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VAGUS NERVE STIMULATION FOR UPPER EXTREMITY PARESIS

Data have shown that adults with stroke have the capacity to improve motor function several months to years after stroke. As the vagus nerves activate the ascending neuromodulator network, releasing plasticity-promoting neuromodulators, vagus nerve stimulation (VNS) has been viewed as potential adjunct to traditional therapy. This study of patients with chronic stroke, evaluated the effect of VNS, added to a home-based treatment of upper limb impairment.

All subjects had a history of unilateral supratentorial ischemic stroke, occurring four months to five years before randomization. Eligible patients scored 20 -50 on the Fugl-Meyer Assessment-Upper Extremity (FMA-UE). After implantation of the VNS device the subjects were randomized to either active or sham VNS, accompanied by six weeks of intensive rehabilitation.

Each rehabilitation program was provided by a blinded therapist who provided detailed instructions for home exercise. At six weeks, the control group crossed over to receive six weeks of active VNS with home therapy. Data included the FMA-UE, the Wolf Motor Function Test, the Box and Block Test, the Nine-Hole Peg Test, the Stroke Impact Scale and the Motor Activity Log.

At one year, 73% of the participants demonstrated clinically meaningful improvement in FMA-UE. No comparison was made between the sham group and the VNS group at six weeks. No significant adverse effects were noted.

Conclusion: This study of patients with chronic stroke demonstrated that home-based vagus nerve stimulation, combined with rehabilitation therapy, is feasible, with clinically significant improvement in upper extremity function found in over 70% of the subjects.

Dawson, J., et al. Vagus Nerve Stimulation Paired with Upper Limb Rehabilitation after Stroke: One-Year Follow-Up. **Neurorehab Neural Repair.** 2020, July; 34(7): 609-615.

IN-HOSPITAL ISCHEMIC STROKE

Of all acute ischemic strokes (AISs), up to 10% occur during hospitalization. These in-hospital strokes (IHSs) are often associated with more severe clinical syndromes and higher rates of poor functional outcome and in-hospital mortality. This study examined the temporal trends in the use of intravenous thrombolysis (IVT) and endovascular (EVT) reperfusion therapies for the treatment of patients with IHS.

Using the American Heart Association's Get with Guidelines-Stroke Registry, data were reviewed for patients 18 years of age or older seen for an AIS between January of 2008 and September of 2018. Data were collected for patients with IHS or out-of-hospital ischemic stroke (OHS) onset who were treated with either IVT or EVT. The primary outcome variables were time intervals to cranial imaging, IVT and EVT. For the OHS group the index time was the time at presentation to the emergency department. For the IHS group, the index time was the time at symptom recognition. Secondary outcomes included rates of IVT within 60 minutes, EVT within 120 minutes, in-hospital mortality, symptomatic intracranial hemorrhage, discharge destination and functional outcome.

Data were reviewed for 2,237,793 patients with AIS, of whom three percent had IHS. Compared to the OHS group, those with IHS had a longer median time to cranial imaging (p<0.001) to IVT bolus (p<0.001), and were less likely to be treated with IVT within 60 minutes (p<0.001), or 120 minutes of the index time (p< 0.001). In addition, those with IHS were less likely to ambulate independently at discharge (p<0.001) and were more likely to die or to be discharged to hospice (p<0.001).

Conclusion: This study of patients with acute ischemic stroke found that, compared to those with out-of-hospital stroke, those with in-hospital onset had longer delays for reperfusion and experienced worse functional outcomes.

Akbik, F., et al. Trends in Reperfusion Therapy for In-Hospital Ischemic Stroke in the Endovascular Therapy Era. **JAMA Neur**. 2020, September 21: doi:10.1001/jamaneurol.2020.3362

C-REACTIVE PROTEIN AS A MEASURE FOR POST-OPERATIVE PAIN

Levels of C-reactive protein (CRP) are commonly used following large joint arthroplasty to monitor infectious complications. As pain is associated with inflammation, this study assessed the relationship between CRP levels and post-operative pain.

This single-center, prospective, cohort study included female patients undergoing a primary total knee arthroplasty (TKA). All underwent the same surgical procedure. Pain was assessed with a visual analogue scale (VAS) before surgery, four to six hours after surgery and on the morning after surgery. Blood was drawn to determine CRP levels before and after surgery.

CRP was associated with pain severity during movement, at four to six hours post-surgery (p<0.001), as well as on the morning after surgery (p=0.001). The increase in CRP (the difference between pre-operative and post-operative CRP levels) was positively related to the severity of pain in the post-operative period (p=0.001). No significant relationship was found between CRP level and pre-operative pain.

