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ASSOCIATION OF BODY MASS INDEX WITH KNEE CARTILAGE DAMAGE

As body mass index (BMI) is a well-established risk factor for the development of symptomatic cartilage damage and osteoarthritis (OA), this study was designed to understand the prevalence of cartilage damage in subjects without knee pain, and its relationship to BMI.

This cross-sectional study included randomly selected, community dwelling adults, 40 to 79 years of age, who had had no complaints of knee pain over the past year. All subjects underwent MRI of the knee, with MR cartilage graded on a Disler scale of zero to four. Self-reported past weight and height at age 25 was documented. Current BMI was determined by examination.

Seventy-three subjects with an average age of 52 years were studied. Of these, 65.4% had MRI detected cartilage damage graded as ≥ 2 . Severe cartilage damage (≥ 3) was found in 28.7%. The adjusted odds ratio (OR) of at least moderate (≥ 2) cartilage damage was 3.04 (statistically significant) among those with a BMI of $\geq 25 \text{ kg/m}^2$ as compared to those with a BMI of $< 25 \text{ kg/m}^2$. A similar though statistically insignificant trend was noted for those with severe cartilage damage (OR 2.63). Similar findings were noted for past BMI (2.44), and for change in BMI (1.41).

Conclusion: This MRI study of asymptomatic adults found a high prevalence of cartilage damage in the knee, with a greater risk for at least moderate damage among those with a body mass index of at least 25 kg/m^2 .

Keng, A., et al. Association of Body Mass Index with Knee Cartilage Damage in an Asymptomatic Population-Based Study. **BMC Musculoskel Disord.** 2017, Dec 8; 18 (1): 517.

CHINESE HERBAL MEDICINE FOR ALZHEIMER'S DISEASE

Herbal medicine has been used for centuries in China for the treatment of dementia. This study of patients with probable Alzheimer's dementia (AD) investigated the efficacy of combining conventional therapy (a cholinesterase inhibitor or an NMDA receptor antagonist) with Chinese herbal medicine.

Subjects were patients diagnosed with probable dementia due to AD. Clinical records were reviewed for diagnostic tests and treatments used. By chart review, the patients were separated by those treated with conventional therapy plus herbal medicine (CT + H) versus conventional therapy without herbal medicine (CT). Donepezil was used to treat patients with mild to severe AD, and memantine for those with moderate to severe AD. In the CT+H group, the GRAPE formula was prescribed for twice per day intake, consisting of Ren shen (Panax ginseng, 10 g/d), Di huang (Rehmannia glutinosa, 30 g/d), Cang pu (Acorus tatarinowii, 10 g/d), Yuan zhi (Polygala tenuifolia, 10 g/d), Yin yanghuo (Epimedium brevicornu, 10 g/d), Shan zhuyu (Cornus officinalis, 10 g/d), Rou congrou (Cistanche deserticola, 10 g/d), Yu jin (Curcuma aromatica, 10 g/d), Dan shen (Salvia miltiorrhiza, 10 g/d), Dang gui (Angelica sinensis, 10 g/d), Tian ma (Gastrodia elata, 10 g/d), and Huang lian (Coptis chinensis, 10 g/d). Global cognitive function was evaluated with the Mini-Mental State Examination (MMSE) at three-month intervals.

Changes in mean MMSE scores differed significantly between the two groups, with those in the CT + H performing better in cognition beginning at three months ($p=0.009$), with significance noted through 24 months ($p=0.000$). At 24 months, those treated with CT + H exhibited stabilization of cognitive function, while those with CT alone continued to deteriorate.

Conclusion: This retrospective study of 344 patients diagnosed with

probable AD found that the addition of traditional herbal Chinese medicine to conventional therapy substantially decelerated cognitive decline.

Shi, J., et al. Adding Chinese Herbal Medicine to Conventional Therapy Brings Cognitive Benefits to Patients with Alzheimer's Disease: A Retrospective Analysis. **BMC Complement Altern Med.** 2017 Dec 13; 17(1): 533.

SALIVA MICRORNA IN CONCUSSION

For most children, concussion symptoms resolve within two weeks, although one third will experience prolonged concussion symptoms (PCS). MicroRNAs are small, noncoding molecules which influence protein translation throughout the body. As previous studies have demonstrated that concentrations of microRNAs are altered in adults with traumatic brain injury (TBI), this study assessed the clinical utility of salivary microRNAs in children with PCS.

Subjects were seven to 21 years of age, all with a clinical diagnosis of mild TBI (mTBI). Medical and demographic characteristics were recorded, with symptoms evaluated with the Sport Concussion Assessment Tool-3 (SCAT3). This measure was repeated by telephone four weeks post-injury. Non-fasting saliva was collected at enrollment. Salivary microRNAs with differential expression between the PCS and acute concussion symptoms (ACS) groups were identified.

Of the 52 patients originally seen, 30 experienced PCS. From the analysis, 15 salivary microRNAs spatially differentiated between the two groups. Levels of five microRNAs (miR-320c-1, miR-133a-5p, miR-769-5p, let-7a-3p and miR-1307-3p) accurately identified patients with prolonged symptoms by logistic regression, with a sensitivity of 80% and a specificity of 75%. Levels of three microRNAs were associated with specific symptoms four weeks

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after injury (memory, fatigue and headaches).

