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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Phenytoin as a Second-line Treatment for Status Epilepticus: What's the Evidence?

By Padmaja Kandula, MD

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Dr. Kandula reports no financial relationships relevant to this field of study.

SYNOPSIS: In this systematic review, the evidence supporting the use of intravenous phenytoin for convulsive status epilepticus was analyzed critically and did not demonstrate strong evidence to support its use as a preferred second-line agent.

SOURCE: Brigo F, Bragazzi NL, Lattanzi S, et al. A critical appraisal of randomized controlled trials on intravenous phenytoin in convulsive status epilepticus. *Eur J Neurol* 2018;25:451-463.

Convulsive status epilepticus (SE) is a neurologic and medical emergency with an incidence rate of up to 41/100,000 cases per year and estimated deaths of 22,000 to 42,000 annually. Yet, most treatment algorithms for benzodiazepine-resistant or second-line treatment in SE largely are based on clinical experience and anecdotal evidence rather than multicenter, randomized, controlled trials (RCT). In this systematic review of RCTs of intravenous (IV) phenytoin for convulsive status, the authors weighed the evidence regarding the use of phenytoin in convulsive status, with attention to second-line treatment.

The authors included eight studies (544 patients) with Cochrane-quality methodology after meeting criteria as an RCT. All studies from 1988-2015 included both adult and pediatric patients. All studies also included convulsive status, although additional SE subtypes, such as subtle generalized convulsive status, also were included in some studies. Six studies used IV phenytoin as first-line or second-line treatment, although not clearly benzodiazepine resistant (concurrent or immediate use of phenytoin along with benzodiazepine). In two of the eight studies with 72 combined patients, phenytoin was used in benzodiazepine-resistant cases as defined by ongoing clinical semiology and/or

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electrographic activity.[1,2] Of the remaining 472 patients, 185 received phenytoin as first drug;[1,2,3] 269 patients received IV phenytoin immediately after IV diazepam[3,4] or lorazepam.[5] In 18 patients, phenytoin was administered simultaneously with IV diazepam.[6]

Treatment success was defined variably in the studies, with the primary endpoint cessation of clinically overt convulsive activity ranging from 42-100%. In those defined as subtle convulsive SE, treatment success was significantly lower at 8.3% with combined diazepam and phenytoin treatment and 7.7% in those with phenytoin alone.

Interestingly, in the two studies with benzodiazepine-resistant cases, use of second-line phenytoin resulted in clinical seizure cessation of 68-96%.[1,2] With either simultaneous or near immediate administration of IV phenytoin after IV diazepam[3,4,6] or IV lorazepam,[5] clinical seizure cessation was 55.8-100% (excluding patients with subtle SE). IV phenytoin used as a first-line drug controlled status in 42-88% of cases.[3,7,8] In a landmark study, Treiman et al found that IV lorazepam was more effective (64.9%) than either phenytoin (43.6%), phenobarbital (58.2%), or diazepam followed by phenytoin (55.8%) for aborting convulsive SE.[3] Misra et al found that IV phenytoin was less effective than sodium valproate (42% vs. 66%) as first-line treatment for convulsive status.[7]

■ COMMENTARY

Historically, benzodiazepines have been the mainstay as initial treatment for convulsive status. The superiority of lorazepam was demonstrated nicely in the Veteran's Affairs Cooperative Study initially published in 1998 by David Treiman. Two decades later, the mainstay of first-line treatment has not changed. However, 20 years later, there is still no evidence-based rationale regarding the use of second-line agents in SE. The waters are even murkier regarding refractory status epilepticus, defined as failure of second-line agents. The authors of this paper challenged the widespread use of an established agent (phenytoin) as second-line treatment in an era of evidence-based medicine. To date, the largest RCT using phenytoin as a second-line agent after demonstrated benzodiazepine failure suffers from a relatively small treatment population (n = 50).[1] Hence, the authors have concluded accurately that the overall evidence favoring the use of phenytoin as second-line treatment for status is relatively weak. Yet, the evidence for other IV options such as valproic acid, levetiracetam, and lacosamide are even more limited. Nonetheless, as SE continues, there is progressive reduction of available synaptic GABA receptors, leading to less GABA-mediated inhibition and need for a potential alternative mechanism of action. The exact role for the second-generation IV anticonvulsants remains to be seen. The promise of an answer may come shortly with the conclusion of the ESETT (Established Status Epilepticus Treatment Trial) study comparing valproic acid, levetiracetam, and fosphenytoin in benzodiazepine refractory status. ■