Conclusion: This study of female patients undergoing a primary total knee arthroplasty found that elevated levels of C-reactive protein were

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associated with elevated pain levels on the day of, and the morning after surgery.

Tarasov D., et al. C-Reactive Protein as Marker of Post-Operative Analgesic Quality after Primary Total Knee Arthroplasty. **Int Orthop.** 2020, April; 44: 1727-1735.

CURCUMIN FOR KNEE OSTEOARTHRITIS

Osteoarthritis (OA) is a collection of different disease pathways, including the critical pathway of inflammatory factors. As Curcuma longa extract (CL) has been used in both Ayurvedic and traditional Chinese medicine to treat OA, this study assessed the effect of CL for the treatment of OA of the knee.

Subjects were over 40 years of age with symptomatic knee OA and synovitis with an effusion. The 70 subjects were randomized to receive either two capsules of a placebo, or two capsules containing 500mg of CL. Outcome measures included knee pain, as assessed by a visual analog scale (VAS), and changes in knee effusion-synovitis volume over 12 weeks, as assessed by MRI. Secondary outcomes included the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the OARSI-OMERACT (Outcome Measures in Rheumatology Clinical Trials), cartilage compositional change and the Assessment of Quality of Life (AQoL)-4D questionnaire.

Between baseline and 12 weeks, VAS knee pain scores improved by 23.8 mm in the treatment group and 14.6 in the placebo group (p=0.039). Changes in the effusion volume did not differ significantly between the groups. Compared with placebo, the treatment group demonstrated greater improvement in WOMAC pain (p=0.006) and function (p=0.047) scores.

Conclusion: This study of patients with osteoarthritis of the knee found that curcumin at 1,000 mg per day could significantly reduce pain.

Wang, Z., et al. Effectiveness of Curcuma Longa Extract for the Treatment of Symptoms and Effusion -Synovitis of Knee Osteoarthritis. A Randomized Trial. **Ann Intern Med.** 2020. doi:10.7326/M20-0990.

RADIOFREQUENCY ABLATION FOR CHRONIC KNEE PAIN

Osteoarthritis (OA) of the knee is the most common cause of chronic knee pain. Previous studies of cooled radiofrequency ablation (CRFA) have shown positive effects in relieving the pain of this condition. This study was designed to compare the efficacy of CRFA with that of hyaluronic acid (HA) injections for the management of pain among patients with OA of the knee.

This randomized, controlled trial included 158 adult patients with radiographically confirmed OA of the knee. Pain was assessed using an 11 -point numerical rating scale (NRS). Subjects were randomized to receive CRFA or an HA injection, with post-treatment data collected at one, three and six months. Those randomized to the CRFA group underwent ablation, while those in the HA group received one intraarticular injection with Synvisc-One. The primary efficacy endpoint was the proportion of subjects whose knee pain was reduced by 50% or more at six months post-treatment.

Compared with the HA group, pain was decreased more in the CRFA group at months one ($p=0.0085$), three ($p<0.001$) and six ($p<0.001$). At six months, 71% of the CRFA group reported at least a 50% reduction in pain, compared with 38% of the HA group ($p<0.001$). Scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) improved by 40% in the CRFA group and 22.6% in the HA group ($p<0.001$).

Conclusion: This randomized, controlled trial involving patients with osteoarthritis of the knee found radiofrequency ablation to be superior to hyaluronic acid for pain reduction and functional improvement.

Chen, A., et al. Cooled Radiofrequency Ablation Compared with a Single Injection of Hyaluronic Acid for Chronic Knee Pain. **J Bone Joint Surg.** 2020, September 2; 102 (17): 1501-1510.

PLASTER CAST VERSUS FUNCTIONAL WALKING BOOT FOR ACHILLES TENDON RUPTURE

In recent years, good outcomes have been reported in patients with acute Achilles tendon rupture (ATR) who were treated nonoperatively.

This study compared traditional cast immobilization combined with prolonged non-weightbearing to that of immobilization with a walking boot combined with early weightbearing.

This prospective, randomized trial included 69 patients, 16 to 60 years of age, who had sustained an acute ATR. Those randomized to a cast group were placed into a complete below-knee cast with the ankle in full equinus for four weeks and then converted to a semi-equinus position for a further four weeks. No weightbearing was allowed while casted. Those in a walking boot group were placed in a walking boot with a three cm internal heel rise with advice to immediately bear full weight. After four weeks, the internal heel rise was reduced to 1.5 cm for two weeks and then no heel rise for two weeks. At eight weeks, physical therapy began for both groups. The primary outcome measure was the Short Musculoskeletal Functional Assessment (SMFA) at each visit for up to 52 weeks from the date of the injury.

