# MUSCULOSKELETAL

## IN REVIEW

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### PLATELET RICH PLASMA FOR HAMSTRING INJURIES

Acute hamstring injury often results in a loss of training and competition time. The best clinical treatment for these injuries is not yet clear. As autologous platelet rich plasma (PRP) injections have received attention as a treatment for other musculoskeletal conditions, this study explored the effects of these injections on patients with grade 2 hamstring injuries.

This single- blind, randomized, controlled trial included patients over 18 years of age presenting with a grade 2 hamstring injury. The participants were randomized to receive either a PRP injection combined with a rehabilitation program or a rehabilitation program alone. The rehabilitation program focused on agility and trunk stabilization exercises. Subjects in both groups were followed until full recovery or the end of the study. The primary outcome measure was time to return to play.

Of the patients eligible for inclusion in this study, 24 were included in the final analysis. The participants' median age was 21 years, with a mean duration of injury before enrollment of 4.6 days. The mean times to return to play were 26.7 days in the treatment group and 42.5 days in the control group. Half of the patients in the PRP group achieved full recovery at week 26, while half of those in the control group achieved full recovery at week 39. Patients in the treatment group had significantly lower pain severity scores than controls at all time points (p=0.007).

**Conclusion:** This randomized, controlled trial of patients with grade 2 hamstring injuries found that platelet rich plasma injections, combined with rehabilitation, were more effective than rehabilitation alone for returning athletes to play.

Hamid, M., et al. Platelet Rich Plasma Injections for the Treatment of Hamstring Injuries. **Amer J Sports Med.** 2014, October; 42(10): 2410-2418.

### PHYSICAL THERAPY FOR TOTAL JOINT REPLACEMENT

Total joint replacement has emerged as the treatment of choice for end-stage arthritis of the hip or knee. Post-acute care spending accounts for 73% of the variation in spending across geographic regions of the United States, and, thus, presents as an opportunity to decrease total costs of joint replacement. This study investigated the association between preoperative physical therapy and post-acute care utilization and cost.

This observational, cohort, comparison study used the Centers for Medicare and Medicaid Services' limited data set files. These files include all claims for payments related to inpatient, outpatient, home health agency, skilled nursing facility, carrier and durable medical equipment within a defined referral cluster in Ohio. The use of preoperative physical therapy was identified for 30 days prior to admission for surgery. Costs were compared between the preoperative physical therapy group and the non-preoperative physical therapy group.

A total of 4,733 cases were available within the targeted cluster for 2008 and 2009. A significantly lower rate of post-acute care ($p<0.0001$) was found for patients receiving preoperative physical therapy (54.2%) as compared to those without preoperative therapy (79.7%). This finding included a lower rate of skilled nursing facility admission, home health service within 90 days of discharge and inpatient rehabilitation facility admission ($p<0.0001$, $p=0.0001$, $p<0.0001$ and $p=0.027$, respectively). The adjusted, absolute difference in costs between the groups was $1,215.

**Conclusion:** This study of patients undergoing hip or knee replacement suggests that preoperative physical therapy can significantly decrease the use of post- acute care services and overall costs.

Snow, R., et al. Associations between Preoperative Physical Therapy and Post-acute Care Utilization Patterns and Costs in Total Joint Replacement. **J Bone Joint Surg (Am).** 2014, Oct 1; 96 (19): e165.

### RETURN TO SPORT AFTER VALGUS OSTEOTOMY

Valgus osteotomy is considered the surgical option of choice for the treatment of early-stage, medial compartmental osteoarthritis (OA) of the knee among patients ages 65 years or less. As return to sport after osteotomy is poorly documented in the literature, this study evaluated recovery of physical and sporting activity after this surgery.

Subjects were 83 patients with a mean age of 50.4 years, each of whom underwent medial osteotomy for symptomatic OA of the knee. The patients were assessed with KOOS, Lysholm, Tegner and UCLA scores. Sports levels before and after the surgery were compared. The participants were followed for an average of 5.75 years.

At follow-up, 85.5% of the patients had resumed sporting activity, with 79.5% noting that their sporting level had not declined postoperatively. Mean Lysholm scores improved significantly after surgery, while Tegner and UCLA scores did not

reach significance in change. The frequency of weekly sport activity did not decrease significantly, although the duration of activity declined from 4.68 hours to 4.25 hours (p=0.04). Of the 20 patients who ran before surgery, 85% were able to return to running.

**Conclusion:** This study of patients with moderate medial compartment osteoarthritis of the knee found that a valgus osteotomy allowed most to return to their sporting activity, with most also able to return at the level at which they had been participating before developing osteoarthritis.

