to monitor the patients who are at risk of developing chronic traumatic encephalopathy.

**Contributed by Aastha Takkar**


Rituximab has been a very useful drug in the management of neuromyelitis optica spectrum disorders (NMOSD). This important study is probably the largest systematic review and meta-analysis till date regarding the efficacy and safety of rituximab in the treatment of NMOSD. Out of 46 studies conducted among 438 patients in whom efficacy measures were measured objectively by various established scales, it was shown that there was reduction in the frequency and severity of NMOSD relapses using this medicine.

**Contributed by Dr. Ravi Yadav**


Interestingly, limited world literature that addresses the failure rates of an uncomplicated optic nerve sheath decompression (ONSD) is available. This retrospective chart review involving 174 consecutive medically refractory patients of idiopathic intracranial hypertension (IIH) investigated whether patients with IIH undergoing ONSD had a higher risk of surgical failure if the opening pressure (OP) on lumbar puncture was more than 50 cm H₂O compared to those with OP less than 50 cm H₂O. The main outcome measure was the relationship between OP on lumbar puncture and the failure of ONSD. Forty patients among the cohort who had an OP >50 cm H₂O, and 6 (15%) had progressive visual loss after an uncomplicated ONSD. In contrast, 6 (4.5%) of the 134 patients with an OP of <50 cm H₂O (P = 0.032) had visual loss. Patients with worse visual acuity at presentation also had a higher risk of progressive visual loss after ONSD (P = 0.001), as did men (P = 0.048). Patients with IIH and a higher OP had a three-fold increased risk of failure of ONSD in preventing progressive visual loss, thus requiring a shunt procedure, when compared to those with an OP of <50 cm H₂O. Visual acuity at presentation and male sex were also associated with progressive visual decline after ONSD. In the follow-up period after an ONSD, signs of further visual deterioration in the presence of these factors would indicate an urgent need for a shunt procedure.

**Contributed by Aastha Takkar**

Uncontrolled pilot studies have suggested the efficacy of focused ultrasound thalamotomy with magnetic resonance imaging (MRI) guidance for the treatment of essential tremor. This trial enrolled 76 patients with moderate-to-severe essential tremor who had not responded to at least two trials of medical therapy. The patients were randomly assigned in a 3:1 ratio to undergo unilateral focused ultrasound thalamotomy or a sham procedure. The Clinical Rating Scale for Tremor and the Quality of Life in Essential Tremor Questionnaire were administered at baseline and at 1, 3, 6, and 12 months. The primary outcome was the between-group difference in the change from baseline to 3 months in hand tremor, rated on a 32-point scale (with higher scores indicating more severe tremor). After 3 months, patients in the sham-procedure group could crossover to active treatment (the open-label extension cohort). Hand-tremor scores improved more after focused ultrasound thalamotomy than after the sham procedure; the between-group difference in the mean change was 8.3 points [95% confidence interval (CI), 5.9 to 10.7; P < 0.001]. The improvement in the thalamotomy group was maintained at 12 months. Secondary outcome measures assessing disability and quality of life also improved with active treatment (the blinded thalamotomy cohort) compared with the sham procedure (P < 0.001 for both comparisons). Adverse events in the thalamotomy group included gait disturbance in 36% of the patients and paresthesias or numbness in 38%; these adverse events persisted at 12 months in 9% and 14% of patients, respectively. MRI-guided focused ultrasound thalamotomy may prove to be an upcoming boon for patients with essential tremors.

