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EFFICACY OF COVID-19 BOOSTER

In Israel, full COVID-19 vaccination in more than half of the population was achieved by the end of March of 2021. The incidence of COVID-19 dropped from 900 cases per million per day in mid-January of 2021 to fewer than two cases per million per day by June of 2021. With the emergence of new variants, a BNT162b2 vaccine booster dose was introduced, initially to high-risk populations and then to persons 60 years of age or older by July 30, 2021. This study evaluated the efficacy of this booster.

Data were obtained from the Ministry of Health database. Subjects were 1,137,804 Israeli residents, 60 years of age or older, who had been fully vaccinated at least five months earlier. Data concerning vaccination dates, viral testing, and hospitalizations were recorded. Severe disease was defined as a resting respiratory rate of more than 30 breaths per minute and oxygen saturation less than 94% on room air, or ratio of partial pressure of arterial oxygen to fractional inspired oxygen of less than 300. The booster vaccination campaign began on July 30, 2021, ending on August 31, 2021.

The rate of confirmed infection was lower in the booster group than in the non-booster group by a factor of 11.3. The rate of severe illness was lower in the booster group than in the non-booster group by a factor of 19.5. The rate of confirmed infection at least 12 days after the booster was substantially lower than the rate four to six days after the booster at a factor of 5.4.

Conclusion: This Israeli study found that a booster dose of BNT162b2 vaccine significantly reduced the rates of both confirmed infection and severe illness among participants 60 years of age or older.

Bar-On, Y., et al. Protection of BNT162b2 Vaccine Booster against COVID 19 in Israel. **N Eng J Med** 2021, Sept 15; 10.1056/ NEJMoa2114255.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AFTER FRACTURE SURGERY

Previous studies have generated concern that nonsteroidal anti-inflammatory drugs (NSAIDS)/ cyclooxygenase (COX-2) inhibitors may increase the risk of bone union impairment after fracture repair. This study was designed to better understand the effect of these medications on the risk of nonunion or delayed union.

Subjects were patients undergoing surgical repair of a fracture between 1998 and 2018. Those who used NSAIDs/COX-2 inhibitors for up to three weeks postoperatively were matched to non-users. The primary outcome variable was nonunion/delayed union, six or more months after surgery. The secondary outcome was reoperation for nonunion/delayed union. Data were compared between those who did and those who did not use NSAID/COX-2s after surgery.

Data were analyzed for 3,264 patients in each group. Among these, 208 experienced nonunion or delayed union. In addition, 64 of the 208 underwent reoperation for a nonunion or delayed union.

The NSAID/COX-2 group had a lower hazard of nonunion as compared to the matched cohort (p=0.04). Adjusted multivariate analysis revealed the hazard ratio to be lower for the NSAID/COX-2 group, although this finding failed to reach statistical significance (HR, 0.73; p=0.068).

Conclusion: This large study of patients undergoing fracture repair found that the use of NSAIDs/COX-2 inhibitors for three weeks after surgery was not associated with an increased risk of a nonunion or delayed union at six or more months.

Kim, H., et al. Do Nonsteroidal Anti-Inflammatory or COX-2 Inhibitor Drugs Increase the Nonunion or Delayed Union Rates after Fracture Surgery? A Propensity Matched Study. **J Bone Joint Surg.** 2021, August 4; 103(15): 1402-1410.

CAPSAICIN FOR NON-FREEZING COLD INJURY

Different clinical injuries have been described among individuals exposed to cold temperatures, which depend on the rapidity, severity, and duration of the cold exposure. Non-freezing cold injury (NFCI), previously called trench foot, results from small fiber neuropathy and neuro- vascular changes, which may account for chronic pain and persistent cold hypersensitivity. As capsaicin has been shown to be effective in other chronic neuropathic conditions, this study investigated the use of this medication for the treatment of NFCI.

Subjects were 16 military personnel diagnosed with NFCI with a mean duration of 49 months since diagnosis. Those participants were exposed to 30 minutes of a capsaicin patch 8%, to the feet and distal calf. Before and after capsaicin treatment, pain symptoms were assessed using a pain diary, using the 11-point Numerical Pain Rating Scale (NPRS). Assessments also included skin biopsy, performed before and three months after treatment.

At three months a significant reduction in NPRS scores was noted for both spontaneous and cold-evoked pain. The mean differences in scores between baseline and three -month follow-up were -1.1 for spontaneous pain (p=0.006) and -1.2 (p=0.006) for cold-evoked pain. Histological analysis found that PGP9.5 sub-epidermal fibers (SENFs) were increased significantly after capsaicin 8% patch application ($p < 0.0001$), as were sub-epidermal nerve fibers positive for GAP43.