Conclusion: This study of children presenting with symptoms of concussion found that concentrations of salivary microRNAs taken at the initial clinical assessment may be useful in determining patients at risk for prolonged symptoms.

Johnson, J., et al. Association of Salivary MicroRNA Changes with Prolonged Concussion Symptoms. **JAMA Ped.** doi:10.1001/jamapediatrics.2017.3884.

MULTIPLE VERSUS SINGLE HYALURONIC ACID INJECTIONS

For patients with osteoarthritis (OA) of the knee, common, nonoperative therapies include nonsteroidal anti-inflammatory drugs, physical therapy, analgesics and intra-articular injections. Recommendations of the major medical societies, including the American Academy of Orthopedic Surgeons, the American College of Rheumatology and the American Medical Society for Sports Medicine, differ in their recommendations for the use of intra-articular hyaluronic acid. This meta-analysis was designed to better understand the effect of single versus multiple injections of hyaluronic acid for the treatment of OA of the knee.

A comprehensive literature search was conducted for articles assessing the efficacy of hyaluronic acid injections for patients with OA of the knee, with outcomes including pain, function and adverse events. Relevant articles were reviewed and included in the meta-analysis.

Studies included were 26, double-blind, randomized, controlled trials and four, single-blind, randomized, controlled trials involving a total of 5,848 patients. Low molecular weight hyaluronic acid was the most frequently used treatment (47%), followed by high molecular weight hyaluronic acid (43%) and moderate weight hyaluronic acid (10%). Compared with intra-articular saline, two to four injections of HA produced the largest reduction in pain at three ($p<0.00001$) and six ($p=0.008$) months. Treatments involving five or more injections were correlated with significant improvement in pain at six months.

Conclusion: This meta-analysis of randomized, controlled trials involving hyaluronic acid for the treatment of osteoarthritis of the knee found that a series of two to four

injections resulted in better outcomes than did single injections, or placebo.

Concoff, A., et al. Efficacy of Multiple versus Single Hyaluronic Acid Injections: A Systematic Review and Meta-analysis. **BMC Musculoskel Dis.** 2017; 18: 542.

PAIN CATASTROPHIZING AND POSTOPERATIVE PAIN AFTER TOTAL JOINT ARTHROPLASTY

Between 1997 and 2010, the rate of total knee arthroplasties (TKA) has doubled, while the rate of total hip arthroplasties (THA) has increased from 11 to 15 per 10,000 population. While these procedures have been effective in reducing pain, a small portion of patients continue to experience chronic, postoperative pain, and to report poor functional outcomes. This study examined the relationship between pain catastrophizing and postoperative pain intensity among patients undergoing joint replacement surgery.

This prospective study included all patients undergoing primary TKA or THA in August of 2013 and March of 2014. All were administered the Pain Catastrophizing Scale (PCS) at their final presurgical visit. From these scores, the patients were divided into catastrophizing and non-catastrophizing cohorts. The primary outcome measure was patient reported postoperative pain at three months post-surgery, as measured on a visual analog scale (VAS).

Of the 123 patients in the analysis, 87 scored <30 (non-catastrophizers) and 36 scored ≥ 30 (catastrophizers) on the PCS. At three months, the average VAS pain score was significantly higher in the catastrophizer group than in the non-catastrophizer group ($p=0.000$), although this level did not meet the pre-established clinically important difference of two points on the VAS. In addition, there were no significant differences between the two groups in the morphine equivalent doses consumed during hospitalization.

Conclusion: This prospective study of patients undergoing total knee or total hip arthroplasty found a statistically, but not clinically, significant difference in pain scores three months after surgery between pain catastrophizers and non-catastrophizers.

Wright, D., et al. Pain Catastrophizing as a Predictor for Postoperative Pain and Opiate Consumption in Total Joint Arthroplasty Patients. **Arch**

SURGERY FOR CLINICALLY POSITIVE AND ELECTRODIAGNOSTICALLY NEGATIVE CARPAL TUNNEL SYNDROME

Treatment for carpal tunnel syndrome (CTS) may include splinting, corticosteroid injections and/or surgery. Electrodiagnostic (EDX) tests to confirm this diagnosis can be negative in up to 15% of patients. This study was designed to determine whether surgical decompression can effectively treat those with clinically positive, but EDX negative CTS.

Subjects were adult patients referred with symptoms of CTS, with normal EDX results. The patients were randomly assigned to surgical decompression or nonsurgical treatment, with the latter including nocturnal wrist splinting or local corticoid injections. Outcomes were measured with a six-point scale for perceived improvement, as well as the Boston Carpal Tunnel Questionnaire, completed at baseline and at six-month follow-up.

At six-month follow-up, more patients in the surgery group (70%) than in the non-surgery group (35.3%) reported important improvement ($p=0.02$). In addition, complete symptom relief was reported by 39.4% of the surgery group and zero percent of the non-surgery group ($p=0.003$).

Conclusion: This study provides evidence that most patients with clinically defined carpal tunnel syndrome and normal electrodiagnostic study results can benefit from carpal tunnel release surgery.