Saragaglia, D., et al. Return to Sports after Valgus Osteotomy of the Knee Joint in Patients with Medial Unicompartmental Osteoarthritis. **Intern Ortho.** 2014, October; 38 (10):2109-2114.

## TOTAL JOINT REPLACEMENT COMPLICATIONS AND ANTICOAGULANT THERAPY BRIDGING

To reduce the risk of perioperative bleeding, oral anti-coagulation is often interrupted prior to major surgery. In 2012, the American College of Chest Physicians (ACCP) updated practice guidelines to include suggestions for bridging therapy of patients undergoing elective surgery. This study was designed to determine whether bleeding complication rates are higher among patients requiring bridging prior to total hip arthroplasty (THA) or total knee arthroplasty (TKA).

Patients receiving primary unilateral THA or TKA between 2011 and 2012 were included, who required bridging therapy according to the protocol based on the ACCP guidelines. Bleeding complications in this group were compared with a previously performed cohort study undergoing surgery by the same group of surgeons.

Major surgical bleeding occurred in 12 of the 13 bridged patients. Of those, nine developed a hematoma, leading to prolonged immobilization. Bleeding complications resulted in intervention in nine patients, with seven (54%) receiving blood transfusions, compared to 0.3% in the total group ($p<0.05$). The mean lengths of stay were 14.2 days in the bridging group and 5.3 days in the control group ($p<0.05$)

**Conclusion:** This study demonstrates a high rate of complications among patients undergoing hip or knee replacement surgery who received low molecular weight heparin bridging therapy prior to surgery.

Leijtens, B., et al. High Complication Rate after Total Knee and Hip Replacement Due to Perioperative Bridging of Anticoagulant Therapy Based on the 2012 ACCP Guideline **Arch Orthop Trauma Surg.** 2014, September; 134(9):1335-1341.

## TOTAL KNEE REPLACEMENT IN YOUNG ACTIVE PATIENTS

As total knee arthroplasty (TKA) is more frequently being performed in younger patients it is important to understand the long-term outcomes of these patients. This study followed a cohort of 88 patients, with an average age of 51 years, each of whom underwent arthroplasty between 1977 and 1992.

All 114 TKAs in 88 patients, originally reviewed in a paper published in 1997, were assessed at long-term follow-up. At the time of the initial review, six TKAs in six patients had been revised, and two patients had died without revision. For the remaining 80 patients, clinical data were obtained, including, when possible, a physical examination. For those unable to visit a physician, telephone interviews were conducted. Patients were assessed with the Tegner and Lysholm activity scores, a Hospital for Specialty Surgery (HSS) score and a Knee Society Score (KSS).

Follow-up data were obtained for 107 of the 113 TKRs, with the latest follow-up at 25.1 years. The average HSS scores for those available for follow-up were 57.9 at the preoperative examination, 92 in 1997 and 85.3 at the long-term follow-up. The KSSs were 94.9 in 1997 and 87.4 at long-term follow-up. There were significant improvements in the activity scores both in 1997 ($p<0.0001$) and at long-term follow-up ($p<0.0001$), as compared to preoperative scores. At the most recent follow-up, 27.8% reported the same activity levels as they did preoperatively, and 72.2% had improved activity levels.

**Conclusion:** This follow-up of middle-aged individuals undergoing total knee arthroplasty found continued improved activity and function scores 25 years post-surgery.

Long, W., et al. Total Knee Replacement in Young, Active Patients: Long-Term Follow-Up and Functional Outcome. **J Bone Joint Surg.** 2014, September: 96: E1 59(1 -7).

## TREATMENT OF OLECRANON BURSITIS

Olecranon bursitis can be characterized as aseptic or septic, with the most common causal organism of infection being *Staphylococcus aureus*. The optimal treatment for this condition lacks consensus. This systematic review assessed clinical outcomes following the treatment of both aseptic and septic bursitis.

Data from eligible studies were extracted, including patient characteristics, treatment protocols and clinical outcomes. The results of various interventions were compared. Twenty-nine studies reporting on 1,278 patients were included in this systematic review. Patients exclusively received nonsurgical management in 10 of 29 studies, including antibiotic therapy, aspiration, corticosteroid injection and/or nonsteroidal anti-inflammatory drugs alone. Patients exclusively received surgical management in seven studies. Treatments for septic bursitis

included antibiotics in 100%, aspiration in 82% and surgery in 47.1%. When septic and aseptic bursitis were analyzed together, clinical resolution was more common after nonsurgical than surgical management (p=0.0476).