At six months, compared to the casted group, those in the walking boot earned slightly better SMFA scores (p=0.50). At one year, there was no difference between the groups in SMFA scores. Patients in the walking boot group returned to driving one week sooner than the casted group *(*p=0.045), but there was no difference in time to return to work (p=0.48). Re-rupture occurred in five patients in the walking boot group and 11 in the cast group (p=0.075).

Conclusion: This study of patients with acute Achilles tendon rupture found that, compared with traditional cast immobilization and non-weightbearing, immobilization with a walking boot and weight bearing provided no significant difference in outcomes.

Maempel, J., et al. A Randomized, Controlled Trial Comparing Traditional Plaster Cast Rehabilitation with Functional Walking Boot Rehabilitation for Acute Achilles Tendon Ruptures. **Am J Sport Med**. 2020, September; 48(11):2755-2764.

PARTIAL TEARS OF THE ULNAR COLLATERAL LIGAMENT

The anterior band of the ulnar collateral ligament (UCL) is thought to be the primary stabilizer against valgus stress at 20° to 120° of elbow flexion. This cadaveric study assessed the stability of the ulnohumeral joint with partial tears of the UCL.

Using 21 adult cadaveric elbows, partial tears were simulated by cutting 50% of the width of the UCL at six locations. These included distal anterior/posterior, mid-substance anterior/posterior, and proximal anterior/posterior. A seventh partial tear was created by partially elevating the undersurface of the distal UCL to simulate the radiographic “T-sign”. Valgus stress of 15 daN was applied to each elbow at 30° of flexion. Joint space was then measured using ultrasound, measuring the difference (delta) in joint space between the unstressed and the stressed conditions.

The mean delta of the intact state was 0.58mm. Both distal partial tears had mean deltas of <0.75mm. Proximal tears and the T-sign lesion demonstrated deltas of 0.99 to 1.23 mm. Mid-substance partial tears demonstrated deltas ranging from 1.57 to 2.03 mm, a delta similar to that of the complete tears. All complete tears had a mean delta of greater than 1.5mm.

Conclusion: This study of cadaveric arms found that partial tears of the medial collateral ligament introduce a variety of instabilities, with mid-substance partial tears demonstrating the greatest instability, similar to that of complete tears.

Ciccotti, M., et al. Medial Elbow Instability Resulting from Partial Tears of the Ulnar Collateral Ligament: Stress Ultrasound in a Cadaveric Model. **Am J Sports Med**. 2020, September; 48(11): 2613-2620.

REMDESIVIR FOR COVID-19

In December 2019 the novel coronavirus SARS-CoV-2 was identified, and designated coronavirus disease 2019, or Covid-19. Remdesivir, an inhibitor of the viral RNA-dependent, RNA polymerase with inhibitory activity against SARS-CoV and the Middle East respiratory syndrome (MERS-CoV) has been identified as a promising therapeutic candidate for Covid 19. This multicenter trial assessed the efficacy of remdesivir for the treatment of patients hospitalized for the treatment of Covid 19.

At 60 trial sites eligible patients were randomized in a one-to-one ratio to receive either remdesivir or placebo. Remdesivir was administered by IV with a 200 mg loading dose on day one, followed by daily infusions of 100 mg on days two to 10, or until departure from the hospital. All patients received supportive care according to the standard of care for the trial site hospital. Patients were assessed daily during their hospitalization, through day 29. The primary outcome was the relative difference in time to recover between the two groups, stratified by disease severity.

Data were completed for 391 patients in the remdesivir group and 340 in the placebo group. Most patients had either one (27.0%) or two or more (52.1%) of the prespecified coexisting conditions at enrollment. These included hypertension (49.6%), obesity (37.0%), and type 2 diabetes mellitus (29.7%). Patients in the remdesivir group recovered at a median of 11 days as compared to a median of 15 days in the placebo group (p<0.001). Patients who underwent randomization within the first 10 days after the onset of symptoms had a rate ratio for recovery of 1.28, compared to those who were randomized more than 10 days after the onset of symptoms. Mortality was numerically, but not statistically lower in the treatment group than the placebo group. Serious outcomes occurred in 21% of the treatment group and 27% of the placebo group.

Conclusion: This study of patients diagnosed with Covid 19 found that treatment with remdesivir shortened the time of recovery, especially among patients for whom treatment was initiated within 10 days.

Beigel, J., et al. Remdesivir for the Treatment of Covid-19-Preliminary Report. **N Engl J Med**. 2020:DOI: 10.1056/NEJMoa2007764.

TEMPOROMANDIBULAR PAIN AND PROPRANOLOL

Painful temporomandibular disorder (TMD) is a common musculoskeletal condition. A recent Cochran review of the pharmacological interventions for TMD concluded that there is insufficient evidence to support the effectiveness of the drugs commonly used to treat this disorder. As TMD has a significant sympathetic component, this study assessed the efficacy of a beta blocker, propranolol, for the treatment of this condition.