De Kleermakeeker, F., et al. Treatment Outcome in Patients with Clinically Defined Carpal Tunnel Syndrome but Normal Electrodiagnostic Test Results: A Randomized, Controlled Trial. *J Neuro.* 2017, Dec; 264(12): 2394-2400.

EVALUATION OF CINNAMON IN HEALTHY ADULTS

In traditional Indian medicine, cinnamon is advocated for many ailments. Cinnamon comes in two main varieties, *Cinnamomum cassia* (*Cinnamomum aromaticum*) and *Cinnamomum zeylanicum* (CZ). As

coumarin levels in cassia are higher than in CZ, the regular use of cassia cinnamon has not been advocated. This study evaluated the pharmacodynamic properties and safety of CZ in healthy adults.

Subjects were healthy adults between the ages of 18 and 60. Each subject was given a daily capsule containing refined CZ at 85 mg the first month, 250 mg the second month and 500 mg the third month. The participants were assessed at baseline, and at each of three monthly follow-ups. Assessments included anthropometrics and lab tests.

Compared with baseline, no significant changes were noted in weight, body mass index, waist circumference or waist to hip ratio. A significant increase in pulse rate was noted between visits two and three ($p<0.05$). Both systolic and diastolic blood pressure readings were significantly reduced during the first month, with this reduction sustained at three months. In addition, significant reductions were noted in total cholesterol ($p<0.05$) and LDL cholesterol ($p<0.001$) at the end of three months. No serious side effects were noted.

Conclusion: This study of healthy adults found that daily ingestion of cinnamon may reduce blood pressure, total cholesterol and LDL cholesterol, with no significant side effects noted.

Ranasinghe, P., et al. Evaluation of Pharmacodynamic Properties and Safety of *Cinnamomum Zeylanicum* (Ceylon Cinnamon) in Healthy Adults: A Phase I Clinical Trial. *BMC Complement Altern Med.* 2017; 17:550.

ACHILLES TENDON RUPTURE TREATED WITH AND WITHOUT SURGERY

After Achilles tendon rupture, the optimal management remains unclear. Studies comparing operative and nonoperative treatment have failed to show a clinically significant difference in outcome. This study was designed to better understand these treatment options.

This cohort study included 200 patients presenting for treatment of an Achilles tendon rupture. The treatment decisions were individualized based upon patient factors including age, activity level, comorbidities and surgeon's preference. Of those presenting, 99 were treated surgically, and 101

nonsurgically. Both groups were kept nonweightbearing in a cast for four weeks, and then placed in a controlled ankle movement walker boot at 20° equinus. Physical therapy was initiated, with the equinus progressively decreased to neutral by weeks six to eight. Weightbearing progressed from partial to full as patient tolerance and range of motion allowed. The orthotic was removed at week eight, with therapy continuing until week 12. The primary outcome variable was patient reported functional outcome, assessed with the Achilles Tendon Total Rupture Score (ATRS).

No significant difference was found between the groups in the rate of rerupture. There was also no significant difference between the groups in ATRS functional scores ($p=0.55$). A logistic regression analysis did not reveal significant effects of age at rupture, gender or mode of treatment on ATRS scores.

Conclusion: This non-randomized study of patients with Achilles tendon rupture failed to demonstrate a better outcome for those treated surgically compared to those treated nonsurgically.

Lim, C., et al. Functional Outcome of Acute Achilles Tendon Rupture with and without Operative Treatment Using Identical Functional Bracing Protocol. *Foot Ankle Int.* 2017, Dec; 38(12): 1331-1336.

CHRONIC INFLAMMATION AND ACHILLES TENDINOPATHY

Recent studies have identified immune-component cells in biopsy specimens from patients with non-ruptured chronic Achilles tendinopathy. This study was designed to better understand the inflammatory component of this disorder.

Subjects were 17 patients with chronic Achilles tendinopathy, presenting for high-volume injections (HVI), and 19 patients with Achilles tendon rupture, presenting for surgical repair. Biopsies from each group were compared with those of hamstring tendons collected from patients undergoing anterior cruciate ligament reconstruction. The biopsies were studied for inflammatory signatures.

Immunohistochemistry of the biopsies of the Achilles groups demonstrated an increased expression of CD14+ and CD68+ cells compared to the healthy hamstring tendons ($p=0.0015$ and $p=0.0007$

respectively). There was no significant difference between the two Achilles groups in the number of these cells found. Compared with the controls, the Achilles groups demonstrated a complex activation protein signature, and expressed markers of interferon and glucocorticoid receptor macrophage activation pathways. Using CD30 1 as a marker of vascularization, increased expression was found in tendinopathy ($p=0.002$) and ruptured Achilles tissue ($p=0.0002$).

Conclusion: This study of patients with Achilles tendinopathy, including those with ruptures, demonstrates evidence of chronic inflammation.

Dakin, S., et al. Chronic Inflammation as a Feature of Achilles Tendinopathy and Rupture. **Br J Sports Med.** 2017; 0: 1-9. doi: 10.1136/bjsports-2017-098161

VITAMIN D SUPPLEMENTATION FOR CHRONIC, WIDESPREAD PAIN

Chronic widespread pain (CWP), including fibromyalgia (FM), is prevalent in the general population, with estimates ranging from 10-18%. As vitamin D has been proposed to be an associated factor in CWP, this meta-analysis was designed to better understand this relationship.