Complications were more common in patients treated for aseptic bursitis, as compared to those treated for septic bursitis (p=0.0108). In patients with aseptic bursitis, persistent infection was more likely after surgical than nonsurgical treatment (p=0.006).

**Conclusion:** This literature review suggests that nonsurgical management of olecranon bursitis leads to better clinical resolution and lower rates of complications than does surgical management.

Sayegh, E., et al. Treatment of Olecranon Bursitis: A Systematic Review. **Arch Ortho Trauma Surg**. 2014, November; 134(11): 15171536.

## ALCOHOL CONSUMPTION AND MORTALITY

Previous studies have demonstrated an association between alcohol consumption and overall mortality, often described as a "J" shaped curve. However, no consensus yet exists concerning the optimal dose at which major benefits accrue. This study performed a dose response analysis, evaluating survival levels according to levels of alcohol consumption.

This study included 88,077 participants in the population based Cohort of Swedish men (COSM) and the Swedish Mammography Cohort (SMC). Subjects were assessed for baseline age, body mass index, smoking status, educational level and lifestyle factors, including alcohol consumption. Mortality was compared by alcohol consumption categories.

Among women, after adjusting for potential confounders, any category of alcohol consumption was found to be associated with substantially improved survival. A rapid increase in survival was found for women up to six g per day, where the improvement in survival was about 1.5 years as compared to lifetime abstainers. Among men, those with an intake of 10 to 15 g per day lived 1.3 years longer than lifetime abstainers, with survival time improving up to 15 g per day. The increase in survival seemed related to a decreased risk of cardiovascular disease for men and of both cardiovascular disease and cancer for women.

**Conclusion:** This study found that alcohol consumption of up to two drinks per day on average was associated with longer survival in both men and women, with the greatest benefits achieved with 0.5 to one drink per day for women and one to two drinks per day for men.

Bellavia, A., et al. Alcohol Consumption and Mortality: A Dose Response Analysis in Terms of Time. **Ann Epidem.** DOI:10.1016/ j.annepidem.2013.12.013. 2014.

## ALCOHOL CONSUMPTION AND MORTALITY

Previous studies have demonstrated that brain derived neurotropic factor (BDNF) is highly expressed throughout the central nervous system. Reduced levels have been observed in the hippocampus and parietal lobe, as well as the serum, of people with mild cognitive impairment and Alzheimer's disease (AD). This study was designed to determine whether serum BDNF levels are associated with the risk for incident dementia and AD.

Data were obtained from the Framingham Heart Study, initiated in 1948, and the offspring study initiated in 1971. Serum BDNF concentrations were measured on previously frozen blood samples. As all Framingham Heart Study participants are under continuous surveillance for impaired cognitive function, these data were available to determine the associations between BDNF and incident dementia and AD.

During a median of 10 years' follow -up, 140 participants developed dementia, with 117 developing AD. After controlling for age, gender and cohort, each standard deviation increment of serum BDNF levels was associated with a 23% lower risk for future dementia (p=0.006) and PD (p=0.01). Compared with the lowest quintile, the top quintile of BDNF levels was associated with less than half the risk for developing AD and other dementias. However, the association between BDNF level and risk for dementia and PD was significant only in women, people age 80 years or older, and participants with a college degree.

**Conclusion:** This community based cohort study of dementia free individuals found that higher levels of BDNF are associated with a reduced risk of developing Alzheimer's disease and other forms of dementia, with this association only apparent in women, those older than 80 years of age and those with a college degree.

Weinstein, G., et al. Serum Brain Derived Neurotropic Factor and the Risk for Dementia: The Framingham Heart Study. 2014, January. **JAMA Neurol.** 2014, January; 71(1): 55-61.

## COGNITIVE ACTIVITY AND DURATION OF POSTCONCUSSIVE SYMPTOMS

While cognitive rest is often recommended after a concussion, limited data are available to support this recommendation. This study assessed the independent effect of cognitive activity on symptom duration.

This single center, prospective cohort study included patients presenting to the Sports Concussion Clinic of Boston's Children's Hospital between 2009 and 2011. The participants were assessed for cognitive activity, using the Cognitive Activity Scale, and for concussion, using the Post-Concussion Scale Score (PCSS). Patients were considered recovered when they were symptom free and no longer taking medications prescribed for concussion symptoms. The primary outcome variable was the duration of concussion symptoms.

During the study period, 335 participants qualified for inclusion in the analysis. The mean duration of symptoms was 43 days. Univariate modeling indicated that patients in the highest quartile of cognitive activity days took significantly longer to recover than did those in the first to third quartiles. Multivariate Cox proportional hazards modeling revealed that the total score on the PCSS at the initial visit and cognitive activity days were independently associated with the duration of symptoms. Interestingly, gender, age, loss of consciousness, amnesia, and number of previous

concussions were not independently associated with time to symptom resolution.