REFERENCES

1. Agarwal P, Kumar N, Chandra R, et al. Randomized study of intravenous valproate and phenytoin in status epilepticus. *Seizure* 2007;16:527-532.
2. Chakravarthi S, Goyal MK, Modi M, et al. Levetiracetam versus phenytoin in management of status epilepticus. *J Clin Neurosci* 2015;22: 959-963.
3. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med* 1998;339:792-798.
4. Sreenath TG, Gupta P, Sharma KK, Krishnamurthy S. Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: A randomized controlled trial. *Eur J Paediatr Neurol* 2010;14:162-168.
5. Mundlamuri RC, Sinha S, Subbakrishna DK, et al. Management of generalised convulsive status epilepticus (SE): A prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam – Pilot study. *Epilepsy Res* 2015;114:52-58.
6. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: A prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. *Neurology* 1988;38:202-207.
7. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: A pilot study. *Neurology* 2006;67:340-342.
8. Gilad R, Izkovitz N, Dabby R, et al. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs phenytoin. *Acta Neurol Scand* 2008;118:296-300.

ABSTRACT & COMMENTARY

Differences Between Type 1 and Type 2 Diabetic Neuropathy

By Russell L. Chin, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Chin reports no financial relationships relevant to this field of study.

SYNOPSIS: Microstructural nerve damage in distal symmetric diabetic neuropathy differs between subjects with type 1 diabetes (T1D) and type 2 diabetes (T2D). The predominant nerve lesions in T1D correlated with hyperglycemia and nerve conduction impairment, while the predominant lesions in T2D correlated with dyslipidemia.

SOURCE: Jende JME, Groener JB, Oikonomou D, et al. Diabetic neuropathy differs between type 1 and type 2 diabetes: Insights from magnetic resonance neurography. *Ann Neurol* 2018;83:588-598.

Diabetes mellitus, specifically type 2 diabetes (T2D), is the most common cause of neuropathy in the United States and Europe. Approximately half of all diabetic patients will develop some form of neuropathy during their lifetime. More than 20 million Americans currently have neuropathy secondary to either prediabetes, type 1 diabetes (T1D), or T2D, and the worldwide prevalence is expected to increase, particularly in countries adopting a more Western diet.[1]

Distal symmetric diabetic neuropathy (DPN) accounts for about 75% of diabetic neuropathies and is characterized by bilateral, symmetric damage to nerves of the feet in a "stocking" distribution with later involvement of hands and mild distal motor weakness. Neuropathic pain is a disabling consequence of DPN, affecting 25-50% of patients. Sensory symptoms include positive symptoms of pain, tingling, prickling sensations, altered sensation (such as allodynia or hyperalgesia), and negative symptoms of numbness.

The pathogenesis of DPN remains elusive, and, consequently, there are no approved disease-modifying therapies that unequivocally prevent or reverse the neuropathy. Vigilance about foot care and neuropathy development, lifestyle changes, and strict glycemic control are counseled. Symptoms are managed, often suboptimally, with pregabalin, duloxetine, and gabapentin. Medications that target ion channels that are more selectively expressed in nociceptors (e.g., Nav 1.7, 1.8, and 1.9) are under investigation.[1]

Research into the pathophysiology of DPN has evolved from a "glucocentric" viewpoint to a broader understanding that the DPN is a complex disorder secondary to multiple linked and cascading reactions. Inflammation, endothelial dysfunction, deposition of advanced glycation end products (AGE), microvascular-induced ischemia, increased aldose reductase activity, and oxidative stress are implicated in nerve damage. Research into whole nerve metabolism and insulin sensitivity and resistance (potentially at the level of the nervous system) also provide clues about the mechanism behind DPN in T2D.[2]