Subjects were adults, 18 to 65 years of age with TMD- related facial pain for at least three months, and with a pain intensity of at least 30 on a 100-point numerical rating scale (NRS). The subjects were randomized to receive either a placebo or propranolol hydrochloride, extended release, 60 mg twice per day. After titrating up to the target dose, the participants were treated for eight weeks. During the study, thermal and mechanical quantitative sensory testing was completed. The primary endpoint was change in the Facial Pain Index (FPI) score.

Data were completed for 174 subjects with a mean time since onset of TMD pain of 11 years. Of these, 52.3% met the criteria for definite or probable migraine. At week nine, the reduction in mean FPI was slightly greater in the propranolol group than in the placebo group, although this finding did not reach statistical significance. The percentage of those who reported at least 30% improvement at week nine was greater in the propranolol group (69%) than in the placebo group (52.6%; p=0.03).

Conclusion: This study of patients with chronic, painful temporomandibular disorder found that propranolol may be helpful in reducing pain.

Tchivileva, I., et al. Efficacy and Safety of Propranolol for Treatment of Temporomandibular Disorder Pain: A Randomized, Placebo Controlled Clinical Trial. **Pain**. 2020, August; 161 (8): 1755-1767.

ENDOVASCULAR TREATMENT AFTER STROKES PRESENTING VERY LATE

Data from the DAWN and DIFFUSE 3 trials determined that reperfusion treatments may be efficacious for those with emergent large vessel occlusions (LVO) with sustained ischemic penumbra. This study analyzed a prospective stroke registry of patients with acute stroke arriving beyond 16 hours from the time of last known well (LKW) who underwent endovascular treatment (EVT), beyond the current time window thresholds.

Subjects were patients hospitalized with ischemic stroke with occlusion of the internal carotid artery or middle cerebral artery, arriving within 16 hours after LKW, all with baseline National Institute of Health Stroke Scale scores of six or more. Acute stroke management was performed according to the institutional protocol based on local and international guidelines using the core-penumbra mismatch from visual inspection of machine-generated images and clinical considerations. Each patient who received EVT was matched with two medical management controls.

Data were available for 450 patients with a mean age of 70.1 years and a median duration between the mean LKW to EVT onset of 43.5 hours. An mRS score of zero to three at three months occurred in 37% of the patients, including 54% who underwent thrombolysis and 33% who received medical treatment only.

Conclusion: This study of patients with anterior circulation large vessel occlusion and moderate to severe neurologic deficits who arrived at least 16 hours after the “last known well” found that endovascular treatment was associated with 11-fold higher odds of having independent functional status at three months.

Kim, B., et al. Endovascular Treatment after Stroke Due to Large Vessel Occlusion for Patients Presenting Very Late from Time Last Known Well. **JAMA Neuro.** 2020. doi:10.1001/jamaneurol.2020.2804.

HIGH-SENSITIVITY C-REACTIVE PROTEIN AND POSTSTROKE FATIGUE

Post-stroke fatigue (PSF) is a common and lasting sequela following stroke. While the pathogenesis of post-stroke fatigue is unclear, it is often linked to both systemic inflammation and immune response disorders. This study assessed the association between plasma high-sensitivity C-reactive protein (hs-CRP), an acute phase reactant and nonspecific indicator of inflammation, and the presence of PSF.

Subjects were adults hospitalized with an acute ischemic stroke. Data included demographic characteristics, stroke severity, as evaluated by the National Institute of Health Stroke Scale (NIHSS) and fasting hs-CRP, drawn on the second morning after admission. Fatigue severity was measured with the Fatigue Scale for Motor and Cognitive Function (FSMC) up to six months post-stroke onset, with PSF defined as a score 43 or higher.

Of the 212 patients, PSF at admission was identified in 68 (32.1%). The remaining participants served as a control group. Those with PSF at admission had significantly higher hs-CRP levels at admission, as compared to the controls. The rates of anxiety and depression were significantly higher in the PSF group than in the control group (p=0.012 and p=0.013, respectively). A multivariate logistic regression found that increased hs-CRP was significantly associated with an increased risk of PSF, with an OR of 3.4 (p<0.001). A hs-CRP level of 0.52 mg/dl was found to be the optimal cutoff, yielding a sensitivity of 77.9% and a specificity of 74.3% for the prediction of PSF (p<0.001).

Conclusion: This study of patients hospitalized with an acute, ischemic stroke found that, at six months, 32.1% experienced fatigue, with plasma levels of high-sensitivity C-reactive protein associated with the development of fatigue.