**Conclusion:** This study of children with concussions found that extensive cognitive activity after concussion is associated with a longer time to recover.

Brown, N., et al. Effect of Cognitive Activity Level on Duration of Post-Concussion Symptoms. **Pediatrics**. 2014, February 1; 133(2): e299-e304.

## MENSTRUAL PHASE AND OUTCOME AFTER MILD TRAUMATIC BRAIN INJURY

Some data suggest that women have a higher incidence of mild traumatic brain injury (MTBI) than men who play similar sports. Other studies have found better post--TBI outcomes for women than men among premenarche or postmenopausal women. This study compared the outcomes of women by the phase of menstrual cycle at the time of injury.

Female patients between the ages of 16 and 60 years who presented to the emergency department within four hours of MTBI were considered for this study. Admission serum progesterone level was used to determine the menstrual cycle phase at the time of injury. For comparison, the patients were divided into a synthetic progestin (SP) group, a follicular phase (FP) group, and a luteal phase (LP) group. In addition, CT results were obtained, and one-month outcome was assessed by phone using the Rivermeade Postconcussion Questionnaire (RPCQ) and quality of life with the EuroQol/EQ5D. The primary outcome measure of interest was post-concussive symptoms at one month using the RPCQ. Outcomes were compared by menstrual phase.

The EuroQol/EQ5D index differed significantly between groups, with the SP group obtaining the highest scores and the LP group the lowest scores. The LP group was the most symptomatic, as measured by RPCQ scores, although, across all measures, none of the differences were statistically significant. For all outcomes, subjects in the LP group had approximately twice the odds of scoring worse on the outcome scale than did subjects in the FP group. The authors suggest that these findings support the hypothesis that the acute withdrawal of progesterone after mild traumatic brain injury may worsen the outcome.

**Conclusion:** This study of women 16 to 60 years of age with a mild traumatic brain injury found that those in the gluteal phase of the menstrual cycle at the time of injury have worse outcomes than do women in the follicular phase, or who were taking synthetic progestins.

Wunderle, K., et al. Menstrual Phase as a Predictor of Outcome after Mild Traumatic Brain Injury in Women. **J Head Trauma Rehab.** 2014. DOI: 1097/HTR.0000000000000006

## CYTISINE VERSUS NICOTINE FOR C-REACTIVE PROTEIN AND HEMORRHAGIC STROKE

After spontaneous intracerebral hemorrhage (sICH), early hematoma growth (EHG) occurs in 20 to 40 percent of patients, resulting in a worse prognosis. As inflammation is a major feature of intracerebral hemorrhage pathology, C-reactive protein (CRP) has been associated with 30-day mortality among these patients. However, its relationship to early hematoma growth (EHG) is unknown. This study was designed to determine the relationship between CRP and EHG after sICH.

This prospective, multi-center observational study included patients 18 years of age or older, with a diagnosis of sICH. Patients were included in the analysis if they presented within six hours of onset, had CRP determined at study entry and completed clinical and imaging data. An initial CT was obtained at admission, with a second CT at 24 hours (or earlier if clinically indicated). The primary outcome variable was EHG, as defined by absolute growth of greater than 12.5 $cm^3$, or relative growth of greater than 33% as measured by a follow-up CT.

Among the 215 men and 184 women included in the final analysis, EHG occurred in 25.8%, occurring more often among those with early neurologic worsening ($p<0.001$). A univariate analysis revealed that EHG and early neurologic worsening were significant more frequent, and hemorrhagic growth significantly greater, among those with a CRP of above 10 mg/ml.

**Conclusion:** This study of patients with spontaneous intracerebral hemorrhage found that elevated plasma C-reactive protein within the first few hours of hemorrhage is associated with both early hemorrhagic growth and early neurologic worsening.

Napoli, M., et al. C-Reactive Protein Predicts Hematoma Growth in Intracerebral Hemorrhage. **Stroke.** 2014, January; 45(1): 59-65.

## HIGH CHOLESTEROL AND LONG-TERM SURVIVAL AFTER ISCHEMIC STROKE

Treatment with statin medications is associated with a reduced recurrence of ischemic stroke, with improvement in survival and functional outcome up to one year after stroke. However, other studies have also indicated a positive association between elevated cholesterol at ischemic stroke onset and improved short-term functional outcomes and 10-year survival. This study sought to further clarify the effects of cholesterol levels and the impact of statin treatment on short and long-term survival after acute ischemic injury.