Medical databases were reviewed for randomized, controlled trials involving patients with CWP, FM and vitamin D supplementation. From those studies were extracted diagnoses, serum vitamin D levels, vitamin D dosing and the results of clinical outcome measures. The primary outcome variables of the meta-analysis were differences in VAS pain scores, Fibromyalgia Impact Questionnaire (FIQ) scores or Discomfort Behavior Scale (DBS) scores between the intervention and the placebo groups.

From the literature review, six randomized, controlled trials were identified and were included in this analysis. The pooled results revealed that patients with CWP who received vitamin D treatment had significantly lower pain scores than those who received a placebo. No significant relationship was found between changes in blood levels of vitamin D and pain scores.

Conclusion: This study of patients with chronic, widespread pain found that vitamin D supplementation can decrease pain

scores, independent of changes in blood levels of vitamin D.

Yong, W., et al. Effect of Vitamin D Supplementation in Chronic Widespread Pain: A Systematic Review and Meta-analysis. **Clin Rheum.** 2017, Dec; 36 (12): 2825-2833.

FREMANEZUMAB FOR PREVENTING CHRONIC MIGRAINE

The global prevalence of migraine has been estimated at 15 to 18%. Chronic migraine, affecting two percent of the population, is defined as the occurrence of migraine headaches at least 15 days per month. Fremanezumab is a humanized, monoclonal antibody which selectively binds to calcitonin gene related peptide, involved in central and peripheral pathophysiologic events of migraine. This study assessed the efficacy of this medication for the treatment of chronic migraine.

Subjects were adults with chronic migraine, who received abdominal subcutaneous injections at baseline, and at weeks four and eight. Those randomized to a fremanezumab-quarterly group received 675 mg of fremanezumab at baseline. Those in a fremanezumab-monthly group received 675 mg of fremanezumab at baseline, and 225 mg at weeks four and eight, while those in the placebo group received placebo injections at all time periods. The primary endpoint was the mean change in the average number of headache days per month.

The mean number of headache days per month was reduced by 4.3 days in the quarterly group, by 4.6 days in the monthly group and by 2.5 days in the placebo group ($p<0.001$ for both, compared to placebo). Significantly more patients treated in the fremanezumab groups reported a reduction of at least 50% in the average number of headache days per month as compared with placebo. There was no elevation in adverse or serious adverse events in the treatment groups as compared with the control group.

Conclusion: This study of patients with chronic migraine found that the monoclonal antibody, fremanezumab, when administered subcutaneously, monthly or quarterly, is effective for the preventive treatment of migraine.

Silberstein, S., et al. Fremanezumab for the Preventive Treatment of

Chronic Migraine. **N Eng J Med.** 2017, Nov 30; 377(22): 2113-2122.

GALCANEZUMAB FOR EPISODIC MIGRAINE PREVENTION

Currently, five medications are approved by the United States Food and Drug Administration for the prevention of migraines, all of which have less than ideal treatment and side effect profiles. As calcitonin gene related peptide (CGRP) has been found to be a promising target for the treatment of migraine, this study assessed the efficacy of a humanized monoclonal antibody (galcanezumab), which selectively binds to CGRP.

This prospective, multicenter study included adult patients with a history of migraine, with or without aura. The participants were randomized to receive a placebo or subcutaneous galcanezumab, at doses of five mg, 50 mg, 120 mg, or 300 mg, administered monthly for three months. The primary outcome variable was the number of migraine days per month (MHD).

Compared with the placebo group, all groups receiving galcanezumab had a significant reduction in MHDs at month one. The overall change from baseline to month three in the number of MHDs was significant for both the 120 mg and 300 mg dose groups, as compared with placebo. The frequencies of adverse events were 51.1% in the placebo group and 53.1% in the treatment group.

Conclusion: This study of patients with migraine headaches found that, compared with placebo, monthly subcutaneous injections of galcanezumab are efficacious and well-tolerated for the prevention of episodic migraines.

Skljarevski, V., et al. Effect of Different Doses of Galcanezumab versus Placebo for Episodic Migraine Prevention. A Randomized, Clinical Trial. **JAMA Neurol.** doi:10.1001/jamaneurol.2017.3859.

STROKE INDUCED SYSTOLIC DYSFUNCTION

Previous studies have demonstrated that ischemic stroke (IS) is associated with changes in autonomic cardiac dynamics, elevated cardiac enzymes and plasma catecholamines. This longitudinal study, (the Stroke-Induced Cardiac Failure in Mice and

Men (SICFAIL)), assessed the effect of ischemic stroke on cardiac function in mice and the effect of beta blockers on cardiac function.

In an animal model, mice underwent induced IS at either the left or the right middle cerebral artery. Cardiac function was assessed by serial transthoracic echocardiography and hemodynamic measurements for eight weeks post-surgery. Blood was collected to assess levels of brain natriuretic protein (BNP), epinephrine, norepinephrine, tumor necrosis factor- α (TNF- α), and cortisol levels. In a follow-up, the animals were treated with metoprolol, a selective beta-1 blocker.