Conclusion: This non-controlled study of patients with non-freezing cold injury found that treatment with capsaicin 8% resulted in a significant decrease in both spontaneous pain and cold-evoked pain, as well as a regeneration and restoration of nerve fibers.

Anand, P., et al. Capsaicin, Eight Percent, Patch Treatment in Non-Freezing Cold Injury: Evidence for Pain Relief and Nerve Regeneration. **Front Neurol.** 2021, August; 12: 722 -875.

NONSTEROIDAL ANTI-INFLAMMATORY MEDICATIONS AFTER ROTATOR CUFF SURGERY

While nonsteroidal anti-inflammatory drugs (NSAIDs) are an accepted means of treating musculoskeletal-related pain, concern about their effect on postoperative healing has limited their use after surgery. This study was designed to better understand the effects of NSAIDs on outcomes after surgery for rotator cuff tears (RCTs).

This double-blind, randomized, placebo-controlled trial included adult patients with RCTs requiring orthoscopic repair. After surgery, the patients were randomized to receive either a placebo or ibuprofen 400 mg every eight hours for 14 days, with prn hydrocodone/acetaminophen (10 mg/325 mg) for breakthrough pain.

Outcome measures included ultrasound evaluation, visual analog scale (VAS) pain scores, shoulder range of motion, American Shoulder and Elbow Surgeons (ASES) scores, the 12-item Short Form Survey (SF-12), and the Disabilities of the Arm, Shoulder, and Hand (DASH) scores, collected up to one year after surgery.

Data were completed for 110 subjects with a mean age of 57.7 years. At one year, seven patients in the ibuprofen group and 13 in the placebo group experienced re-tears of the rotator cuff (p=0.20). The ibuprofen group required less opioid medication in the first week after surgery than did the placebo group (p=0.04).

Conclusion: This study of patients undergoing surgical repair of rotator cuff tears found that postoperative ibuprofen reduces opioid requirements and patient pain levels in the first week after surgery, with no evidence of an increased risk of tendon repair.

Tangtiphaiboontana, J. et al. The Effects of Nonsteroidal Anti-Inflammatory Medications after Rotator Cuff Surgery: Randomized, Double-Blind, Placebo-Controlled Trial. **J Should Elbow Surg.** 2021, Sept 1; 30: 1990-1997.

KINESIOTAPE IN PREGNANT WOMEN WITH SACROILIAC JOINT PAIN

The sacroiliac joint (SIJ) is a frequently neglect cause of low back and hip pain. The SIJ is an especially common cause of pain during pregnancy. This study examined the efficacy of kinesiotape on SIJ pain in pregnant women.

This randomized, clinical trial included 58, consecutive, pregnant women with low back pain. The women were randomly allocated to receive kinesiotape or sham kinesiotape. Both groups received instructions on exercises, including quadriceps stretching, hip abduction stretching, hip abductor isometric exercise and trunk rotation for sacroiliac pain. The participants were encouraged to exercise regularly during the course of the weekly kinesiotape applications. Kinesiotape was applied once a week for five weeks. In the sham group, kinesiotape was applied to the sacral iliac region without tension. Baseline measures included a visual analog scale (VAS) for pain, the Pelvic Girdle Questionnaire (PGQ), and the Rowland Morris Disability Questionnaire (RMDQ).

No significant differences were found between groups at baseline for scores on the VAS, RMDQ, or PGQ scores. At five weeks, the kinesiotape group had significantly improved on all parameters, with no such improvement in the sham group.

Conclusion: This randomized, controlled trial of pregnant women with sacroiliac joint pain found that kinesiotape for five weeks.

Ordahan, B., et al. Effectiveness of Kinesiotaping in Pregnant Women with Sacroiliac Joint Pain: A Randomized, Controlled Study. **Intern J Clin Pract**. 2021 Sep;75(9): e14432. doi: 10.1111/ijcp.14432.

RISK OF ACUTE STROKE AMONG PATIENTS WITH SEVERE COVID-19

Infection with severe COVID-19 has been linked to altered blood coagulability and an increased risk of thromboembolic complications. This study explored the association between a COVID-19 infection and acute stroke.

Subjects were adult patients with confirmed COVID-19, admitted to one of four participating hospitals. Data obtained included age, gender, and vascular comorbidities. The clinical

course of COVID-19 was followed using the classification by the National Health Commission guidelines on the diagnosis and treatment of COVID-19. The authors performed a systematic review of the literature to compile data from observational studies of acute stroke in COVID-19 patients.

The cohort consisted of 165 patients with confirmed COVID-19. Of these, seven experienced an acute ischemic stroke or transient ischemic attack (4.2%). In five of those seven (71.4%) patients, the index stroke was the primary reason for hospital admission, whereas two (28.6%) patients experienced an acute stroke following admission for COVID-19. A multivariable analysis revealed that admission to the intensive care unit was the only variable independently associated with acute stroke ($p = 0.05$).