This retrospective study included patients admitted to the stroke unit of the Karolinska University Hospital. Clinical and biochemical data were obtained by record review. All participants underwent admission computed tomography and/or magnetic resonance tomography of the brain, echocardiogram, carotid ultrasound and lab work, and were followed for up to seven years.

Of the 169 one-month survivors, 159 had available data regarding admission cholesterol. Three-month survival rates were 92% and 100% in the low and high cholesterol groups, respectively. The one, two, and five-year survival rates were 87%, 81% and 57% in the low cholesterol group, and 98%, 95% and 84% in the high cholesterol group ($p=0.001$).

The annual mortality rate in patients with low cholesterol was approximately seven percent after the first year, reaching 58% by the end of the observation period in the low cholesterol group. In contrast, the high cholesterol group had an annual mortality of three percent,

reaching 31% after seven years. A multivariate analysis revealed that low admission cholesterol was an independent predictor of long-term mortality after adjusting for age at admission and NIHSS scores.

**Conclusion:** This retrospective study found that, in patients with acute ischemic stroke, higher admission cholesterol levels were associated with improved long-term survival.

Markaki, I., et al. High Cholesterol Levels are Associated with Improved Long-Term Survival after Acute Ischemic Stroke. **J Stroke Cerebrovas Dis**. 2014, January; 23 (1): E 47-E 53.

## DULOXETINE FOR NEUROPATHIC PAIN IN MULTIPLE SCLEROSIS

Individuals with multiple sclerosis (MS) often report neuropathic pain. Despite extensive therapies to treat this pain, few controlled studies have focused on the treatment of this condition. This study assessed the efficacy and tolerability of duloxetine for reducing pain severity in patients with MS.

This randomized, double-blind, placebo-controlled trial included 2,039 adult patients with MS who complained of neuropathic pain of at least three months' duration. Those randomized to the duloxetine treatment group received 30 mg for one week, and then 60 mg for five weeks. Those in the placebo group received placebo once daily for six weeks. The primary efficacy measure was change from baseline average pain intensity (API) at six weeks after randomization. Secondary measures included change from baseline in the weekly mean of night pain intensity (NPI) ratings, Clinical Global Impression of Severity Scale scores, Brief Pain Inventory scores, and scores on the Multiple Sclerosis Quality-Of-Life - 54 instrument.

The mean change in weekly API ratings from baseline to week six was greater in the duloxetine group than in the placebo group (p=0.001). This difference was significant as early as week one (p=0.016), and remained significant at each subsequent week of acute phase therapy (p<0.01 for each). More patients in the treatment group withdrew from the study due to adverse events, with the most common being dizziness and somnolence.

**Conclusion:** This study of patients with multiple sclerosis accompanied by neuropathic pain found duloxetine to be an effective intervention for this pain.

Vollmer, R., et al. A Randomized, Double-Blind, Placebo-Controlled Trial of Duloxetine for the Treatment of Pain in Patients with Multiple Sclerosis. Pain Practice. 2014, November; 14(8): 732–744.

## FLUID COLLECTIONS, AMPUTATIONS AND INFECTION

Combat related amputations are often complicated by gross contamination, bacterial colonization and frequent infections. Postoperative fluid collections in amputations have been the focus of previous studies. However, there is little guidance in the literature regarding the management or clinical relevance of post-amputation fluid collections. This study was designed to better understand the frequency and clinical applications of postoperative fluid collections in combat related amputations.

This retrospective study included 300 consecutive, major lower extremity amputations treated before 2009. All patients were injured in combat operations and had sustained at least one major lower extremity amputation. Data collected included demographics, description of surgery, and clinical parameters, including white blood cell count, maximum temperature, presence of bacteremia, tachycardia and oxygen desaturation, as well as extremity examination and radiographic findings. Wound infection was defined as returning to the operating room with a positive deep wound culture.

Of the subjects included in the final analysis, 55% demonstrated fluid collection in the early postoperative period. The presence of a fluid collection on cross-sectional imaging was not associated with infection. An association was found between objective clinical signs of infection, including erythema and/or drainage, and the presence of infection (p<0.001). The only radiologic or imaging parameter significantly associated with infection was the presence of air (p = 0.027)

**Conclusion:** This study demonstrated that fluid collections are common in combat-related amputations, especially in the early postoperative period, and were not found to be associated with an increased risk of wound infection.

Polfer, E., et al. Fluid Collections in Amputations Are Not Indicative or Predictive of Infection. **Clin Ortho Related Res**. 2014, October; 472: 2978-2983.