Rigorous glycemic control, while reducing the incidence of DPN in T1D, has little to no effect in the more common T2D, indicating different mechanisms underlying the DPN in each disorder. It is likely that components of the metabolic syndrome promote the onset and progression of DPN in T2D, as evidenced by the higher rates of dyslipidemia and obesity in T2D compared with T1D.[3,4]

In this study, 120 patients (35 with T1D and 85 with T2D), of whom 84 had DPN, were evaluated. Detailed medical history, clinical and electrodiagnostic findings, blood studies, and objective and subjective scoring data were obtained. High-resolution MR neurography of the right leg in a 3.0T magnetic resonance scanner was obtained. The earliest and most prominent nerve lesions in DPN have been reported to occur at the level of the distal sciatic nerve, so calculation of the T2-weighted hyperintense and hypointense lesions was performed for the sciatic nerve at the mid-thigh level. Both kinds of lesions were elevated in DPN and associated with an increased severity of clinical symptoms.

T2-weighted hypointense lesions appeared hyperintense on T1-weighted images, strongly suggesting a high lipid content. The lipid volume in these lesions was higher in T2D compared to T1D patients with and without DPN, and there was a positive correlation with neuropathy symptoms and triglyceride levels and a negative correlation with serum HDL levels. The authors hypothesized that these lesions might represent an imaging correlate of intraneural aggregates of lipids or microvascular lipid deposits inside the wall of perineural blood vessels.

However, T2-weighted hyperintense lesion load was higher in T1D compared with T2D, and there was a positive correlation with hemoglobin A1c level and impairment of nerve conductions. The authors hypothesized that these lesions represent an imaging correlate of AGEs in the extracellular matrix of myelinating cells.

■ COMMENTARY

MR neurography allows unprecedented in vivo evaluation of DPN, offsetting the limitations of human nerve accessibility and rodent models of DPN. The differing patterns of nerve damage described in this article provide additional evidence of the unique pathophysiologic mechanisms behind the two types of DPN and help explain the limited benefit of glycemic control in T2D DPN. An improved basic understanding of the disease process is crucial to clinical trials, which have been disappointing to date. Mechanism-based treatments are desperately needed for this global epidemic. ■

REFERENCES

1. Feldman EI, Nave KA, Jensen TS, Bennett DLH. New horizons in diabetic neuropathy: Mechanisms, bioenergetics, and pain. *Neuron* 2017;93:1296-1313.
2. Kobayashi M, Zochodne DW. Diabetic neuropathy and the sensory neuron: New aspects of pathogenesis and their treatment implications. *J Diabetes Investig* 2018;13: doi: 10.1111/jdi.12833.
3. Callaghan BC, Little AA, Feldman EL, Hughes RAC. Enhanced glucose control for preventing and treating diabetic neuropathy. *Cochrane Database Syst Rev* 2012;(6):CD007543.
4. Pop-Busui R, Boulton AJ, Feldman EL, et al. Diabetic neuropathy: A position statement by the American Diabetes Association. *Diabetes Care* 2017;40:136-154.

ABSTRACT & COMMENTARY

Sleep Habits and the Development of Dementia

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Segal reports no financial relationships relevant to this field of study.

SYNOPSIS: The relationship between quality of sleep and the development of dementia is controversial and not yet clearly elucidated nor understood.

SOURCE: Suh SW, Han JW, Lee JR, et al. Sleep and cognitive decline: A prospective nondemented elderly cohort study. *Ann Neurol* 2018;83:472-482.

Quality sleep is known to facilitate the consolidation of memory and enhance daytime cognitive function. Over the long term, sleep also may protect against the development of dementia. Restorative sleep, both stage three (slow-wave sleep) and rapid eye movement sleep, have been shown to reduce the deposition of amyloid beta (Aβ) in the brain and facilitate Aβ clearance. Sleep also has been shown to enhance the so-called "glymphatic" system of the brain, widening gap junctions and allowing drainage of metabolic toxins.