Conclusion: This study found that among patients hospitalized for COVID-19, admission to the intensive care unit was the only independent variable related to the occurrence of an acute stroke.

Siepmann, T., et al. Increased Risk of Acute Stroke among Patients with Severe COVID-19: A Multicenter Study and Meta-analysis. **Euro J Neurol**. 2021; 28(1): 238-247.

SMOKING IN YOUNG STROKE PATIENTS

Recent studies of stroke have demonstrated a strong positive correlation between recanalization and tobacco abuse, indicating that thrombolytic therapy acts more effectively in smokers. This phenomenon is referred to as Smokers' Paradox. This study evaluated the effect of smoking status on stroke outcomes in young stroke patients.

Data were obtained from the Taiwan Stroke Registry program, which started in 2006. This program enrolled patients,20 to 50 years of age, presenting to the hospital with a stroke. A smoker was defined as one who had been actively smoking tobacco, more than one cigarette per day, for more than six months at the time of the stroke. Those who had stopped smoking more than two years before the stroke were excluded. The participants were assessed with the National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) scores. Mortality and functional outcome were compared at three months between smokers and nonsmokers.

Data were reviewed for 4,303 smokers and 4,784 nonsmokers. At three months, the overall mortality rates per 1,000 person-days were 0.53 in the nonsmoking group and 0.5 in the smoking group (adjusted HR 0.89). While not reaching statistical significance, greater mortality was found for nonsmokers among those with ischemic infarcts and transient ischemic attacks. Conversely, greater mortality was found in the smoking group among those with intracerebral hemorrhage and subarachnoid hemorrhage, although this finding did not reach statistical significance. Multivariate analysis found no significant association between smoking categories and mortality at three months.

Conclusion: This study of patients 20 to 50 years of age, hospitalized for a cerebrovascular accident or transient ischemic attack, found no significant difference in mortality at three months between smokers and nonsmokers.

Liang, C., et al. Smoking Status and Functional Outcomes in Young Stroke. **Front Neurol**. 2021, September; 12: 658582.

DIRECT TO ANGIOGRAPHY FOR ACUTE STROKE

Endovascular treatment has become the standard of care for acute ischemic stroke due to large vessel occlusion. The time from symptom onset to reperfusion is a strong indicator of clinical outcome. Despite efforts to reduce the time from emergency department admission to artery puncture [door to puncture (DTP) time], clinical trials have shown difficulties in decreasing this time to a target time of below 60 minutes. This study assessed the clinical efficacy of direct transfer to the angiography suite (DTAS) for patients presenting with a large vessel occlusion (LVO).

The ANGIOCAT trial was a prospective, open, randomized, clinical trial of patients with an LVO. At emergency room arrival, the participants were randomized to a DTAS group or routine treatment involving direct transfer to CT scan (DTCT). For the DTAS group, a flat panel computed tomography (FPCT) was performed to exclude ICH or large established ischemic lesions that would contraindicate EVT. A diagnostic angiogram was obtained to confirm the presence of LVO. The primary outcome measure was the modified Ranking Scale (mRS) score at 90 days.

Data were analyzed for 174 patients with a mean age of 73.4 years and a median NIHSS admission score of 18. The door to perfusion times were 57 minutes in the DTAS group and 84 minutes in the DTCT group ($p<0.001$). In the modified intention-to-treat population, EVT was performed for 100% of the patients in the DTAS group and 87.7% in the DTCT group ($p=0.002$). Compared with the DTAS group, the DTCT group was more likely to have a one-point improvement on the mRS ($p=0.09$).

Conclusion: This study found that, for patients with large vessel occlusion admitted within six hours of symptom onset, a workflow involving direct to angiography increased the likelihood of, and reduced the time to reperfusion, resulting in better functional outcomes at 90 days.

Requena, M., et al., Direct to Angiography Suite without Stopping for Computed Tomography Imaging for Patients with Acute Stroke. Randomized, Clinical Trial. **JAMA Neurol**. 2021, September;78(9):1099 -1107.

URINE METABOLOMICS AFTER CONCUSSION

The Centers for Disease Control and Prevention estimates that 3.8 million sports-related concussions (SRCs) occur each year in the United States. Using metabolomics (the systematic study of chemical metabolites found in tissues and biofluids as the result of various biochemical reactions), this study investigated changes from baseline in the urinary metabolome of male winter sports athletes with an SRC.

Subjects were 423 Canadian athletes participating in the WinSport Concussion Clinic from August of 2015 to 2016. At baseline, urine samples were collected for a ^{1}H NMR metabolomic urinary analysis. In addition, a detailed physical examination was completed, including the Sport Concussion Assessment Tool-3 (SCAT3).