Contributed by Aastha Takkar


Intravenous thrombolysis with alteplase alone cannot reperfuse most large-artery strokes. This randomized controlled trial conducted in 26 centres in France aimed to determine whether mechanical thrombectomy in addition to intravenous thrombolysis improves clinical outcome in patients with acute ischemic stroke. The study population included 414 patients, aged 18–80 years, with acute ischemic stroke and proximal cerebral artery occlusion. They were randomly assigned to receive either intravenous thrombolysis alone (IVT group) (n = 208) or intravenous thrombolysis plus mechanical thrombectomy (IVTMT group; n = 204). IVT had to be started within 4 h and thrombectomy within 5 h of symptom onset. Occlusions had to be confirmed by computed tomographic or magnetic resonance angiography. The primary outcome was the proportion of patients achieving functional independence at 3 months, as defined by a score of 0–2 on the modified Rankin scale. Safety outcomes were analyzed in the per-protocol population. Eight-five (42%) of the 202 patients in the IVT group and 106 (53%) of 200 patients in the IVTMT group achieved functional independence at 3 months. The two groups had no significant differences in mortality at 3 months or symptomatic intracranial hemorrhage at 24 h. The common adverse events related to thrombectomy were vasospasm and embolization in a new territory. Thus, mechanical thrombectomy along with standard intravenous thrombolysis improved functional independence in patients with acute cerebral ischemia. There was no evidence of increased mortality.
In this prospective, multicenter, randomized control trial, the authors set out to clarify the effect of decompressive craniectomy on clinical outcomes in patients with refractory traumatic intracranial hypertension. Spanning over a period of 10 years (2004–2014), the study comprised 408 patients with traumatic brain injury and refractory elevated intracranial pressure (>25 mmHg), randomized to either undergo decompressive craniectomy (n = 201) or to receive ongoing medical care (n = 188). Extended Glasgow Outcome Scale (GOS-E) at 6 months was used for follow-up analysis. The authors found a significant difference in GOS-E distribution between the two groups (P < 0.001). At 6 months, the mortality in the surgical arm was nearly half (26.9% versus 48.9%) compared to the medical arm, and this difference was marked with respect to patients in vegetative state (8.5% versus 2.1%); lower severe disability (dependent on others for care: 21.9% versus 14.4%); upper severe disability (independent at home: 15.4% versus 8.0%); moderate disability, (23.4% versus 19.7%); and good recovery (4.0% versus 6.9%). Similar figures persisted at a 12-month follow-up, although the difference did even up with respect to moderate disability (22.2% versus 20.1%) and good recovery (9.8% versus 8.4%). Patients in the surgical arm had a higher rate of adverse events (16.3% versus 9.2%, P = 0.03). Thus, the trial concluded that decompressive craniectomy in patients with traumatic brain injury and refractory intracranial hypertension does lead to a lower mortality and higher rates of vegetative state, lower severe disability, and upper severe disability than medical care. The rates of moderate disability and good recovery were, however, similar in both the groups.

Contributed by Dr. Kuntal Kanti Das


In this study, the authors report the results of a new synthetic osteoregenerative biomaterial on animal models. The authors generated the new product, termed hyperelastic bone (HB), to circumvent the current deficiencies of osteoregenerative biomaterials such as unsatisfactory new bone regeneration, high costs, limited manufacturing capacity, and lack of surgical ease of handling. The material comprised 90 weight % (wt%) hydroxyapatite and 10 wt% polycaprolactone or poly lactic-co-glycolic acid. It could be rapidly, three-dimensionally (3D) printed (up to 275 cm^3/hour) at room temperature. The resulting 3D-printed HB was tested to exhibit elastic mechanical properties (~32–67% strain to failure, ~4–11 MPa elastic modulus), was found to be highly absorbent (50% material porosity), and supported the cell viability and proliferation. The material induced osteogenic differentiation of bone marrow–derived human mesenchymal stem cells cultured in vitro over 4 weeks without requirement of any osteoinducing factors in the medium.
The authors evaluated HB in vivo in a mouse subcutaneous implant model for material biocompatibility (7 and 35 days), in a rat posterolateral spinal fusion model for new bone formation (8 weeks), and in a large, non-human primate calvarial defect case study (4 weeks). The authors found that HB did not elicit a negative immune response, became vascularized, quickly integrated with the surrounding tissues, and rapidly ossified and supported new bone growth without the need for added biological factors.