Most studies of sleep and cognition, including this work by Suh et al, rely on patient questionnaires rather than hard data from polysomnography. This introduces a significant degree of subjectivity into the analysis. Furthermore, it can be difficult to distinguish whether poor sleep is a cause or effect of cognitive decline (since effects may be "bidirectional"), and there may be pathological effects at the extremes of sleep, which may be protective in a more moderate range (with U- or J- shaped relationships). For example, exceedingly short or long sleep duration may both be more damaging than moderate sleep times, and such extremes of sleep duration may be more of an effect of dementia rather than a truly causal factor. Further ambiguity is created by the plethora of sleep-related variables used. These include latency to sleep onset (falling asleep), sleep disruption (poor sleep architecture or frequent waking after sleep onset), overall sleep duration (which does not itself account for fragmentation), advance or delay of sleep phase (so-called "night owls" or "larks"), use of hypnotics/other psychotropic medications, and a variety of other subjective patient perceptions of sleep quality.

Suh et al studied 2,238 Korean, non-demented individuals prior to the development of significant cognitive change. A smaller cohort of 655 subjects with mild cognitive impairment also was included. There was an association found between long sleep latency (> 30 minutes) and cognitive decline (odds ratio [OR], 1.4). Additionally, long sleep duration (> 8 hours) showed a similar risk for dementia (OR, 1.67), and there appeared to be a protective effect for subjects with an overall delay in their sleep phase. The odds of cognitive decline was 0.61 in subjects with a "mid-sleep" time later than 3 a.m. (having an overall sleep schedule generally later than 11 p.m. to 7 a.m.). Among the participants with established mild cognitive impairment, a proportion

(approximately 30%) reverted to "normal cognition" at four-year follow-up, but this was significantly less common among subjects with long sleep latency times.

■ COMMENTARY

These results, particularly those regarding long sleep latencies, can be considered a valuable supplement to the large existing literature exploring sleep and cognition. However, these findings conflict with large cross-sectional epidemiological analyses, which not only associate prolonged sleep latency with dementia, but also implicate a deleterious effect of truncated sleep duration. Suh et al found the opposite, with longer sleep times associated with cognitive decline. Additionally, because Suh's data are prospective, conclusions can be drawn regarding cause and effect relationships that cannot be drawn from other studies. Although prior studies have suggested an association between cognitive compromise and "advanced sleep phase" (with early bed and wake times), Suh's data suggested that this circadian shift may not be the result of dementia, but rather, may be a risk factor for dementia or at least a predictive, pre-existing condition. When studied prospectively, starting at a younger, normal cognitive state, "larks" appear more likely than "night owls" to subsequently develop cognitive impairment. ■

ABSTRACT & COMMENTARY

Rapid Screening for Future Risk of Parkinson's Disease Dementia

By Claire Henchcliffe, MD, PhD

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Dr. Henchcliffe reports she is a consultant for ACADIA Pharmaceuticals and US WorldMeds.

SYNOPSIS: The Montreal Parkinson Risk of Dementia Scale provides a simple eight-item screening tool with high predictive value for developing Parkinson's disease dementia.

SOURCE: Dawson BK, Fereshtehnejad SM, Anang JBM, et al. Office-based screening for dementia in Parkinson disease: The Montreal Parkinson Risk of Dementia Scale in four longitudinal cohorts. *JAMA Neurol* 2018; Mar 26. doi:10:1001/jamaneurol.2018.2054. [Epub ahead of print].