Those diagnosed with an SRC underwent a repeat SCAT3 and provided a urine sample 24 to 72 hours post-injury. Symptoms and symptom severity were assessed and the number of days to return to play (RTP) was recorded. The urine underwent ^{1}H NMR metabolomic urinary analysis.

Urinary analysis revealed 18 features which separated pre- versus post-concussive samples. A significant, positive relationship was found between the post-SRC concentrations of 2-hydroxybutyrate and the time to return to play ($p=0.02$). A significant relationship was also seen between the number of symptoms and the post-SRC normalized concentration of lactose ($p=0.036$).

Conclusion: This study of Canadian athletes found that ^{1}H NMR metabolomic urinary analysis can correctly classify sports-related concussions, with an accuracy of 81.6%.

Wanner, Z., et al. Alterations in Urine Metabolites following Sport-Related Concussion: A ^{1}H NMR-Based Analysis. **Front Neurol.** 2021, August; 12: https://doi.org/10.3389/fneur.2021.645829.

NEUTROPHIL TO LYMPHOCYTE RATIO FOLLOWING MILD HEAD INJURY

Among patients with mild to moderate traumatic brain injury (TBI), the activation of inflammatory mechanisms is thought to be one of the primary pathologic pathways leading to secondary brain injury. This study assessed the effect of the neutrophil to lymphocyte ratio (NLR) for the early prediction of delayed neurologic impairment in patients with mild to moderate head injury.

This retrospective review included all patients referred to a Level I Trauma Center with brain contusion and a Glasgow Coma Scale score of 10 or greater at presentation. For each patient, potential predictors of adverse outcomes were collected from the medical record, including the neutrophil to lymphocyte ratio and the presence of anemia, hyponatremia, hyperglycemia, and/or hypoglycemia. The primary outcome variable was a delayed clinical deterioration (DCD) within five days, defined as a Glasgow Coma Scale (GCS) score of less than 10 and/or the need for mechanical ventilation.

Among the 115 patients studied, 16 had DCD. The NLR was higher among those with DCD than among those without. An NLR of above 15 was independently associated with the occurrence of DCD, with an odds ratio of 10.1. The only other factor significantly associated with the primary outcome was a CT finding of a cerebral contusion of over 30 mm on the admission CT, with an odds ratio of 7.2.

Conclusion: This study of patients seen in the emergency department for traumatic brain injury found that the neutrophil to lymphocyte ratio at admission is an independent indicator of delayed clinical deterioration among patients with a Glasgow Coma Scale score of 10 or more.

LeBail, A., et al. Ability of Neutrophil to Lymphocyte Ratio to Predict Secondary Neurologic Impairment in Patients with Mild to Moderate Head Injury. A Retrospective Study. **Am J Emerg Med.** 2021, December; 50: 46-50.

ONE YEAR OUTCOMES AFTER MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) represents a major cause of both morbidity and mortality. This study was designed to better understand the trajectory and outcome of patients with moderate to severe TBI at one year.

The Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study was completed at 18 level I trauma centers in the United States. Patients were assessed at two weeks and then at three, six and 12 months. The primary outcome measures were the Glasgow Outcome Scale-Extended (GOS-E) and the Disability Rating Scale (DRS). A favorable outcome was defined as a GOS-E score of four to eight, suggesting independence at home, although the patient might still require assistance for activities outside the home.

Data were analyzed for 484 patients, including 362 with severe TBI and 122 with moderate TBI. Of these, 60.2% received inpatient rehabilitation. At two weeks post-injury, 12.4% of those with severe TBI and 41% of those with moderate TBI experienced favorable outcomes. By 12 months, 52.4% of those with severe TBI and 75% of those with moderate TBI achieved favorable outcomes. No disability was reported at 12 months in 19.3 % of those with severe TBI and 32% of those with moderate TBI.

Conclusion: This prospective study of patients hospitalized for a traumatic brain injury found that, at 12 months, a favorable outcome occurred in 52.4% of those with severe, and 75% of those with moderate, traumatic brain injury.

McCrea, M., et al. Functional Outcomes over the First Year after Moderate to Severe Traumatic Brain Injury in the Prospective, Longitudinal TRACK-TBI Study. **JAMA Neurol.** 2021, August 1; 78 (8): 982-992.

BIOMARKERS FOR CENTRAL NERVOUS SYSTEM INJURY

Since the onset of the COVID- 19, several neurologic complications have been described. Recent neurochemical evidence suggests an acute central nervous system injury in some patients with COVID-19, shown in the form of increased plasma levels of neurofilament light chain (NfL) proteins. This study reviewed the results of cerebral spinal fluid analysis in patients with COVID- 19, describing clinical characteristics associated with CSF findings.

This prospective, single center study included patients with confirmed COVID-19 and at least one new onset neurologic symptom. A neurologic evaluation was completed for each patient documenting the worst time point during the disease before a lumbar puncture (LP) and at the time of the LP. In patients for whom there was no strong indication for LP, the procedure was optional.