**Contributed by Dr. Kuntal Kanti Das**


In this paper, the authors intended to assess the outcomes of combined anterior and posterior lumbar rhizotomy for the treatment of mixed hypertonia in the lower extremities of children with cerebral palsy (CP). These children generally have a combination of dystonia with variable grades of spasticity, thus leading to considerable difficulties in locomotive functions. In this prospective study, 50 children with CP were subjected to combined anterior and posterior lumbar rhizotomies. Clinical outcome measurements were recorded preoperatively as well as postoperatively at 2, 6, and 12 months. The operative techniques involved a laminotomy from L1-S1 and intraoperative monitoring was performed in all cases. All patients underwent an intensive postoperative physiotherapy program. Changes in muscle tone, range of motion at joints, and dystonia were significantly improved (\( P = 0.000 \)) at follow-up visits.

**Contributed by Dr. Kuntal Kanti Das**


In this study, the authors analyzed the effectiveness of cognitive-behavioral therapy (CBT) in persistent postconcussional symptoms (PCS). PCS remains a source of distress and disability after traumatic brain injury (TBI) and is often resistant to treatment. In this two-center, randomized, waiting list controlled trial, 46 adult patients with persistent PCS after TBI were subjected to a 12-session individualized, formulation-based CBT program. The investigators observed an improvement in the primary outcome measures relating to quality of life (using the Quality of Life Assessment Schedule and the Brain Injury Community Rehabilitation Outcome Scale). Treatment effects were observed for several secondary outcome parameters as well including measures of anxiety and fatigue (but not for depression or posttraumatic stress disorder; PTSD). Improvements were more apparent for those completing CBT sessions over a shorter period of time. However, they were unrelated to the medicolegal status, injury severity, or length of time since the injury. Thus, this study suggests that CBT can improve the quality of life for adults with persistent PCS.

**Contributed by Dr. Anant Mehrotra**

The authors conducted a multicentre, randomized, controlled, triple-blind trial in patients with probable or definite amyotrophic lateral sclerosis (ALS) in 12 ALS centres in France. Seventy-four ALS patients who had moderate respiratory involvement (forced vital capacity 60–80% predicted) and were older than 18 years and had bilateral responses of the diaphragm to diagnostic phrenic stimulation were randomly assigned to either the active stimulation (n = 37) or to the sham stimulation group (n = 37). The primary outcome was noninvasive ventilation-free survival, analyzed in the intention-to-treat population. Safety outcomes were also assessed in the intention-to-treat population. During the course of the trial, another trial showed excess mortality with diaphragm pacing in patients with hypoventilation, and hence an unplanned masked analysis was done. The authors analyzed the mortality in their study and found excess mortality (death from any cause) in the active stimulation group and the study was terminated. The median noninvasive ventilation-free survival was 6.0 months (95% CI 3.6–8.7) in the active stimulation group versus 8.8 months (4.2–not reached) in the control (sham stimulation) group [hazard ratio 1.96 (95% CI 1.08–3.56), P = 0.02]. Serious adverse events (mainly capnothorax or pneumothorax, acute respiratory failure, venous thromboembolism, and gastrostomy) were frequent [24 (65%) patients in the active stimulation group vs 22 (59%) patients in the control group]. No treatment-related death was reported. The authors concluded that diaphragm pacing is not indicated at the early stage of ALS-related respiratory involvement.