The Montreal Parkinson Risk of Dementia Scale (MoPaRDS) was developed based on predictors of developing dementia identified in a prospective study of individuals with Parkinson's disease (PD) in Montreal. The scale comprises eight items: age, sex, falls and/or freezing, bilateral symptom onset, history suggestive of REM sleep behavior disorder (RBD), visual hallucinations, orthostatic hypotension, and mild cognitive impairment. Dawson et al extracted MoPaRDS scores from four independent cohorts combined into three groups for analyses: 1) the original Montreal cohort with established PD (n = 80); 2) a combined group with established PD, comprising individuals recruited from two local PD clinical trials (n = 52) and a cohort from Tottori, Japan (n = 82); and 3) the Parkinson Progression Marker Initiative (PPMI) for individuals with PD diagnosed within two years and not yet taking medications (n = 393). Age at diagnosis was 66.0 ± 8.2 years (original), 68.5 ± 10.1 years (combined), and 61.3 ± 9.8 years (PPMI). All patients were free of dementia at baseline visits, although mild cognitive impairment was identified in 51% and 46.3% in the original and combined cohorts (results imputed for the Tottori cohort), and in 21.6% in PPMI. A greater percentage were younger than 70 years of age in the PPMI group than in the other groups. Additionally, fewer had features suggestive of RBD, hallucinations, orthostatic hypotension, presence of falls or freezing, or history of bilateral onset in PPMI when compared to the other groups. MoPaRDS scores were analyzed using the primary endpoint of dementia status at the subject's last office visit, judged by global cognitive decline to Mini-Mental Status Examination (MMSE) < 26, with impairment in > 1 cognitive domain resulting in significant impairment in activities of daily living (ADL). This endpoint was reached in 11.5% of all individuals (but only 3.3% in PPMI alone) over mean 4.4 ± 1.3 years (range, 1-8 years) follow-up. When stratified by MoPaRDS scores, the annual risk of dementia was 0.6% (score, 0-3), 5.8% (score, 4-5), and 14.9% (score, 6-8). Predictive validity, as examined by receiver operating characteristic (ROC) curves, was 0.879 (95% confidence interval [CI], 0.816-0.942), and the determined optimal cutoff score of at least 4 resulted in a positive predictive value of 43.9% (95% CI, 37.8-50.2) and negative predictive value of 96.7% (95% CI, 95.0-97.9).

■ COMMENTARY

Dementia is more common in PD patients than the general population and has a profound effect, not only on the patient's function, quality of life, and life expectancy, but also on the caregiver. It is a common cause

of placement in nursing homes, and treatment options are limited. It is critical that we better understand the nature of PD dementia and establish improved counseling and treatment pathways. A number of studies have determined various clinical and non-clinical risk factors for PD dementia, for example greater age, presence of hallucinations, or RBD. The MoPaRDS now may provide a step forward in combining a small number of easily assessed items. Its strength lies in its ease of administration and the simplicity of the data required to generate a MoPaRDS score. Several items can be simply extracted from the clinical chart, such as age, sex, and whether symptom onset was bilateral. Others either already may be obtained or could be added easily to a visit at intervals (for example, measuring orthostatic changes or recording items derived from the Movement Disorders Society Unified Parkinson Disease Rating Scale). Therefore, the resulting MoPaRDS score ultimately may be useful for rapid screening of future dementia risk in the clinic. It also is important that in the PPMI cohort, the baseline MoPaRDS score correlated with potential molecular biomarkers previously identified in cerebrospinal fluid: Ab42/tau and tau concentrations. However, it is too early to recommend routine use in the clinic. There was some variability between cohorts in how particular scores were collected, and certain results were imputed. The definition for the primary endpoint may have missed some cases of dementia. Moreover, the scale performed better in men than women, for unclear reasons. Overall, though, the MoPaRDS appears to be a highly promising approach that merits testing in larger cohorts, and once again serves to draw attention to a challenging feature in PD. ■

ABSTRACT & COMMENTARY

Opioids Not Better for Chronic Back Pain

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study.

SYNOPSIS: Chronic use of opioids for management of back pain is controversial and hotly debated. This randomized trial showed no benefit of opioids over multimodality non-opioid treatments, consistent with many other observational studies.

SOURCE: Krebs EE, Gravely M, Nugent S, et al. Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain. *JAMA* 2018;319:872-882.

Traditionally, chronic low back pain is treated with nonsteroidal anti-inflammatory agents, tricyclic antidepressants, antiepileptic drugs, and serotonin/norepinephrine reuptake inhibitors. Epidural steroid injections also may be offered, but long-term benefit, lasting six months or longer, is not appreciated. Opioids are often administered, but no randomized trials comparing opioids to placebo are available to evaluate opioid long-term effectiveness or safety. Are long-term opioids better than non-opioid medications in the management of moderate to severe chronic back pain?