The National Institutes of Health's COVID-19 severity grading was used to classify patients as mild, moderate, severe, or critical. An LP was completed to analyze NFL protein, glial fibrillary acidic protein (GFAp) and total tau (T-tau). Autoantibodies in CSF and serum (NMDAR, LGI1, CASPR2, GABAB1R, GABAB2R, AMPA1, AMPA2, Ri, Yo, Ma2, CV2, Hu, and amphiphysin) were analyzed using a commercial assay.

Subjects were 19 patients with COVID-19, with a median of 23 days between the onset of symptoms and LP. The most common neurologic symptoms were altered mental status (43%) and headaches (43%), followed by peripheral weakness (33%). Neuronal autoantibody testing was negative in all patients. Increased CSF levels of NfL protein, T-tau and GFAp were seen in 63%, 37% and 16% of patients, respectively. Increased NfL protein correlated with disease severity, time in intensive care and level of consciousness.

Conclusion: This small study found that cerebral spinal fluid levels of NfL protein, GFAp, and total tau are often elevated in COVID-19 patients with neurological symptoms.

Virhammar, J., et al., Biomarkers for Central Nervous System Injury in Cerebral Spinal Fluid are Elevated in COVID-19 and Associated with Neurological Symptoms and Disease Severity. **Euro J Neurol.** 2021, October; 28(10): 3324-3331.

SALT SUBSTITUTION AND CARDIOVASCULAR EVENTS

Elevated dietary sodium consumption is associated with high blood pressure and an increased risk of cardiovascular disease and premature death. The Salt Substitute and Stroke Study (SSaSS) was designed to define the overall balance of benefits and risks of salt substitute (SS), as compared to regular salt, concerning cardiovascular events death, and clinical hyperkalemia.

This open-label, cluster-randomized trial was conducted in 600 villages in rural China. Participants were adults, 60 years of age or older, who had a history of stroke and poorly controlled blood pressure. The control villages continued to use regular salt. The villages randomized to the SS group used a substitute containing 75% sodium chloride and 25% potassium chloride by mass. Regular salt was 100% sodium chloride. The primary outcome variable was a stroke, with secondary outcomes including major adverse cardiovascular events and death from any cause.

Data were collected for 20,995 persons, with a mean age of 65.4 years. The rates of stroke in the SS group were 29.14 events per 1,000 person-years, while that in the control (salt) group was 33.65 events per 1,000 person-years (p=0.006). The rates of major cardiovascular events and death were also worse in the salt group than in the SS group (p<0.001 for both).

Conclusion: This prospective study of patients with a history of stroke or who were 60 years of age or older, with poorly controlled hypertension found that the rates of stroke and major cardiovascular events were lower among those who used a salt substitute instead of regular salt.

Neal, B., et al. Effect of Salt Substitution on Cardiovascular Events and Death. **N Eng J Med.** 2021, September 16; 385 (12): 1067-1077.

DIETARY PATTERNS AND MORTALITY

A clear relationship has been established between certain dietary habits and health. This literature review was designed to better understand the relationship between dietary patterns and all-cause mortality (ACM).

A literature search was conducted for studies of dietary patterns and health outcomes. From this review, 152 observational studies and one randomized, controlled trial (RCT) were chosen for review. In the RCT, participants at high-risk for cardiovascular disease (CVD) were randomized to a Mediterranean diet with extra-virgin olive oil (or mixed nuts) or to a control diet. Both the nut and the olive oil Mediterranean diets resulted in a significant reduction in the risk of ACM, as compared to the control condition.

In the observational studies, all 12 studies that examined Dietary Approaches to Stop Hypertension (DASH) diet scores found that a higher adherence to the DASH diet was associated with lower risk of ACM. The 44 articles that examined a Mediterranean-type index or score suggested that higher adherence was associated with lower risk of ACM. Foods associated with a higher risk of ACM included beef, pork, sausage, red meat, processed meats, and high -fat dairy products.

Conclusion: This literature review found that dietary patterns associated with a lower risk of all-cause mortality were consistently characterized by a higher intake of vegetables, legumes, fruits, nuts, fish, non-refined grains, cereals and unsaturated vegetable oils, as well as a lower consumption of red meat, processed meat, and high-fat dairy products.

English L., et al. Evaluation of Dietary Patterns and All-Cause Mortality: A Systematic Review. **JAMA Net Open.** 2021, August; 4(8): e2122277. doi:10.1001/ jamanetworkopen.2021.22277.

BOLUS EPINEPHRINE FOR HYPOTENSION

Hypotension has been associated with significant morbidity and mortality. In many situations, a fluid bolus is not an option during symptomatic hypotension. Vasopressors are not routinely provided outside of acute hospital settings. This study evaluated the effect of IV epinephrine for patients with symptomatic hypotension.