Contributed by Dr. Anant Mehrotra

Bell EJ, et al. Hepatocyte growth factor is positively associated with risk of stroke. the mesa (multi-ethnic study of atherosclerosis). Stroke. DOI http://dx.doi.org/10.1161/STROKEAHA.116.014172

Hepatocyte growth factor (HGF) has been associated with hemorrhagic and ischemic stroke risk factors. The authors conducted a study to determine any association of circulating HGF with incident stroke using data from the Multi-Ethnic Study of Atherosclerosis (MESA). Out of 6711 participants (aged 45–84 years) whose HGF was measured, 233 had an incident stroke on follow up. Cox proportional hazards regression was used to calculate hazard ratios and 95% confidence intervals for incident stroke. A secondary analysis stratified results by the adjudicated stroke type (n = 183 ischemic; n = 39 hemorrhagic; n = 11 other). After adjustment for potential confounding variables, the risk of stroke was 17% higher with each standard deviation increase in HGF (hazard ratio, 1.17; 95% confidence interval, 1.03–1.34). The few hemorrhagic and other types of stroke were not associated with HGF. The authors conclude that HGF may have utility as a prognostic marker of stroke risk.

Contributed by Dr. Anant Mehrotra


To identify the risk factors for placement of a shunt after aneurysmal SAH (aSAH), the authors used 1533 aneurysmal subarachnoid haemorrhage (aSAH) patients from the population-based Eastern Finland Saccular Intracranial Aneurysm Database. The risk model was built and internally validated in random split cohorts. External validation was conducted among 946 aSAH patients from the Southwestern Tertiary Aneurysm Registry (Dallas, TX) and tested using receiver-operating characteristic curves. A total of 17.7% of the patients, who were alive for 14 days or more, required a shunt procedure. Six groups were defined with successively increasing risk for placement of a shunt based on the recursive partitioning analysis. These groups were also assessed for successive risk stratified functional outcome at 12 months, shunt complications, and time-to-shunt rates. The area under the curve–receiver-operating characteristic curve for the exploratory sample and internal validation sample was 0.82 and 0.78, respectively, with an external validation of 0.68. The authors concluded that prediction modelling of shunt dependency is feasible with clinically useful yields.

Contributed by Dr. Anant Mehrotra


Patients with secondary progressive multiple sclerosis (SPMS) are commonly enrolled for the purpose of evaluation of observational or an intervention-based outcome. However, the diagnosis of SPMS is retrospective and there is no definition that is universally acceptable. In order to formulate an objective definition of SPMS, Lorscheider et al., used a global observational cohort of multiple sclerosis, MSBase. They observed that physicians tended to diagnose the progressive forms of MS late in the course of the disease and the decisions were more specific than being sensitive. With this background, a longitudinal data of 17,356 patients from 113 MS centres from 34 countries was analyzed. It was concluded that the best definition was obtained using a 3-strata progression paradigm where the patient had an
Expanded Disability Status Scale score of $\geq 4$ with a duration criteria of 3 months. This definition, compared with the consensus diagnosis of neurologists, has been shown to be more sensitive but at the cost of some decrease in specificity. It was concluded that the application of this definition to trials can potentially increase the reproducibility and accuracy of the studies and promote the timely diagnosis of SPMS.

**Contributed by Dr. Hardeep Singh Malhotra**


Migraine is an important cause of headache-related disability and is an important point of concern in terms of therapeutic benefit and financial burden. In an interesting systematic review, Hougaard and Tfelt-Hansen assessed the quality of randomized controlled trials (RCTs) in terms of inclusion of a placebo arm in patients with migraine. It may be noted that the Clinical Trials Subcommittee of the International Headache Society recommends the inclusion of a comparative placebo arm in all RCTs evaluating the prophylactic drug therapy for migraine. RCTs published in the English literature from 2002 to 2014 were reviewed using Cochrane’s Search Strategy. Strikingly, only 3 of the 31 studies used a placebo arm as a comparator, and in just 2 of 28 superiority trials, could one actually ascertain the superiority of one drug over the other. It was revealed that the majority of trials conducted without a placebo in effect did not show any significant difference between the treatment groups. The authors concluded that omission of a placebo arm was indeed hampering the recognition of potential drugs, which might otherwise have had a good efficacy as a prophylactic agent in patients with migraine.