Liu, X., et al. Elevated Plasma High-Sensitivity C Reactive Protein at Admission Predicts the Occurrence of Post-stroke Fatigue at 6 Months after Ischaemic Stroke. **Euro J Neurol**. 2020, October; 27(10): 2020-2030.

HIGH FLOW OXYGEN WITH CAPPING VERSUS SUCTIONING FOR TRACH REMOVAL

While 15% of patients undergoing mechanical ventilation also undergo tracheostomy, data regarding the readiness for decannulation are limited. The Reducing Decannulation Time Limiting Capping (REDECAP) trial compared the traditional capping trial with an assessment based on suctioning frequency.

This randomized trial included critically ill adult patients with a first tracheostomy, all of whom had been free from mechanical ventilation for 24 consecutive hours. The participants were randomized to undergo a 24-hour capping trial plus intermittent high flow oxygen therapy (traditional), or to receive continuous, high-flow oxygen therapy with frequency of suctioning recorded (intervention group). The primary outcome variable was time to decannulation.

Subjects were 330 patients, 161 in the traditional (control) group and 169 in the intervention group. The median times to decannulation were six days in the intervention group and

13 days in the control group. Recannulation occurred in 5.6% of the control group and 2.4% of the intervention group. Pneumonia occurred in 9.9% of the control group in 4.1% of the intervention group. The median durations of hospital stay were 62 days in the control group and 40 days in the intervention group.

Conclusion: This study of critically ill, adult patients with a tracheostomy tube found that the time to decannulation was shorter among those whose decannulation was based on suctioning frequency plus continuous high flow oxygen therapy than among those receiving the standard capping trial procedure.

Martinez, G., et al. High Flow Oxygen with Capping or Suctioning for Tracheostomy Decannulation. **N Engl J Med**. 2020, September 10; 383 (11): 1009-1017.

PULSE OXIMETER FOR SLEEP APNEA

Sleep disordered breathing (SDB) is present in approximately 70% of patients after stroke or transient ischemic attack. While some recommendations call for SDB screening for all stroke patients, this evaluation is often omitted. This study was designed to determine the predictive value of pulse oximetry for the detection of patients with moderate to severe SDB.

This prospective study enrolled patients hospitalized with acute stroke from March of 2019 through February of 2020. The patients were assessed using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS). Data included clinical and demographic characteristics of patients with medical records reviewed for medical conditions and medications. A pulse oximetry monitor from 10 P.M. to 6 A.M. was used within seven days from the stroke onset. Desaturation was defined as a drop in oxygen level of over three percent, with a duration of over 10 seconds. The average number of desaturations during one hour was defined as the desaturation index (DI). For comparison, standard, overnight polysomnography was conducted.

Subjects were 49 patients with acute ischemic stroke who received both pulse oximetry screening and subsequent polysomnography. Of the 49 patients tested, 26 had a positive DI. Among those, the presence of moderate to severe SDB was found during polysomnography in 73.1%. Of those with negative screening results, moderate to severe SDB was found in 8.7%. These findings resulted in a sensitivity of 90.5% and a specificity of 75%, with a positive predictive value of 73.3% and a negative predictive value of 91.3%.

Conclusion: This study suggests that a pulse oximeter is a good screening tool for detecting moderate to severe sleep apnea.

Siarnik, P., et al. Pulse Oximetric Routine Examination of Sleep Apnea in Acute Stroke (PRESS). **Sleep Med.** 2020, September; 73:208-212.

DELAYED OR AVOIDED MEDICAL CARE DUE TO COVID CONCERNS

Temporary disruptions in routine and non-emergency medical care have been observed during periods of community transmission of COVID-19, with some patients reporting delayed or avoided care due to concern about COVID-19. This study estimated the magnitude and characteristics of this avoidance.

During June 24 through 30, 2020, a nationwide, representative sample of U.S. adults was conducted, with 5,412 completing the survey. Respondents were asked whether they had delayed or avoided medical care due to concerns related to COVID-19. Medical care was classified as “emergency” (immediate life-threatening conditions), “urgent” (immediate nonlife threatening conditions) or “routine” (such as annual checkups). Covariates included gender, age, race/and ethnicity, disability status, presence of one or more selected underlying medical conditions known to increase the risk for severe COVID -19, education, employment status, and health insurance.

Of the 4,975 participants, 40.9% reported a delay or avoidance of medical care due to concerns about COVID-19. Of the total group, 12% avoided emergency or urgent care. A multivariate regression analysis revealed that urgent or emergency care avoidance was higher among persons with two or more underlying medical conditions (Odds Ratio (OR) 1.9), persons with health insurance (OR 1.8) black adults vs white adults (OR 1.6), Hispanic adults vs white adults (OR 1.5), adults 18 to 24 years of age vs adults 25-44 (OR 1.5), persons with a disability (OR 1.3) and unpaid caregivers of adults compared to non-caregivers (OR 2.9).