This retrospective chart review evaluated adult patients presenting to the emergency department of a Level I Trauma Center over a period of four years. Data were included for those administered one 10mL syringe of a 10 µg/mL epinephrine solution by Emergency Management System (EMS) personnel before hospital arrival. The primary outcome was the change in systolic blood pressure after administration of the medication.

Data were collected for 55 patients who received 96 doses of IV epinephrine. The primary diagnosis of most patients was cardiac arrest with the majority noted to be unresponsive upon EMS arrival. The most common individual dose was 10 µg. The median increase in systolic blood pressure was 14 mmHg and the mean increase in diastolic blood pressure was 13 mmHg. No significant change was found in the median heart rate. Those who received an epinephrine dose of greater than 10 µg had a significantly greater median increase in the SBP compared to those received less than 0.2 µg /kg.

Conclusion: This study of patients with hypotension found that a bolus of epinephrine could effectively raise blood pressure without increasing heart rate.

Weant, K. et al., Efficacy of Bolus-Dose Epinephrine to Manage Hypotension in the Prehospital Setting. **Am J Emerg Med**. 2021, July; 50:71-75.

VITAMIN D AND MIGRAINES

Current pharmacological treatments for migraine demonstrate limited efficacy in some patients and have adverse effects in others. Some studies have suggested that vitamin D may be an effective component of migraine intervention. This literature review and meta-analysis explored the impact of vitamin D treatment in patients with migraines.

A review of the medical literature was completed for studies of patients with migraine headaches that reviewed the effect of vitamin D on the number of headache attacks per month. From the search, six, randomized, controlled trials were included in the meta-analysis, all published between 2015 and 2019. Vitamin D was administered in doses from 7,000 international units per week, with treatment duration ranging from 10 to 24 weeks.

A negative correlation was found between serum vitamin D concentration and recency of migraine headaches. Of the 101 subjects, those with vitamin D supplementation had fewer headaches per month than those in the placebo group ($p<0.00001$). Vitamin D supplementation had no effect on the duration or severity of migraine headaches when they occurred.

Conclusion This Meta-analysis suggests that Vitamin D supplementation may reduce the frequency of migraine headaches per month.

Hu, H. et al., Vitamin D Supplementation for the Treatment of Migraine: A Meta-analysis of Randomized, Controlled Studies. **Amer J Emerg Med.** doi.org/10.1016/j.ajem.2021.07.062.

COMBINATION THERAPY IN SPINAL MUSCLE ATROPHY TYPE I

Nusinersen, onasemnogene abeparvovec-xioi (onasemnogene), and risdiplam (oral) are currently approved by the United States Federal Drug Administration (FDA) for the treatment of spinal muscular atrophy (SMA). This retrospective case series examined the outcomes of four children with SMA1, treated with a combination of these medications.

The subjects were four children with SMA type I. Patient one received onasemnogene one month following SMA diagnosis and was subsequently placed on nusinersen therapy. Patient two received onasemnogene at the time of SMA diagnosis, with risdiplam therapy initiated five months later. Patient three received onasemnogene at the time of SMA diagnosis, followed by risdiplam seven months later. Finally, patient four received nusinersen two months after the SMA diagnosis and received an onasemnogene infusion four months after his last nusinersen dose.

Patient one improved with nusinersen but plateaued and was switched to risdiplam therapy four months after the last nusinersen dose. Patient two experienced improved motor activity and strength in the upper and lower extremities two months following risdiplam therapy and was able to roll and sit without assistance. Patient three was able to sit unassisted and swallow small amounts of liquids six months after risdiplam therapy. Patient four experienced fatigue, decreased strength, and increased respiratory secretions within two weeks of starting risdiplam. His symptoms of fatigue and decreased muscle activity resolved within one month. However, his congestion persisted.

Conclusion: This study of patients with SMA type I demonstrates that a therapy strategy involving both onasemnogene and risdiplam may be more beneficial than either medication alone.

Oechsel, K., et al., Combination Therapy with Onasemnogene and Risdiplam in Spinal Muscular Atrophy Type 1. **Muscle Nerve.** 2021, October: 64 (4): 487-490.

ESTROGEN RECEPTORS IN KNEE CARTILAGE

It is well known that women are at a higher risk of developing hip and knee osteoarthritis (OA). This study assessed the presence of estrogen receptor alpha (ER- α) in articular cartilage and its association with the severity of osteoarthritis (OA).

This prospective, single institution, controlled cohort study included adult women scheduled for primary knee anterior cruciate ligament reconstruction for acute ACL tears (controls) or primary total knee arthroplasty (TKA) for severe OA. At enrollment, the patients completed the Knee Injury and Osteoarthritis Outcome Score questionnaire (KOOS) and the Original Patient Questionnaire, consisting of demographics, medications, history of menarche, menopausal status, use of hormone replacement therapy and history of OA and joint disease. On the day of surgery, blood samples were taken for estradiol analysis, and cartilage samples were obtained for immunohistochemistry analysis to assess for ER-α.