**Contributed by Dr. Hardeep Singh Malhotra**

**Cortés-Vicente E, et al. Clinical characteristics of patients with double-seronegative myasthenia gravis and antibodies to cortactin. JAMA Neurol 2016;73:1099-104**

The immunopathogenesis of myasthenia gravis is evolving and has come a long way since acetylcholine receptor antibodies were detected in 1976. It is apparent that antibodies, either acetylcholine receptor antibodies or muscle-specific kinase antibodies, may not be detected in all patients; such patients are known as double-seronegative myasthenia gravis (dSNMG). In a retrospective cross-sectional analysis, Cortés-Vicente et al., included 250 patients with definite myasthenia gravis and estimated cortactin antibodies in the stored serum samples. Of the 38 patients with dSNMG, cortactin antibodies were detected in 9 patients (23.7%); though they were co-detected in 19 patients (9.5%) positive for acetylcholine receptor antibodies, the difference in the rate of positivity was statistically significant. Cortactin antibodies were not detected in controls or in patients positive for muscle-specific kinase antibodies. It was noted that patients with cortactin antibodies were young at the onset of disease, more commonly presented with ocular myasthenia gravis, on evolution had milder generalized form, and had lesser bulbar involvement. Cortactin antibodies seem to diagnose, although partially, the dSNMG subset, and authors conclude that such an estimation should be made a part of routine diagnostic assessment.

**Contributed by Dr. Hardeep Singh Malhotra**


The pleotropic effects of statins have for long intrigued the researchers and have spanned almost all systems of the body. In one such evaluation Lin et al., tried to assess the association between the use of statin and the risk of Parkinson’s disease (PD) in patients with diabetes. The study was conducted among Taiwanese patients and a randomly selected sample of one million patients, who were followed from 2001 to 2008, was used for analysis. The patients were diagnosed on the basis of International Classification of Diseases, Ninth Revision, Clinical Modification. Of a selected cohort of 50432 patients (statin users versus nonstatin users), first the propensity of developing PD was assessed followed by the assessment of relationship of dosage of statin vis-à-vis PD. The analysis showed that the incidence of PD among diabetics who used statins was lower than those who did not use a statin. This effect was slightly more pronounced in female (crude hazard ratio of 0.65) than that in male patients (crude hazard ratio of 0.6) when compared with the nonstatin users. It was also shown that the reduction in the risk of PD was essentially a class effect of statins, except for lovastatin, and that the effect was dependent on the dose of statin used. It was concluded that, in the Taiwanese population, statins have a dose-dependent beneficial effect in reducing the risk of PD. The study reiterated the pleiotropy associated with their usage.

**Contributed by Dr. Hardeep Singh Malhotra**

Large hemispheric infarctions are commonly observed and contribute to significant morbidity and mortality in patients with stroke. It is well‑known that brain edema is instrumental in influencing this sequelae and efforts have been made to reduce brain edema to prevent decompressive interventions as well as improve the outcome of the patient. Glyburide is one such agent that has shown promise in preclinical trials to reduce brain edema and improve outcome in experimental stroke. In order to assess the effect of glyburide in patients with large anterior circulation hemispheric stroke, Sheth et al., conducted a double‑blind, randomized, placebo‑controlled phase 2 trial. Patients in the age group 18–80 years, presenting within 10 hours of having sustained a large anterior circulation hemispheric stroke, were enrolled from 18 centres in the USA. Glyburide was administered intravenously as a bolus followed by an infusion at the predestined rates for a total of 72 hours. Patients, who did not undergo decompressive craniectomy, were assessed on per protocol basis evaluating their attainment of a modified Rankin scale (mRS) score 0–4 at 90 days; data on the safety of the drug was similarly collected. The study was stopped because of issues associated with funding after enrolling 86 patients. In 77 patients, analyzed on per protocol basis, it was observed that there was no statistically significant difference in the mRS score between the group receiving glyburide and the one receiving placebo. It was concluded that the intravenous use of glyburide was well‑tolerated, and further evaluations are required to assess the potential of the drug in reducing brain edema significantly.