Conclusion: This study found that 41% of U.S. adults report that they have delayed or avoided medical care due to concerns about COVID-19.

Czeisler, M., et al. Delay or Avoidance of Medical Care Because of COVID-19 Related Concerns–United States, June, 2020. **MMWR Morb Mortal Wkly Rep.** 2020 September 11; 69(36): 1250-1257.

LIGHT THERAPY FOR FATIGUE IN MULTIPLE SCLEROSIS

Fatigue is the most common symptom reported by patients with multiple sclerosis (MS). Bright white light therapy has been found to reduce fatigue in individuals with seasonal affective disorder, Parkinson’s disease, cancer and traumatic brain injury. Therefore, this study was designed to determine whether bright light can be an effective intervention for patients with moderate to severe, MS associated fatigue.

Subjects were patients diagnosed with relapsing-remitting or secondary progressive MS, 18 to -70 years of age, all with fatigue, defined as a Fatigue Severity Scale (FSS) score of 36 or higher. Twenty participants were randomized to receive whole spectrum bright light (BWLT) or the same light using a single layer, dim-red light filter (DRLT). The participants were instructed to sit in front of the light box with their face approximately 36 inches from the light source, one hour, twice per day for four weeks. The subjects were measured at baseline and at four weeks for fatigue severity, quality of life and adverse events.

Compared to baseline, at four weeks, the mean FSS score was significantly decreased in both the BWLT group (p=0.04) and the DRLT group (p=0.03), with no significant difference between the groups. Similar findings were noted for quality of life scores.

Conclusion: This study of patients with multiple sclerosis and complaints of fatigue found no difference in the improvement of fatigue or quality of life scores between those treated with whole spectrum bright light and those treated with red filtered light.

Mateen, F., et al. Light Therapy for Multiple Sclerosis-Associated Fatigue: A Randomized, Controlled, Phase II Trial. **J Neurol**. 2020, August; 267(8): 2319-2327.

INTRANASAL KETAMINE FOR PEDIATRIC PAIN

Concern for opioid abuse for patients with moderate to severe pain has propelled investigations of alternative interventions. This literature review and meta-analysis was designed to better understand the efficacy and safety of intranasal analgesic-dose ketamine for the treatment of acute pain in the emergency room.

A literature review was completed for randomized, controlled trials evaluating the analgesic efficacy and safety of intranasal ketamine, as compared to intranasal fentanyl. From the data were chosen four studies involving a total of 276 participants, of whom 138 were randomized to receive ketamine and 132 to receive fentanyl.

This meta-analysis found that decreases in pain scores from baseline to post-intervention time points, up to 60 minutes, were similar between the two intervention groups. Only one serious side effect was reported, a case of hypertension in the fentanyl group. The use of rescue medicine was not inferior in the ketamine group.

Conclusion: This systematic review and meta-analysis of studies involving the management of acute pain in children in the emergency department found that intranasal ketamine is as effective and tolerable as intranasal fentanyl for the reduction of pain.

Oliveira, L., et al. Intranasal Ketamine for Acute Pain Management of Children: A Systematic Review and Meta-analysis. **Am J Emerg Med.** 2020, June 1; 38(9): 1860-1866.

PROTEIN INTAKE AND MORTALITY

Adherence to a high protein diet has become a popular means to achieve weight loss, preserve muscle mass and increase strength. This literature review and meta-analysis was designed to better understand the association between dietary protein intake and mortality.

A literature review was completed for prospective studies which investigated the association between the intake of total protein, animal protein and plant protein, and mortality from all causes, cardiovascular disease and cancers. From this review, 31 papers were identified for inclusion in this meta-analysis.

With data from 480,304 participants, a significant inverse association was found between protein intake and all-cause mortality ($p<0.001$). No significant association was found for animal protein, while plant protein was inversely associated with mortality, with a significant difference found between the highest and lowest intake groups ($p=0.002$). No significant association was noted between protein intake and cardiovascular disease mortality. However, an inverse association was found between plant protein consumption and cardiovascular disease mortality ($p=0.003$). For cancer risk, no association was noted for total, animal or plant protein intake.

Conclusion: This meta-analysis found a significant, inverse association between total protein intake and all-cause mortality, with plant protein intake inversely associated with the risk of cardiovascular disease mortality.

Naghshi, S., et al. Dietary Intake of Total, Animal and Plant Proteins and Risk of All Cause, Cardiovascular and Cancer Mortality: Systematic Review and Dose Response Meta-Analysis of Prospective Cohort Studies. **BMJ.** 2020; 370: M2412.