The immunohistochemical assessment found that the ER-α expression in normal and reactive chondrocytes was 57.9 and 80.8, respectively, in the OA subjects, and 23.3 and 10, respectively, in the ACL subjects ($p=0.006$ and $p=0.0002$). Radiographic OA severity was significantly related to age, body mass index and percentage of reactive chondrocytes positive for ER - α. Plasma estradiol levels were higher in the ACL than in the OA group ($p=0.045$), and positively related to age and percentage of reactive chondrocytes staining positive for ER- α.

Conclusion: This study found that ER-α activity, proliferative/ reactive cells and decreased plasma estradiol levels are linked to increasing OA severity.

Hughbanks, M. et al., Estrogen Receptor Alpha and Human Knee Articular Cartilage of Healthy and Osteoarthritic Females. **J. Ortho.** 2021, September-October; 27: 1-8.

COVID-19 AND FEMUR FRACTURE

During the COVID–19 pandemic, the medical systems of the world were forced to reallocate resources and to alter procedures. This study analyzed the perioperative complication rate, including the mortality rate, of patients with fractures to the neck of the femur who presented during the COVID-19 pandemic.

This single-center, cross-sectional study analyzed a consecutive series of neck of femur fracture patients who required surgical repair between March 1, 2020, and May 15, 2020. These patients were compared to those treated during the same period in 2019, before the onset of the pandemic. Data were recorded for the operative procedure, complications, medical comorbidities, and demographics.

Comparing surgical information and hospital quality measures, delayed surgery was noted in 25% of the pandemic group and 11.8% of the control group ($p<0.001$). The perioperative complication rates were 31.2% in the control group and 29.3% in the pandemic group. The 30-day mortality rates were 13.5% in the pandemic group and 4.2% in the control group ($p=0.039$). During the pandemic, 71.4% of those who tested positive for COVID–19 experienced postoperative complications, as compared with 25.9% of the COVID-negative group ($p=0.021$).

Conclusion: This study of patients undergoing surgical repair of a femoral neck fracture found that, during the COVID-19 pandemic, delayed surgery occurred more often, and the 30-day mortality rate was higher, as compared with one year earlier.

Lim, J., et al. The Impact of COVID-19 on Neck of Femur Fracture Care: A Major Trauma Center Experience, United Kingdom. **Arch Bone Joint Surg.** 2021, July; 9(4): 453-460.

ULTRASOUND-GUIDED THORACIC PARAVERTEBRAL BLOCK FOR MASTECTOMY

Breast cancer surgery is frequently associated with moderate to severe postoperative pain. This study assessed the efficacy of a thoracic paravertebral block (TPVB) on the quality of recovery after a modified radical mastectomy.

This prospective, randomized, double-blind, clinical trial included patients 18 to 60 years of age scheduled to undergo a unilateral modified radical mastectomy. The participants were randomized to receive preoperative TPVB with 20 mL of 0.5% ropivacaine (TPVB) or 0.9% saline (a control condition). The intervention was performed 30 minutes before the induction of anesthesia. The primary outcome variable was quality of recovery 24 hours postoperatively using the Chinese version of the QoR-40 questionnaire, with scores ranging from 40 (poor quality) to 200 (excellent quality).

The median global QoR-40 scores at 24 hours were 161 in the control group and 173 in the treatment group ($p<0.001$). Pain at 12 hours was significantly less in the treatment group than in the control group ($p<0.001$). The median times to first rescue analgesia after surgery were 9.7 hours in the TPVB group and 1.7 hours in the control group ($p<0.001$).

Conclusion: This randomized trial involving adult Chinese women undergoing modified radical mastectomy found that a thoracic paravertebral block before surgery improved the global quality of recovery scores at 24 hours.

Rao, F., et al., Ultrasound-Guided Thoracic Paravertebral Block Enhances the Quality of Recovery after Modified Radical Mastectomy: Randomized, Controlled Trial. **J Pain Res.** 2021, Aug; 14: 2563-2570.

TRANSCRANIAL DIRECT CURRENT STIMULATION PLUS AEROBIC EXERCISE FOR PAIN

Aerobic exercise (AE) is among the treatments recommended for chronic pain. However, patients with chronic pain often report a decreased tolerance for this exercise. As transcranial direct current stimulation (tDCS) has been shown to provide analgesic benefits for a wide variety of painful conditions, this study examined the analgesic effects of combining AE and tDCS.