## HYPERCHOLESTEROLEMIA AND FROZEN SHOULDER

Frozen shoulder is a common disorder with many known risk factors. These include systemic diseases such as thyroid disorders and diabetes mellitus. Some have suggested hyperlipidemia as a possible risk factor for frozen shoulder, noting similarities in pathologic findings between this disorder and those of Dupuytren's contracture. This study tested the hypothesis that elevated serum lipid levels are associated with frozen shoulder.

Subjects were 300 patients diagnosed with primary frozen shoulder between October of 2009 and April of 2013. The control group comprised 900 age- and gender-matched adults who presented for general checkups. The subjects were excluded if they had diabetes, thyroid dysfunction, previous shoulder surgery or trauma. All underwent laboratory evaluations, including a serum lipid profile.

A univariate analysis of serum lipid levels revealed that primary frozen shoulder is significantly associated with total cholesterol lipoprotein (p=0.001), high density lipoprotein (p=0.001), and non-high- density lipoprotein cholesterol (p<0.001). No associations were found between serum triglyceride levels and frozen shoulder. In addition, measured hyper low-density lipoproteinemia (p<0.001), hyper high density lipoproteinemia (p<0.001) and hyper non-high-density lipoprotein cholesterolemia (p<0.001) were significantly associated with primary frozen shoulder.

**Conclusion:** This study found that hypercholesterolemia and inflammatory lipoproteinemia are associated with primary frozen shoulder.

Sung, C., et al. Are Serum Lipids Involved in Primary Frozen Shoulder? A Case Control Study. J Bone Joint

Surg (Am). 2014, October; 96 (21):1828-1833.

## OPIOID USE AND ANDROGEN DEFICIENCY

Previous studies have demonstrated an association between opioid use and androgen deficiency in men with chronic pain. This study examined the association between the opioid duration of action and the risk of development of androgen deficiency.

This retrospective cohort included 1,585 men, 18 to 80 years of age. All had been dispensed 90 days of opioid prescriptions, and had at least one testosterone level measured between January 1, 2007, and December 31, 2011. The opioids were defined as either long acting or short acting. Those taking more than two different opioids during the study period were excluded. Daily doses of opioids were converted to a morphine standardized equivalent (MSE).

Bivariate analysis revealed that men who used long-acting opioids were more likely to be androgen deficient than were men taking short-acting opioids ($p<0.001$). In addition, men with diabetes ($p<0.001$), hypertension ($p<0.001$), hyperlipidemia ($p=0.002$), those taking statins ($p<0.001$), or those with a body mass index of at least 30 ($p<0.001$), were more likely to have an androgen deficiency. The median MSE for androgen deficient men was 60 mg, while the median MSE for those not androgen deficient was 40 mg.

**Conclusion:** This study found that, among men taking opioids, the duration of action of the opioid is inversely related to testosterone level.

Rubenstein, A., et al. Elucidating Risk Factors for Androgen Deficiency Associated with Daily Opioid Use. **Am J Med**. 2014, December; 127 (12): 1195-1201.

## INJECTION SAFETY IN PATIENTS ON WARFARIN

While some studies suggest that joint or soft tissue injections are relatively safe for patients undergoing anti-coagulation, many recommend reversing anti-coagulation before administering these procedures. This study was designed to further understand the safety of these joint injections in patients prescribed warfarin.

This study reviewed the outcomes of patients before and after a protocol change in a rheumatology department. The protocol prior to September of 2011 was to withhold warfarin for five days prior to an elective joint or soft tissue injection. At that time, warfarin was replaced with low molecular weight heparin, which was not given on the day of the procedure. After September of 2011, the new protocol allowed warfarin to be continued, with the procedure performed if the INR was less than three. All procedural complications within four weeks were identified through contact with the telephone helpline or with a medical practitioner. In the initial cohort, 32 procedures were performed in 18 patients. No clinical hemarthroses or other complications occurred. In the later cohort, 32 procedures were performed in 21 patients. Among these patients, there were also no clinical hemarthroses or other complications. One patient, with a history of deep venous thrombosis, experienced a recurrence when warfarin was withheld for a joint injection.

**Conclusion:** This study of patients undergoing joint or soft tissue injections found no significant bleeding events among patients who received injections while taking warfarin and with the international normalized ratio within therapeutic range.

Hoo, J., et al. Safety of Joint and Soft Tissue Injections in Patients on Warfarin Anticoagulant Action. **Clinical Rheum.** 2013, December; 32(12): 1811-1814.

## MILK INTAKE AND RISK OF MORTALITY AND FRACTURES

Increased milk intake has been promoted to prevent osteoporosis and fractures. However, as the main dietary source of D-galactose, milk has been found to have negative effects on health. Animal studies have in fact demonstrated that D-galactose may accelerate aging. This study examined the effect of milk intake on mortality and fracture risk in women and men.