To address this question, a 12-month, randomized trial with masked outcome assessment, the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial, was performed through 62 Minneapolis Veteran Affairs primary clinics from June 2013 to December 2016. Patients who, despite analgesic use, experienced chronic back pain or hip or knee osteoarthritic pain were included if they had moderate to severe pain nearly every day for at least six months or more, with moderate to severe pain defined as a score of ≥ 5 on the three-item pain intensity, interference with enjoyment of life, and interference with general activity (PEG) scale (range, 0 to 10). Patients already on long-term opioid therapy, or whose life expectancy was less than 12 months, were excluded. Both opioid and non-opioid medication groups followed a treatment strategy to improve pain and function in three steps. Immediate-release (IR) opioids were administered to the opioid group, starting with morphine IR, hydrocodone/acetaminophen, or oxycodone IR. Step 2 offered morphine sustained-action (SA) or oxycodone SA, and Step 3, transdermal fentanyl. For the non-opioid group, acetaminophen or a nonsteroidal anti-inflammatory drug was the first step, with adjuvant oral medications added as Step 2, including nortriptyline, amitriptyline, gabapentin, or topical analgesics (i.e., capsaicin, lidocaine), and Step 3 included drugs requiring prior VA clinic authorization, such as pregabalin, duloxetine, or tramadol. Medications in both groups were adjusted per individual patient response.

Pain-related function was the primary outcome measure, as measured by the seven-item Brief Pain Inventory (BPI) interference scale, whereas secondary outcome measures comprised several questionnaires, including, among others, the Veterans RAND 12-item Health Survey quality-of-life measure, the 11-item Roland-Morris Disability Questionnaire measure of pain-related physical function,

and the eight-Item Patient Health Questionnaire depression measure. Statistical analysis comprised the two-sided t tests and $\chi 2$ tests, with a P value < 0.05 considered statistically significant.

Among 275 patients enrolled, 240 were randomized, with excellent follow-up rates, 92% at three months, 97% at six months, 90% at nine months, and 98% at 12 months. Mean age was 58.3 years, 65% (n = 156) had back pain, 35% had hip or knee osteoarthritis pain, and 13% were women. No significant difference in pain-related function or health-related quality of life was found between the two groups over 12 months, whereas pain intensity was significantly better in the non-opioid group, and the opioid group had significantly more medication-related symptoms. Opioids are not superior to non-opioids for moderate to severe chronic back pain and their use cannot be supported.

■ COMMENTARY

Based on the National Health Statistics Report from the Centers for Disease Control and Prevention, low back pain is the most common condition for which patients seek complementary and alternative medicine care — and for good reason. Despite a 629% increase in Medicare expenditures for epidural steroid injections, a 423% increase in expenditures for opioids for back pain, a 307% increase in the number of lumbar magnetic resonance images among Medicare beneficiaries, and a 220% increase in spinal fusion surgery rates, no population-level improvements in patient outcomes, disability rates, or reduction in morbidity of low back pain have been appreciated. Alternative methods of alleviating chronic low back pain are needed, and limiting, if not eliminating, opioid use would seem to be a step in the right direction. ■

Neurology [ALERT®]

Stroke Alert

By Matthew E. Fink, MD

Postoperative Atrial Fibrillation After Coronary Artery Bypass Graft

SOURCE: Butt JH, Xian Y, Peterson ED, et al. Long-term thromboembolic risk in patients with postoperative atrial fibrillation after coronary artery bypass graft surgery and patients with nonvalvular atrial fibrillation. *JAMA Cardiol* 2018; Mar 28. doi:10.1001/jamacardio.2018.0405. [Epub ahead of print].