After a focal, right (but not left) hemispheric IS, the mice showed a significant change in LV ejection fraction ($p < 0.05$) and an increase in heart rate ($p < 0.01$). In addition, the IS led to an upregulation of BNP ($P < 0.01$) and TNF- α ($p < 0.05$) expression. Eight weeks after surgery, the IS mice had increased levels of plasma norepinephrine, epinephrine and cortisol, as compared with the control and sham surgery mice ($p < 0.05$ and $p < 0.01$). In a follow-up study, as compared to placebo treated controls those treated with metoprolol had a significant decrease in heart rate ($p < 0.05$), end-systolic volume ($p < 0.05$), end-diastolic volume ($p < 0.001$) as well as BNP ($p < 0.01$), TNF- α ($p < 0.05$), and MMP-9 gene expression ($p < 0.05$).

Conclusion: This animal study found that right ischemic stroke, leading to the development of chronic systolic dysfunction, driven by increased sympathetic activity, which was suppressed by beta blockade.

Bieber, M., et al. Stroke-Induced, Chronic, Systolic Dysfunction Driven by Sympathetic Overactivity. *Ann Neurol*. 2017, November; 82 (5): 729-743.

PROCHLORPERAZINE AND SPASTICITY AFTER SPINAL CORD INJURY

In mature neurons, low intracellular chloride (CL-) levels are required for post-synaptic inhibition, with these levels maintained by the potassium-chloride cotransporter, KCC2. After spinal cord injury (SCI), the disinhibition of motor neurons is linked to a dysfunction of KCC2, leading to a predisposition to spasticity. This study assessed the effects of different medications within a drug library, in order to identify

those with KCC2 activation capacity, with these then applied to an animal model of SCI.

In the initial screening process, molecules of off-patent approved drugs, were screened to identify a new KCC2 enhancer in a bioavailable and safe formulation. From this screen were identified piperazine phenothiazine derivatives as pharmacologically active agents for activating KCC2. Among these molecules, prochlorperazine dimaleate (PCPZ) exhibited the most potent effect with the lowest minimal effective concentration. In the clinical study, spasticity was induced in Wistar rats who underwent a T8-level transection. Spasticity was assessed by rate-dependent depression (RDD) of the H1-reflex.

In the immunohistochemical studies, levels of KCC2 labeling surrounding motoneurons were higher in the PCPZ-treated compared to placebo-treated animals but did not return to the level found in sham-operated rats ($p < 0.05$). The reduction of the RDD was more pronounced in PCPZ-treated animals at 1 Hz and remained comparable to that of baclofen-treated rats at higher frequencies of stimulation.

Conclusion: This animal study found that prochlorperazine is a positive modulator of KCC2, which was found to be as effective as baclofen for the control of spasticity after spinal cord injuries.

Laibeuf, S., et al. Prochlorperazine Increases KCC2 Function and Reduces Spasticity after Spinal Cord Injury. *J Neurotrauma*. 2017, Dec 15; 34 (24): 3397-3406.

ORAL ANTICOAGULATION AFTER INTRACEREBRAL HEMORRHAGE

Studies have shown that intracerebral hemorrhage (ICH) accounts for 10 to 20% of all acute cerebrovascular events, as well as a significant amount of stroke related disability and mortality. Studies have also demonstrated that oral anticoagulation treatment (OAT) is associated with an increased risk of ICH. This study was designed to determine whether the resumption of OAT after an ICH is associated with long-term outcome.

Data were analyzed from three, large studies of intracerebral hemorrhage, including RETRACE, OAT-ICH and ERICH. In all studies, adult patients diagnosed with ICH had been taking OAT at the time of the hemorrhage as a treatment for

atrial fibrillation (a-fib). All subjects were followed by phone interviews for up to one year for OAT resumption, mortality, modified Rankin scale scores (mRS) and new stroke events.

Data were analyzed for 1,012 survivors. Anticoagulation was resumed in 178 of 633 of those with non-lobar ICH (28%) and 86 of 379 of those with lobar (23%) ICH. There was no significant association between OAT resumption and early mortality for either non-lobar or lobar ICHs. The resumption of OAT was associated with a decrease in all-cause mortality ($p = 0.002$), all-cause stroke ($p = 0.003$), ischemic stroke ($p = 0.002$) and a good outcome (scores of zero to three) on the mRS ($p < 0.0001$).

Conclusion: This study of patients with intracerebral hemorrhage, each taking oral anticoagulants for atrial fibrillation, found that the resumption of oral anticoagulants was associated with decreased mortality and improved functional outcome.

Biffi, A., et al. Oral Anticoagulation and Functional Outcome after Intracerebral Hemorrhage. *Ann Neurol*. 2017, Nov; 82(5): 755-765.

ANTIPLATELET THERAPY IN MILD TRAUMATIC BRAIN INJURY

While the risk of bleeding is known to increase among those taking antiplatelet therapy, the relative risk is not well understood for those with mild traumatic brain injury (mTBI). This literature review and pooled analysis was designed to better understand the risk of intracranial hemorrhage (ICH) among those presenting to the emergency room (ER) with a mTBI.