In two large Swedish cohorts, 61,433 women and 45,339 men answered food frequency questionnaires. From those were obtained consumption patterns concerning milk, fermented milk, yogurt and cheese. In addition, a clinical subcohort from each of the two studies underwent urine and serum analysis for markers of oxidative stress and inflammation. Those data were compared with mortality from all causes, as well as fracture events.

The median follow-up for women was 22 years, and for men was 13 years. Among women, compared with the consumption of less than one glass per day, consumption of three or more glasses per day had a greater risk of total mortality (hazard ratio=1.93) for any fracture (hazard ratio=1.16) and for hip fracture (hazard ratio=1.60). Conversely, women with a high intake of cheese or fermented milk products had lower mortality and fracture rates compared to those with low intake ($p<0.001$). For men, the excess risk was less pronounced for mortality, with no reduction in fractures noted with increased milk intake by men. Milk intake was positively associated with 8-iso-PGF2 alpha in both genders, and with interleukin six in men.

**Conclusion:** This study found that higher consumption of milk in women and men is not accompanied by a lower risk of fracture, and may be associated with a higher risk of death.

Michaelsson, K., et al. Milk Intake and Risk of Mortality and Fractures in Women and Men: Cohort Studies. BMJ. 2014; 349: g6015

## MEDICATIONS FOR DIABETIC NEUROPATHY

Diabetic neuropathy is a common, long-term complication that can decrease quality of life. While various neuropathic agents are useful for treating this pain, choosing one or the other can be challenging. This systematic review investigated the relative effectiveness of various medications used for the treatment of diabetic neuropathy.

Databases were reviewed for randomized, controlled trials published between January of 2012 and April of 2014. The trials

assessed the efficacy of medications for treating diabetic neuropathy, and compared the medication to placebo or to another medication.

Sixty-five, randomized, controlled trials, including 27 medications with 12,632 patients analyzed. By drug class, SNRIs, topical capsaicin, TCAs, and anticonvulsants all resulted in larger and statistically significant reductions in pain, as compared with placebo. Head-to-head trials showed that SNRIs and TCAs reduced pain more than did anticonvulsants and topical capsaicin. Studies that evaluated long-term efficacy found that the aldose reductase inhibitors fidarestat, duloxetine and oxcarbazepine are all more effective than placebo. Indirect and direct comparisons among specific medications revealed greater pain control with carbamazepine, venlafaxine, duloxetine and amitriptyline as compared with placebo.

**Conclusion:** This systematic review and meta-analysis of pharmacologic interventions for painful diabetic neuropathy found that carbamazepine, venlafaxine, duloxetine and amitriptyline are significantly better than placebo for controlling pain.

Griebeler, M., et al. Pharmacologic Interventions for Painful Diabetic Neuropathy. **Ann Intern Med.** 2014, November 4; 161(9): 639-649.

## NOVEL ORAL ANTICOAGULANTS AND INTRACRANIAL HEMORRHAGE

Individual trials have shown a decreased risk of intracranial hemorrhage (ICH) with use of novel oral anticoagulants (NOACs). Currently, three such medications are approved for stroke prevention in patients with atrial fibrillation. These include dabigatron, rivaroxaban and apixaban. This study was designed to better understand the relative risk of each of these medications for ICH.

This meta-analysis reviewed databases for randomized trials which contained studies of the relevant NOACs. Six, randomized trials compared one of these NOACs with conventional warfarin or aspirin. Endpoints abstracted from the studies included ICH and/or hemorrhagic stroke.

The authors identified six studies with NOACs compared with warfarin and aspirin, enrolling a total of 57,491 patients. The mean time in the therapeutic range was 61.2% for warfarin, with a minimum duration of follow-up of 12 weeks, and a maximum of two years. The absolute risk of ICH was 0.52% for dabigatran, 0.78% for rivoxaban and 0.52% for apixaban, as compared to 1.24% for warfarin. The differences between the NOACs did not reach statistical significance.

**Conclusion:** This review and meta-analysis found a reduced risk of intracranial hemorrhage with the use of novel oral anticoagulant medications, as compared with warfarin or aspirin.

Chatterjee, S., et al. New Oral Anticoagulants and the Risk of Intracranial Hemorrhage. Traditional and Bayesian Meta-Analysis and Mixed Treatment Comparisons of Randomized Trials of New Oral Anticoagulants in Atrial Fibrillation. **JAMA-Neurol.** 2013, December; 70 (12): 1486-1490.