Contributed by Dr. Hardeep Singh Malhotra


For any stroke specialist involved in thrombolysis, presence of cerebral microbleeds (CMBs) has also been a source of concern. In order to assess the clinical relevance of CMBs in patients undergoing thrombolysis, an International Meta‑Microbleeds initiative undertook the task of reviewing the literature in this regard and present meta‑analysis of the same. The prethrombolysis MRI of patients with acute ischemic stroke were evaluated to investigate whether these were associated with an increased risk of symptomatic hemorrhage or a poor outcome. Pooled odds ratios were calculated from the available PubMed indexed studies for symptomatic intracerebral hemorrhage (ICH) as well as for poor outcome. Poor outcome was defined as a modified Rankin Scale score of >2, and was assessed at 3 and 6 months.

In total, data from 2601 patients were fetched from 8 eligible studies and analyzed. It was found that the cumulative prevalence of CMBs was 24% (95% confidence interval (CI) = 18–30). The pooled incidence of symptomatic ICH was significantly higher in patients with CMBs compared to those without CMBs (5% versus 3%), with an odds ratio of 2.18 in favor of patients with CMBs. Patients with CMBs had a poor functional outcome (pooled incidence 52% versus 41%) with an odds ratio of 1.58 for patients with CMBs. It was thus demonstrated that patients with an ischemic stroke who have CMBs in their pretreatment MRI of the brain are more likely to have symptomatic ICH as well as a poorer functional outcome. However, it may be noted that the meta‑analysis does not consider this association as prohibitive toward administration of thrombolytic agent and finds the risk acceptable (Level B recommendation: nonrandomized Class IIa evidence).

Contributed by Dr. Hardeep Singh Malhotra


The approved botulinum toxin A products are fraught with certain drawbacks, viz. reconstitution and a potential for dose miscalibration and transmission of infection during diluent mixing. AbobotulinumtoxinA solution for use (injection) in patients with dystonia is a ready‑to‑use liquid formulation, which may avert the need of reconstitution prior to usage. Poewe et al., conducted a Phase 3 multicentric, prospective, double‑blind, randomized placebo‑controlled trial to study the efficacy of abobotulinumtoxinA in patients with cervical dystonia. The trial was directed towards demonstrating the superiority of abobotulinumtoxinA solution versus a placebo and noninferiority of abobotulinumtoxinA solution versus a dry‑formulation of abobotulinumtoxinA. The objective of this study was to demonstrate the superior efficacy of abobotulinumtoxinA solution for injection to a placebo, and to test the noninferior efficacy of abobotulinumtoxinA solution for injection versus abobotulinumtoxinA (dry formulation) in cervical dystonia.
A total of 369 patients were enrolled and 500 U of abobotulinumtoxinA solution, dry abobotulinumtoxinA, or a placebo was administered for up to 4 cycles. The Toronto Western Spasmodic Torticollis Rating Scale total score was used to assess the outcome at week 4 of the injection. It was found that abobotulinumtoxinA (solution as well as dry-formulation) was superior to placebo. However, the trial was unable to demonstrate the noninferiority of abobotulinumtoxinA solution against abobotulinumtoxinA dry-formulation in terms of a change in baseline scores. The efficacy otherwise was stated to be similar in both the groups with an acceptable adverse effect profile. Maybe, a study looking at an outcome beyond 4 weeks can provide more insight into the utility of the newer formulation.