After an extensive literature review, ten articles were chosen for inclusion. These included seven retrospective cohort studies, two prospective cohort studies and one retrospective case control trial. Patients with mTBI, with and without traumatic ICH, were compared by antiplatelet use.

The pooled data included 2,966 in the antiplatelet group and 18,281 in the control group. The pooled analysis found that, compared with controls, the Odds Ratio (OR) for ICH among those taking antiplatelet therapy was 1.87. Of note, the majority of patients in these studies were taking clopidogrel at the time of the trauma.

Conclusion: This pooled analysis of studies of patients presenting to

the emergency room with mild traumatic brain injury found that the risk of intracranial hemorrhage is higher among those taking antiplatelet medications at the time of the trauma.

McIlville, L., et al. Is Antiplatelet Therapy an Independent Risk Factor for Traumatic Intracranial Hemorrhage in Patients with Mild Traumatic Brain Injury? **Ann Em Med.** 2017, Dec; 70(6): 910-911.

TISSUE FLOSSING, JUMP AND SPRINT PERFORMANCE

Previous studies have demonstrated that tissue flossing can be useful in improvement of ankle range of motion and single leg jump performance. This study investigated the effect of tissue flossing at different time points following the application of the bands.

Subjects were 69, healthy, recreational athletes. The participants were randomized to either a FLOSS group or a control group (CON). Following a standardized warmup, both groups were asked to perform several athletic maneuvers, including a weight-bearing lunge test (WBLT), a counter movement jump and a 15-meter sprint test. Those in the FLOSS group had a band attached to each ankle before beginning warmup exercises, while the CON group had none.

A significant intervention-time interaction was found for the WBLT in favor of FLOSS as compared to CON ($p < 0.05$). These results were associated with trivial to small effect sizes at all time points. As compared to CON, better, but non-significant, improvement in CMJ force and sprint times were seen in the FLOSS group ($p > 0.05$) at up to 45 minutes after the bands were removed.

Conclusion: This study revealed that applying FLOSS bands to the ankle (talocrural) joint for two minutes may improve ROM, jump and sprint performance for up to 45 minutes after removing the bands.

Driller, M., et al. Tissue Flossing on Ankle Range of Motion, Jump and Sprint Performance: A Follow-Up Study. **Phys Ther Sport.** 2017, Nov; 28: 29-33.

CHILDHOOD BODY MASS INDEX AND ADULT ISCHEMIC STROKE

Ischemic stroke (IS) is a major cause of death and disability

worldwide. Studies investigating the association between childhood body mass index (BMI) and adult IS have produced inconsistent results. This study was designed to better understand this relationship.

Data for this study were retrieved from the Copenhagen School Health Records Register, including information for 372,636 children born from 1930 to 1989, with follow-up conducted using the National Health Registers through 2012. From records of physical examinations, BMI data were calculated. Data were included for adults at least 25 years of age at study entry, with follow-up ending on the date of a first ever IS, death or study completion on December 31, 2012.

Of the 307,677 individuals followed, no association was found between childhood BMI and risk of IS after 55 years of age. However, an association was found between early occurring IS and BMI at ages seven to 13. Using the BMI at age 13 of 16.7-17.9 kg/m² as a reference, the hazard ratios (HR) for early ischemic stroke were 1.71 for females with a BMI of greater than 23.3 kg/m² and 1.77 for a BMI of greater than 22.5 kg/m² in males. In addition, an increase in BMI between ages seven and 13 was associated with an increased risk of early IS in both males and females (HR 1.10 and 1.14, respectively).

Conclusion: This large Danish study found that childhood obesity at age 13, as well as increasing obesity between ages seven and 13, are associated with an increased risk of early ischemic stroke.

Gjaerde, L., et al. Association of Childhood Body Mass Index and Change in Body Mass Index with First Adult Ischemic Stroke. **JAMA Neurol.** 2017, Nov 1; 74(11): 1312-1318.

AEROBIC EXERCISE AND COGNITIVE CONTROL IN CHRONIC STROKE

Cognitive control/executive dysfunction is particularly associated with reduced functional capacity among patients with a chronic stroke. This study examined the immediate effect of a single session of aerobic exercise on cognitive control and attention among patients with chronic stroke.

Subjects were adults with a history of ischemic or hemorrhagic stroke at least six months prior, and full use of at least one arm and one

hand. The participants completed baseline assessment in two experimental sessions. During an exercise session, two minutes of self-paced warm-up was followed by 20 minutes of exercise, corresponding to 45% to 55% of the individual's heart rate reserve. An EEG was recorded throughout the procedure. The subjects were assessed before and after exercise with a modified Eriksen Flanker task.

The data revealed improvements in EEG measures after exercise. P300 amplitude at Fz was greater 40 minutes after exercise as compared with after rest ($p = 0.007$). P300 latency was also shorter at 20 minutes after exercise as compared with after rest for both congruent ($p = 0.02$) and incongruent ($p = 0.003$) conditions at the central electrode on the lesional side. Analyses of performance variables revealed no significant difference between the exercise and control groups.