New onset of atrial fibrillation in the early postoperative period after coronary artery bypass graft (CABG) surgery is a common occurrence and is reported in between 11% and 40% of cases. The condition is thought to be transient and benign, but evidence is increasing that these patients face a greater risk of postoperative complications and prolonged hospital stay. In addition, it is unclear whether these patients should be treated with anticoagulant therapy in a similar fashion as patients who have nonvalvular atrial fibrillation that occurs spontaneously, and it is unclear what the long-term risk of stroke might be for these patients. Butt et al and other investigators in Denmark performed a retrospective cohort study to try and answer these questions.

The investigators retrieved data from a clinical cardiology surgery database and Danish nationwide registries to identify patients who underwent CABG surgery for the first time and developed atrial fibrillation in the postoperative period, from years 2000 through 2015. The patients were matched for age, sex, CHA_2DS_2–VASc score, and the year of diagnosis, to a group of patients who had nonsurgical, nonvalvular atrial fibrillation in a 1 to 4 ratio. The major outcomes and measures were 1) the proportion of patients initiating oral anticoagulant therapy within 30 days of hospital discharge, and 2) the rates of thromboembolism.

Investigators identified 2,108 patients who developed atrial fibrillation after CABG surgery, and they were matched with 8,432 patients with nonvalvular atrial fibrillation. In the total population, the median age was 69.2 (63.7-74.7) years, and 82.3% of patients were men. Oral anticoagulation was initiated 30 days postdischarge in 175 patients with postoperative atrial fibrillation (8.4%) and 3,549 patients with nonvalvular atrial fibrillation (42.9%). The risk of thromboembolism was significantly lower in the postoperative atrial fibrillation group than in the nonvalvular atrial fibrillation group (18.3 vs. 29.7 events per 1,000 patient-years; P < 0.001). Anticoagulation therapy during the follow-up was associated with a lower risk of thromboembolism in both groups of patients, compared with patients who did not receive any anticoagulant therapy. Overall, the risk of thromboembolism was not significantly higher in patients with postoperative atrial fibrillation compared with those who did not develop postoperative atrial fibrillation after CABG surgery.

The data from this study do not indicate that new-onset postoperative atrial fibrillation should be regarded as having the same risks as primary nonvalvular atrial fibrillation in terms of long-term thromboembolic risk, and that anticoagulation in this group may not be necessary unless the atrial fibrillation is persistent. ■

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CME QUESTIONS

1. **In the VA Cooperative Study, a statistically significant difference in aborting convulsive status epilepticus was noted with which agent?**
   a. Diazepam
   b. Phenobarbital
   c. Phenytoin and Diazepam
   d. Lorazepam

2. **Which of the following statements about distal symmetric diabetic neuropathy (DPN) is *false*?**
   a. MR neurography findings in DPN in type 1 diabetes were associated with elevated hemoglobin A1c and impaired nerve conduction studies.
   b. MR neurography findings in DPN in type 2 diabetes were associated with low HDL and high triglycerides.
   c. Approximately 50% of all diabetic patients will develop neuropathy during their lifetime.
   d. Strict glycemic control has a similar effect on the incidence of DPN in type 1 diabetes and type 2 diabetes.

3. **Which of the following statements regarding sleep habits and cognitive function is *false*?**
   a. Quality sleep at night enhances daytime cognitive function.
   b. Dementia causes disruption of normal sleep.
   c. Sleeping medication may aggravate dementia in elderly people.
   d. Poor sleep causes Alzheimer's disease.

4. **Which of the following risks of developing dementia in Parkinson's disease is *not* assessed by the Montreal Parkinson Risk of Dementia Scale score?**
   a. Orthostatic hypotension
   b. Age
   c. Cerebrospinal fluid total tau concentration
   d. Bilateral symptom onset

5. **For the treatment of chronic low back pain, randomized clinical trials have demonstrated that:**
   a. long-term opioids are of greater benefit than anti-epileptic drugs.
   b. opioids are more efficacious than nonsteroidal anti-inflammatory agents.
   c. Both a and b
   d. Neither a nor b

6. **New-onset postoperative atrial fibrillation after CABG surgery should be managed in the same way as spontaneous nonvalvular atrial fibrillation with antithrombotic therapy.**
   a. True
   b. False

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

[IN FUTURE ISSUES]

Update on Concussion