Contributed by Dr. Hardeep Singh Malhotra

Swallow DM, et al. Statins are underused in recent-onset Parkinson’s disease with increased vascular risk: Findings from the UK Tracking Parkinson’s and Oxford Parkinson’s Disease Centre (OPDC) discovery cohorts. J Neurol Neurosurg Psychiatry 2016;87:1183-90

Statins are known for their pleiotropic effects in addition to their function as lipid lowering agents. Does the influence of cardiovascular disease (CVD) help in modifying the phenotype of Parkinson’s disease (PD) as well? The statins being administered for addressing the risk factors associated with CVD may play a role in influencing the manifestations of PD. Swallow et al., evaluated the UK Tracking Parkinson’s and Oxford Parkinson’s Disease Centre (OPDC) discovery cohorts to study the differences between vascular risk, and phenotype and severity of PD in recent onset disease. They quantified the cardiovascular risk factors using the QRISK2 calculator (high ≥20%, medium ≥10 and <20%, and low risk <10%). The Movement Disorder Society Unified PD Rating Scale (UPDRS) and the Montreal cognitive assessment scales were used to quantify the motor and the cognitive changes, respectively.

In total, 2909 individuals with recent-onset PD were assessed. It was observed that patients with a higher vascular risk and those with an established CVD belonged to the older age group, and had a worse motor score, phenotype, as well as cognition. Compared to patients with an established CVD, only approximately half with a high vascular risk received a statin which was even lower with other risk strata. The authors concluded that more that 60% patients with PD are candidates for statin use, which may modify outcomes in patients with recent-onset PD. This study may also be assessed in the light of results of another study where statin therapy has been shown to benefit patients (Taiwanese population) of PD with diabetes mellitus (Lin KD, et al. Statin therapy prevents the onset of Parkinson disease in patients with diabetes. Ann Neurol 2016;80:532-40).

Contributed by Dr. Hardeep Singh Malhotra


It is well-known that specific or disease-modifying therapy for amyotrophic lateral sclerosis (ALS) does not exist. There may be numerous factors that might influence health-related quality of life (HRQL) in patients with ALS, however, the knowledge of these factors is poor. A modification of these factors may be instrumental in achieving an improved outcome or quality of life. Sandstedt et al., planned a study to determine these factors in patients with ALS by using certain questionnaires as well as by assessing the HRQL. The predictors were shortlisted using a multivariate regression analysis.

They enrolled 60 people with ALS and showed that a higher severity of disease and a lower frequency of social and lifestyle activities were associated with worse HRQL in terms of physical scores, whereas a higher severity of disease, weak coping capability, and anxiety and/or depression were associated with worse HRQL in terms of psychosocial scores. Similarly, presence of fatigue and use of mechanical ventilator were associated with worse HRQL. The shortlisting of these factors might help the physicians as well as the care-givers in identifying patients tending to be low in terms of HRQL. In addition to this therapy, both pharmacological as well as psychosocial counselling, may be targeted in such patients to help them.

Contributed by Dr. Hardeep Singh Malhotra


Presentations of childhood stroke may be varied as well as not uniformly classifiable. The issues of individual opinions and classification schemes complicate the issues further. Because the data in this regard is limited, the International Pediatric Stroke Study (IPSS) collaborators decided to formulate the CASCADE criteria (Childhood AIS Standardized Classification and Diagnostic Evaluation) and test its inter-rater reliability in children with acute ischemic stroke.
Out of a prospective cohort of 113 children with acute ischemic stroke (arterial), clinical, and neuroimaging data of 64 children, selected randomly, were evaluated by 8 raters from the IPSS. They classified the findings using the CASCADE criteria and results were statistically analyzed for agreement among raters by unweighted $\kappa$ statistic. There was moderate inter-rater reliability of the applied CASCADE criteria, higher for cardioembolic stroke, and bilateral cerebral arteriopathy compared to other arteriopathies of childhood.

The collaborators suggest that results of this evaluation are likely to help in standardizing the classification scheme for childhood ischemic stroke and can be used for multicentric studies for achieving a better homogeneity. As a future directive, they suggest that the inter-rater reliability needs to be improved for other subsets, for which it is presently on the lower side.

*Contributed by Dr. Hardeep Singh Malhotra*