Conclusion: This study suggests that cognitive control may be augmented 20 to 40 minutes after aerobic exercise among people with chronic stroke.

Swatridge, K., et al. The Acute Effects of Aerobic Exercise on Cognitive Control among People with Chronic Stroke. **J Stroke Cerebrovasc Dis.** 2017, Dec; 26(12): 2742-2748.

ELECTROACUPUNCTURE OF LANGUAGE-IMPLICATED ACUPOINT TONJII

Previous studies have suggested that combining electroacupuncture (EA) with traditional language therapy can be useful in treating post-stroke aphasia. As Tongli (HT 5) is a language-implicated acupoint, this study investigated the brain activity patterns of normal subjects stimulated at the HT 5 region.

Twenty healthy adults were studied. Half of the subjects were randomized to receive EA stimulation at Tongli, while the other half received stimulation at a sham acupoint. Both groups underwent fMRI analysis during a picture naming task, and then during electroacupuncture. Both groups underwent two, two-minute stimulation blocks, separated by 13 minutes of rest.

The fMRI studies demonstrated that EA produced brain activation across a very broad distribution of brain regions in both groups. However only in the Tonji group were

significant activations observed in the anterior language region, including BA 45, the pars opercularis and the pars triangularis.

Conclusion: This study of healthy adults found that electroacupuncture at the language-implicated acupoint HT 5 can induce significant activation of the anterior and posterior language regions, consistent with activation during a language task.

Lin-ling, L., et al. Electroacupuncture Stimulation of Language-Implicated Acupoint Tongli (HT 5) in Healthy Subject: MRI Evaluation Study. *Chin J Integr Med*. 2017. DOI: <https://doi.org/10.1007/s11655-017-2924-8>.

CORTICAL THICKENING AFTER MILD BRAIN INJURY

Previous studies have demonstrated cortical volume reduction within one month after a mild traumatic brain injury (mTBI). This study investigated the correlation between gray matter biomarkers, and neuromorphological alterations in the brain after an mTBI.

Subjects included 49 patients with acute mTBI and 49 age and education matched controls. At the time of injury, subjects had a normal CT exam and a Glasgow Coma Scale score of 13-15. All patients underwent neuroimaging and clinical evaluations within 2-7 days after injury and one year later. All underwent a comprehensive neuropsychological and clinical examination as well as MRI scans.

Compared with controls, patients with mTBI had lower cognitive performance across multiple neuropsychological tests including attention (alertness, selective attention/inhibitory control, divided attention). Most cognitive and clinical scores improved significantly over time except for that of divided attention. The MRI studies revealed cortical thickening in patients with mTBI and cortical thinning in controls ($p=0.0002$). The thickness increases were statistically significant in the right prefrontal cortex ($p=0.027$) but not in the left ($p=0.4$). No differences in cortical thickness were identified between patients and controls in the acute phase (Visit 1). One year later, however, mTBI patients, compared with controls, showed increased thickness within the prefrontal regions ($p=0.0002$ for anterior prefrontal cortex and DL prefrontal cortex).

Conclusion: This study of patients with mild traumatic brain injury found that, over the first year, cortical thickening occurred bilaterally in structures of the prefrontal cortex.

Acqua, P et al. Prefrontal Cortical Thickening after Mild Traumatic Brain Injury: A One-Year Magnetic Resonance Imaging Study. *J Neurotrauma*. 2017; 34:3270–3279.

SODIUM VALPROATE AND RECURRENT ISCHEMIC STROKE

Previous studies have demonstrated an association between an increased risk of ischemic stroke and a genetic variant on chromosome 7p21.1. The underlying gene is thought to be a histone deacetylase 9 (HDAC9). As sodium valproate (SVA) is an inhibitor of HDAC9, this study explored the association between exposure to SVA and the subsequent risk of recurrent stroke.

Data for this study were pooled from three prospective studies of patients with previous stroke or transient ischemic attack (TIA). These included the South London Stroke Register, the Vitamins To Prevent Stroke Study, and the Oxford Vascular Study. Data included in the analysis were age, sex, diagnosis of epilepsy, medications, and included SVA exposure before recurrent stroke. The SVA exposure populations were compared with control populations. Survival time was calculated from the index event (stroke or TIA) to the date of recurrent stroke.

A total of 11,949 patients were included in the analysis, all with a confirmed ischemic event at entry. Compared with other antiepileptic drugs, the recurrent stroke rate was lower among those taking SVA ($p=0.002$).

Conclusion: This study of patients with ischemic stroke or transient ischemic attack found that exposure to sodium valproate may be associated with a lower risk of recurrent events.

Brookes, R et al. Sodium Valproate, a Histone Deacetylase Inhibitor, is Associated with Reduced Stroke Risk after Previous Ischemic Stroke or Transient Ischemic Attack. *Stroke*. 2018, January; 49(1): 54–61.

CARDIAC OUTPUT AND CEREBRAL PERFUSION AFTER A STROKE

Restoring penumbral perfusion is the key therapeutic target in patients with acute ischemic stroke. In cases of insufficient or unsuccessful vessel recanalization, maintaining normal to higher mean arterial pressure (MAP)

is an accepted goal. MAP is expected to improve cerebral perfusion (CP), as constant cerebral blood flow (CBF) is maintained over a wide range of MAP due to vessel autoregulation. This study assessed to relationship between CP and CO.