ZOLEDRONIC ACID USE AFTER SPINAL CORD INJURY

Following acute traumatic spinal cord injury (SCI), increased bone loss is common, due to rapid bone remodeling. This study examined the efficacy of bisphosphonate zoledronic acid (ZA) for the treatment of patients with acute, traumatic SCI.

This double blind, placebo-controlled trial randomized fifteen patients with C4-T10 AISA SCI to receive either five mg IV zoledronic acid or a placebo, beginning within 21 days of an acute SCI. Bone mineral density (BMD) of the hip and knee were measured by DEXA. Bone formation and resorption markers (procollagen N-1 terminal propeptide and serum C-telopeptide, respectively) were measured prior to injection, two weeks post-infusion and then four months and 12 months post -injury.

At four months, compared to the control group, the BMD was greater in the ZA in all locations. At 12 months, BMD was maintained at the hip, but not at the knee. At 12 months, in the treatment group the total proximal femur and intertrochanteric femur had declined by 8.4%, while the femoral neck had declined by 4.8% (60-77% less than the control group). The bone resorption markers decreased in the ZA group and increased in the control group as measured at two weeks and four months, with a significant difference at 12 months. Those in the ZA group had lower serum calcium relative to controls and required oral or IV calcium supplementation.

Conclusion: This controlled study of patients with acute, traumatic spinal cord injury found that zoledronic acid, given within 21 days of injury, reduced the loss of bone mineral density at the hip and femur at four months post-injury, remaining stable at 12 months.

Oleson, C., et al. The Effect of Zoledronic Acid on Attenuation of Bone Loss at the Hip and Knee following Acute, Traumatic Spinal Cord Injury: A Randomized, Controlled Study. **Spinal Cord**. 2020; 58: 921-929.

VITAMIN D, CARDIOVASCULAR HEALTH AND COGNITION

Cardiovascular risk factors are known to affect the risk of cardiovascular disease and brain health. This study was designed to determine whether cardiovascular health is associated with cognition and whether serum vitamin D status influences this association.

The Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) was designed to study risk factors for cardiac metabolic diseases. Subjects were healthy adults, 30 to 64 years of age, all without severe disease history (defined as cancer within two years, myocardial infarction, stroke or heart failure). Cognitive function was assessed at age 50 years or older. Using a tool developed by the American Heart Association to assess cardiovascular health, “Life’s Simple Seven” (LS7), data were collected, including blood pressure, glucose control, serum lipids, physical activity, diet, obesity and smoking. Using the LS7, subjects were divided into three groups (0 to 3, Poor LS7; 4 to 7, Moderate LS7; above 7, High LS7). Cognitive function was tested

using the Mini-Mental State Examination for dementia screening (MMSE-DS). Blood samples were obtained to assess levels of lipids, glucose and vitamin D.

Data were gathered for 840 men and 1,811 women with a mean age of 57.2 years. Among the women, those in the High LS7 group earned significantly higher MMSE scores than did those within the Low LS7 group (p=0.018). This association was not significant among men. However, among men with vitamin D levels of at least 20ng/ml, compared to the Poor LS7 group, those in the High LS7 group scored significantly higher on the MMSE-DS (p=0.03).

Conclusion: This study of the association between cardiovascular health and cognition found that, among men, vitamin D modifies this association.

Jeon, Y., et al. Does Serum Vitamin D Level Affect the Association between Cardiovascular Health and Cognition? Results of the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) Study. **Eur J Neurol.** 2020. doi.org/10.1111/ene.14496.

CAPSAICIN VERSUS PIROXICAM FOR ACUTE MUSCULOSKELETAL PAIN

Multiple studies have focused on the use of topical capsaicin for the treatment of various chronic pain conditions. However, non-steroidal anti-inflammatory drugs are the most commonly prescribed medications for acute musculoskeletal pain. This study compared the analgesic efficacy of topical piroxicam with that of topical capsaicin for the treatment of acute musculoskeletal pain.

This double-blind, randomized, controlled trial included adult patients who presented to an emergency department within two hours of upper extremity trauma with pain scores of five or higher on a visual analogue scale (VAS). The participants were divided into two groups, group one receiving piroxicam and group two receiving capsaicin.

The subjects were randomized to topically apply capsaicin gel, 0.05%, or piroxicam gel, 0.5%, administered to the painful area with a maximum application of 5 x 5 cm. The patients were advised to apply the medication three times a day for three days. A 10-point VAS was used to record pain levels upon presentation, as well as at 60 and 120 minutes post-treatment. The participants were reached by telephone to determine VAS scores at 24 and 72 hours.