## OSTEOPOROTIC COMPRESSION FRACTURES TREATED WITH A RIGID BRACE, SOFT BRACE OR NO BRACE

Benign osteoporotic compression fractures without neurologic deficits are inherently stable fractures, most often treated nonoperatively. As treatment often includes wearing an orthosis, this study compared the outcomes of patients treated with no brace, a rigid brace or a soft brace.

Sixty patients, with an average age of 72.25 years and with an acute, one -level, osteoporotic compression fracture, were randomized to receive a soft brace, a rigid brace or no brace. The patients were instructed to wear the brace at all times except when lying down, for a total of eight weeks. The primary outcome measure was the Oswestry Disability Index (ODI) score at 12 weeks after fracture.

At 12 weeks after fracture, ODI scores were 35.95 points in the no brace group, 37.83 points in the soft brace group and 33.54 points in the rigid brace group. In addition, no significant differences were found in secondary outcomes, including visual analogue scale scores for back pain and body compression ratios. No significant differences were noted among the three groups in use of opioids at 12 weeks.

**Conclusion:** This prospective, randomized study of patients with osteoporotic compression fractures found no difference in pain or disability scores at 12 weeks between those treated with no brace and those treated with either a soft or rigid brace.

Kim, H., et al. Comparative Study of the Treatment Outcomes of Osteoporotic Compression Fractures without Neurologic Injury Using a Rigid Brace, a Soft Brace and No Brace. **J Bone Joint Surg (AM).** 2014; 96(23): 1959-1966.

## OUTCOMES OF A SINGLE CORTICOSTEROID INJECTION FOR TRIGGER FINGER

Trigger finger is one the most common pain disorders, with an estimated lifetime risk of 2.6% in the general population. Prior studies have shown the success of corticosteroid injections to be in the range of 61% to 84% with one to three injections. This study investigated the long-term effectiveness of a single corticosteroid injection for trigger finger.

This retrospective case series involved successive patients treated for trigger finger from January of 2000 to December of 2007. The records were examined for primary outcome of treatment failure, defined as a subsequent injection or surgical release of the affected digit. Success was identified as an absence of symptoms at subsequent follow-up visits, or by telephone interview.

Of the 366 patients, 44% had multiple trigger fingers, and 24% were diabetic at the time of the injection. Of those, 54.6% had repeat injection or surgical release, and 45.4% had no further intervention. Treatment success occurred in 49.2% of females and 38.1% of males ($p<0.05$). Of those with treatment failure, 64% required repeat injection and 33% underwent surgical release. Of those with single digit trigger fingers, 50.7% had treatment success, as compared with 30.5% of those with multiple trigger fingers ($p<0.05$).

**Conclusion:** This retrospective study of patients undergoing a single corticosteroid injection for trigger finger found that 45% experienced long-term treatment success.

Wojahn, R., et al. Long-Term Outcomes following a Single Corticosteroid Injection for Trigger Finger. **J Bone Joint Surg (AM)**. 2014, November 19; 96(22): 1849-1854.

## PLATELET RICH PLASMA FOR PRESSURE ULCERS

Pressure ulcers are one of the major, secondary complications of spinal cord injury (SCI). These ulcers can be difficult to heal, and can be a source of morbidity and even mortality. As platelet rich plasma (PRP) is considered to be an advanced wound therapy for both chronic and acute wounds, this study evaluated the effect of this treatment on patients with pressure ulcers related to a SCI.

This prospective study included 25 adult patients with SCI, each with an injury below C-4 and at least two, non-healing pressure ulcers. The larger of the ulcers was chosen for the twice weekly PRP treatment, while the smaller ulcer underwent daily saline dressing. Progress was monitored over five weeks using the Pressure Ulcer Scale for Healing, wound surface area and punch biopsies of the wound margin for histopathology.

While scores on the Pressure Ulcer Scale for Healing improved over five weeks in both groups, no significant difference was seen between the two groups. The decrease in wound surface area was significant in the PRP group, but not in the control group. At five weeks, 60% of the PRP group showed well- formed granulation tissue and epithelialization, as compared to 30% in the control group. Also at five weeks, 96% of the ulcers in the PRP group demonstrated improvement, as compared to 60% in the control group.

**Conclusion:** This study of patients with spinal cord injury and chronic pressure ulcers found that platelet rich plasma, applied topically to the wound may be superior to standard saline dressings for ulcer healing.

Singh, R., et al. Role of Local Application of Autologous Platelet Rich Plasma in the Management of Pressure Ulcers in Spinal Cord Injury Patients. **Spinal Cord.** 2014, November; 52(11): 809-816.

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# *MUSCULOSKELETAL*

## *IN REVIEW*

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