Subjects were ten consecutive inpatients with a large ischemic stroke in the middle cerebral artery (MCA) territory. Symptom severity was assessed using the the National Institute of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) on admission and at discharge. Following hemodynamic baseline measurements, all patients were monitored with transcranial color-coded duplex sonography (TCCD) and transcranial perfusion sonography (TPS). Cerebral perfusion was assessed by transcranial color-coded duplex and transcranial perfusion sonography. Time-to-peak (TTP) values of defined regions of interest (ROI), as well as hemodynamic parameters, were assessed, including MAP and cardiac index (CI).

The analyses of CI and MAP levels, TTP and MCA velocity revealed highly significant inverse correlations of CI and TTP in the affected and unaffected basal ganglia ($p<0.001$) and ($p<0.0001$), respectively.

Conclusion: This study of patients with acute ischemic stroke suggests that the cardiac output may be more relevant than mean arterial pressure as a guide while optimizing cerebral penumbral perfusion.

Fuhrer, H et al Paradigm change? Cardiac Output Better Associations with Cerebral Perfusion than Blood Pressure in Ischemic Stroke. *Front Neurol*. 2017, December 22; 8(706).

TRANSCRANIAL MAGNETIC STIMULATION FOR THE ELDERLY WITH COGNITIVE IMPAIRMENT

Medications to improve cognitive impairment among patients with Alzheimer's Disease include acetylcholinesterase inhibitors and N-Methyl-D aspartate receptor antagonists. However, these drugs often have only limited and transient effects. As recent studies have suggested that repetitive transcranial magnetic stimulation (rTMS) may be effective for improving cognition in older adults, this systematic review and meta-analysis was designed to clarify the efficacy of this treatment modality for patients with mild cognitive impairment.

After completing an extensive medical literature search, the authors

(Continued from page 2)

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identified 13 published studies of which 9 were randomized controlled trials. From these, 7 parallel-group randomized controlled trials with complete outcome data were used for the final analysis. Most of the subjects had mild to moderate cognitive impairment at the onset of the trials.

Subjects included elderly patients with cognitive impairment, with 107 in the active and 87 in the sham treatment. The most common target of the rTMS was the dorsolateral prefrontal cortex. With sessions ranging from 1-30 per study treatment, and most including five sessions per week, those treated with rTMS were found to have a moderate improvement in cognition ($p=0.01$). No serious side effects were reported in the studies.

Conclusion: This study found that high frequency repetitive transcranial magnetic stimulation may improve cognition among elderly patients with mild to moderate cognitive impairment.

Cheng, C et al. Effects of Repetitive Transcranial Magnetic Stimulation on Improvement of Cognition in Elderly Patients with Cognitive Impairment: A Systematic Review and Meta-analysis. *Int J Geriatr Psychiatry*. 2018; 33: e1-e13.

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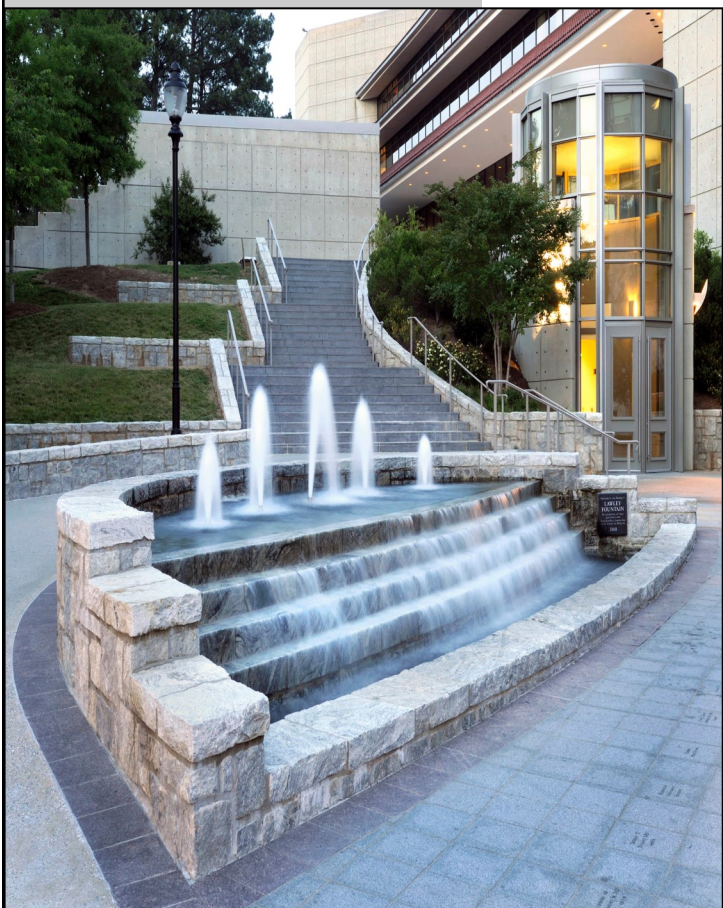
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