Of the 136 patients, 67 were assigned to the piroxicam group and 69 to the capsaicin group. Fifty percent or greater decreases in pain scores were realized by 87% of the patients in the capsaicin group and 62.7% in the piroxicam group (p<0.01). At 72 hours those with a pain score of four or less included 85.5% in the capsaicin and 50.7% in the piroxicam group (p<0.001).

Conclusion: This study of patients presenting to an emergency room with trauma-induced arm pain found that topical capsaicin improved pain to a greater degree than did topical piroxicam.

Kocak A., et al. Comparison of Topical Capsaicin and Topical Piroxicam in the Treatment of Acute, Trauma-Induced Pain: A Randomized, Double-Blind Trial. **Am J Emerg Med.** 2020, September; 38 (9): 1767-1771.

RADIATION VS INDOMETHACIN FOR HETEROTOPIC OSSIFICATION PROPHYLAXIS

Formation of heterotopic ossification (HO) after surgery can lead to decreased mobility and poor functional outcomes. The most common methods of prophylaxis include nonsteroidal anti-inflammatory drugs (NSAIDs) and external beam radiation therapy (XRT). While previous studies have shown no difference in their efficacy for preventing HO, NSAIDs have been associated with an increased risk of fracture nonunion, and XRT with impaired wound healing and risk of nonunion. This study compared these two treatments for the risk of wound complications.

This retrospective study included 473 adult patients treated surgically for acetabular fractures. Of these, 167 received indomethacin, 104 received XRT, and 202 receive no prophylaxis. All patients received preoperative antibiotics within one hour before incision, and were made non-weight-bearing or toe-touch weight-bearing with posterior hip precautions postoperatively. Outcomes of interest included surgical site infection (SSI) and noninfectious wound complications defined as hematoma, seroma, wound dehiscence, or increased drainage that required use of incisional wound vacuum-assisted closure (VAC).

An SSI occurred in 4.8% of the indomethacin group, 7.7% of the radiation group, and 8.9% of the no prophylaxis group (p=0.28). Significant differences were noted in noninfectious complications which occurred in 20.2% of the XRT group, 6.6% of the indomethacin group and 5.0% of the no prophylaxis group (p=0.0007).

Conclusion: This study of patients undergoing surgical repair for an acetabular fracture found no difference in surgical site infection between those treated with prophylactic indomethacin and those treated with radiation treatment. Those treated with radiation however had a significant increase in the risk of noninfectious wound complications.

Cichos, K., et al. Do Indomethacin or Radiation for Heterotopic Ossification Prophylaxis Increase Rates of Infection or Wound Complications After Acetabular Fracture Surgery? **J Orthopaed Trauma.** 2020, September; 34(9) 455-461.

BLOOD FLOW RESTRICTION AND KIDNEY DISEASE PROGRESSION

Recent studies have demonstrated that physical exercise can contribute to the prevention and treatment of chronic kidney disease (CKD). This study compared the effect of blood flow restriction (BFR) exercise to conventional exercise on the progression of CKD.

Subjects were 229 male and female patients with stage II CKD. Subjects were randomized to one of three groups: Control group(C), resistance training group (RT), or a RT plus BFR (RT-BFR) group. Randomization was stratified according to baseline variables including sex, body weight, body mass index and medication. Patients were assessed for their individual one repetition maximum (1-Rep Max) at each selected muscle group. Both treatment groups underwent six months of programming with intensity adjusted every two months. In the RT -BFR group resistance was set at 50% of the measured systolic blood pressure. Blood samples were collected at baseline and after six months to analyze renal function and inflammation. In the RT group resistance was set at 50-70% of the 1 -Rep Max and for the RT-BFR group it was set at 30-50% of the 1-Rep Max.

At follow up 70% of the control group progressed from stage two to

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stage three CKD, compared to 25.7% in the RT and 17.1% of the RT+BFR. Improved uremic parameters, as well as inflammation (IL-6; IL-10; IL-15; IL-17a; IL-18; TNF-α) and the Klotho-FGF23 axis were noted in both treatment groups ($p<0.05$). At six months creatinine concentrations in the urine were increased in the CTR group but remained stable in the treatment groups ($p < 0.05$). Cystatin C increased less in both treatment groups compared to the CTL group ($p < 0.05$). An increased urea was noted in the CTL group but not in the treatment groups ($p < 0.05$).

Conclusion: This study of patients with chronic kidney disease found that six months of resistance training both with and without blood flow restriction could improve the progression of kidney disease.

Correa, H., et al. Blood Flow Restriction Training Blunts Chronic Kidney Disease Progression in Humans. **Med Sci Sports Exer**. 2020, August 21; Publish Ahead of Print - Issue - doi: 10.1249/MSS.0000000000002465.

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