This single center, cross-over design study included ten, healthy adults, randomly exposed to 20-minute sessions involving tDCS, AE or tDCS+AE. In the tDCS condition, stimulation was performed 2 mA for 20 minutes. For sham tDCS, stimulation was stopped after 30 seconds. For the AE condition, exercise intensity was set at a Borg scale of 11 to 13. Pain was measured using the pressure pain threshold (PPT).

The change of the PPT (PPTΔ) at each time point was obtained using the PPT presession as a reference. As peak alpha frequency (PAF) on electroencephalography (EEG) is associated with pain, the PAF was measured during the protocols. Mood was assessed using the Profile of Mood States-Brief (POMS-B), which is a shortened version of the original 65-item POMS.

The combined tDCS+AE group experienced an 83% increase (improved) PPTΔ. The PPTΔ was improved more in the tDCS+AE condition than in the other conditions ($p=0.02$). In addition, the analgesic effect was of greater duration in the tDCS+AE condition than in either of the others. A mood state improvement was observed in all sessions. Significant differences in PAF were found in the occipital area between the Sham tDCS/AE and tDCS/AE sessions.

Conclusion: This study found that aerobic exercise combined with transcranial direct current stimulation can provide better analgesia than either alone.

Sato, G., et al. Effect of Transcranial Direct Current Stimulation Combined with Aerobic Exercise on Pain Thresholds and Electroencephalography in Healthy Adults. **Pain Med.** 2021, September; 22(9): 2057-2067.

NERVE TRANSFER FOR FOOT DROP SECONDARY TO PERONEAL NERVE INJURY

For patients with foot drop due to peroneal nerve injury, treatment options have included ankle-foot orthoses or anterior transfer of the tibialis posterior tendon. This study assessed the efficacy of a novel nerve transfer technique for patients with foot drop of six months or longer.

Subjects were 31 patients with neurologic foot drop resulting from an isolated injury to the common peroneal nerve, occurring six to 12 months prior. During surgery, the motor branch fascicles to the lateral head of the gastrocnemius and the flexor digitorum longus/flexor hallicus longus muscles were sutured to the deep peroneal nerve. The knee was immobilized for one month, after which a foot drop orthosis was used until active ankle dorsiflexion commenced.

The participants were followed monthly for a minimum of one year with assessments of motor power of the tibialis anterior (TA), gastroc-soleus, flexor hallucis longus, and flexor digitorum longus. A primary outcome was motor recovery measured by the British Medical Research Council (MRC) scale (1-5) of the tibialis anterior (TA), extensor hallucis longus (EHL), extensor digitorum longus (EDL).

At one-year, antigravity strength was achieved in the TA by 48.4%, in the EHL by 41.9%, and in the EDL by 38.7% of the patients. Only two patients reported weak toe plantar flexion. At one year, 32% of the subjects failed to restore ankle dorsiflexion.

Conclusion: This study of patients with a peroneal injury resulting in foot drop found that double nerve transfer could produce antigravity dorsiflexion in over half of the patients.

El-Taher, M., Foot Reanimation Using Double Nerve Transferred to Deep Peroneal Nerve: A Novel Technique for Treatment of Neurologic Foot Drop. **Foot Ankle Int.** 2021, August; 42 (8): 1011-1021.

COMPUTED TOMOGRAPHY AND ADVERSE OUTCOMES AFTER MILD TRAUMATIC BRAIN INJURY

After a traumatic brain injury (TBI), computed tomography (CT) is a common early test. This study explored the implication of specific lesions on one-year functional outcomes. Data were included from two, large, prospective studies.

The Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study enrolled patients with TBI who presented to the emergency departments at one of 18 United States level I trauma centers. The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study included data from 55 trauma centers in Europe. Data were examined for adult patients with Glasgow Coma Scale (GCS) scores of 13 to 15 upon

(Continued from page 2)

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emergency department arrival. The initial CT results were compared to scores on the Glasgow Outcome Scale-Extended (GOSE) at up to 12 months post-injury.

Data were completed for 1,935 patients in the TRACK-TBI study and 2,594 in the CENTER-TBI study. Contusion, subarachnoid hemorrhage, and/or subdural hematoma were associated with incomplete recovery (GOSE<8), with odds ratios (ORs) of 1.8 in the TRACK-TBI study and 2.73 in the CENTER-TBI study. Epidural hematoma had no such association. Intraventricular and/or petechial hemorrhage was associated with a greater number of unfavorable outcomes at one year (OR 3.47; TRACK-TBI).

Conclusion: This study of patients hospitalized for mild traumatic brain injury found that different pathological CT findings at admission carry different prognostic implications at one-year post-injury.

Yuh, E., et al. Pathological Computed Tomography Features Associated with Adverse Outcomes after Mild Traumatic Brain Injury. A TRACK-TBI Study with External Validation in Center-TBI. **JAMA Neurol.** 2021, September; 78(9): 1-12.

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