Pain Management Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

BMD = bone mineral density; **CBT** = cognitive behavioural therapy; **NRS** = numerical rating scale; **PTSD** = post-traumatic stress disorder; **RCT** = randomised clinical trial; **SCS** = spinal cord stimulation; **TDCS** = transcranial direct current stimulation.

Welcome to issue 48 of Pain Management Research Review.

Among the papers selected for this issue, there are several meta-analyses, including comparisons of the effectiveness and safety of perineural versus intravenous dexamethasone for peripheral nerve block, and of surgical techniques for managing painful neuromas, and concluding with an assessment of intra-articular injections of botulinum toxin for refractory joint pain. However, we begin this issue with research reporting on the efficacy of an intensive interdisciplinary pain rehabilitation programme for patients with post-laminectomy pain after failing SCS (spinal cord stimulation).

I hope you will find these papers as interesting as I have, and I look forward to hearing any thoughts you may wish to share on these articles and other pain research.

Kind Regards,

Dr Tim Ho

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The effectiveness of an intensive interdisciplinary pain rehabilitation program in the treatment of post-laminectomy syndrome in patients who have failed spinal cord stimulation

Authors: Bailey JC et al.

Summary: These researchers retrospectively reviewed the charts of 43 patients with post-laminectomy syndrome who had failed SCS enrolled into an interdisciplinary pain rehabilitation programme, comparing before and after data. Participation in the programme was associated with an improvement among participants in 6-minute walk distance of 104m, a decrease in average NRS pain score of 1.4 points, an increase in average MPI (Multidimensional Pain Inventory) life control score of 8.3 points, a decrease in average MPI interference score of 5.3 points, an increase in average SF-36 (Short Form-36) score of 6.5 points, an increase in average PCS (Pain Catastrophizing Scale) score of 4.4 points, an increase in average PSEQ (Pain Self-Efficacy Questionnaire) score of 18.1 and an improvement in average mood score, on the CES-D (Center for Epidemiologic Studies Depression Scale), of 4.2 points.

Comment: While SCS has been shown to provide sustained pain reduction in post-laminectomy syndrome patients, a subset of patients who fail to respond to SCS present a challenge. This is a small retrospective chart review showing that an intensive pain management programme moderately improved, on discharge, pain severity, pain coping, function (MPI, SF-36, CES-D, PCS, PSEQ) and opioid reliance in post-laminectomy syndrome patients who had failed an SCS trial or implant, between 2011 and 2014. It is interesting that all patients on opioids (108 mg/day oral morphine equivalents) tapered off all opioids. The programme was CBT based and function focused, and consisted of three sessions of CBT per day and three sessions of physical reconditioning per day for 3 weeks. A further prospective study with long-term outcomes is warranted.

Reference: Pain Med 2018;19:385–92
Abstract

Dexamethasone injected perineurally is more effective than administered intravenously for peripheral nerve blocks

Authors: Zorrilla-Vaca A & Li J

Summary: This was a meta-analysis of 13 RCTs comparing intravenous (n=464) with perineural (n=473) administration of dexamethasone for peripheral nerve block. Compared with intravenous administration, perineural dexamethasone was associated with significantly longer durations of both analgesia (standardised mean difference, 0.48 hours [95% CI 0.18–0.79]) and sensory block (0.74 [0.53–0.94]); subgroup analyses showed that perineural dexamethasone 4–5mg continued to be superior to intravenous administration for prolonging analgesia (0.48 hours [0.24–0.72]), but doses ≥8mg were not (0.33 hours [–0.11 to 0.77]). Perineural dexamethasone was also beneficial for prolongation of motor block duration and reducing pain scores, opioid consumption and postoperative nausea and vomiting.

Comment: There has been debate regarding perineural action or systemic action of dexamethasone as an adjuvant in peripheral nerve block. This is a meta-analysis of 13 RCTs showing perineural dexamethasone (4–5mg) produced significantly more prolonged analgesia (mean difference of 0.48 hours) and sensory block as compared with intravenous injection. This suggests some nerve-specific action in addition to its anti-inflammatory effect. Studies in rats have shown glucocorticoid receptor expression can modulate nociceptive behaviour. *In vitro* research has shown perineural corticosteroids suppress transmission of C fibres but not myelinated Aβ fibres. Despite animal studies showing dose-dependent dexamethasone neurotoxicity, there has been no clinical evidence of human neurotoxicity at a dexamethasone dose of 8mg. Further mechanistic study is warranted.

Reference: Clin J Pain 2018;34:276–84
Abstract

The effect of epidural steroid injections on bone mineral density and vertebral fracture risk

Authors: Kerezoudis P et al.

Summary: These authors conducted a systematic review and critical literature appraisal on the effect of epidural injections of triamcinolone, dexamethasone or methylprednisolone on BMD (bone mineral density) and vertebral fracture risk. Eight studies involving 7233 patients who received means of 1–14.7 steroid injections with average cumulative doses of 80–8130mg methylprednisolone equivalents and average follow-up duration of 6–60 months were included. Four of six studies reported significant decreases in BMD and one of two studies reported increased vertebral fracture risk with exposure to epidural steroids. Significant reductions in BMD were associated with cumulative methylprednisolone equivalent doses of 200mg and 400mg over 1- and 3-year periods, respectively, but not with doses <200mg among postmenopausal women, or for doses ≥3g in healthy men. Patients receiving anti-osteoporotic medications during their treatment course had lower risks of osteopenia and osteoporosis.

Comment: Recent studies have yielded conflicting results regarding effect of epidural steroid injections on BMD. This is a systematic review of eight retrospective single-centre studies showing that methylprednisolone cumulative doses of over 200mg in 1 year and 400mg over 3 years were associated with decreased BMD. The risk was lower in those receiving anti-osteoporotic medication. The study by Mandel had 90% of the cohort, but was not used in the analysis of BMD change and osteoporosis outcome. Five of the studies were conducted in postmenopausal women only. It is difficult to extrapolate a causal effect from observational studies, especially when studying rare adverse outcomes. Caution is needed, and the study does not provide a definitive answer. Further large longitudinal multicentred study with a broad patient population is needed.

Reference: Pain Med 2018;19:569–79
Abstract

Surgical interventions for the treatment of painful neuroma

Authors: Poppler LH et al.

Summary: This was a comparative meta-analysis of 54 articles reporting efficacy of various surgical strategies for treating painful neuromas in the extremities (excluding Morton's neuroma and compression neuropathies). Most studies did not control for confounding and there was significant variation in the reported outcomes. The overall success rate for surgical treatment of neuroma pain was 77%, with no significant differences among the various surgical techniques used (excision-only, excision plus transposition, excision plus cap, excision plus repair and neurolysis plus coverage). Among studies in which participants had a mean pain duration >24 months, or in those in which the median number of operations was >2 prior to definitive neuroma pain surgery, meaningful pain reductions were significantly more likely using excision plus transposition or neurolysis plus coverage compared with other operative techniques. The authors also highlighted the need for standardisation of reporting for surgical techniques, outcomes and confounding factors in future studies.

Comment: The role of neuroma surgery remains controversial. This is a meta-analysis of 54 studies (1381 patients), 7% with a prospective design, showing a clinically meaningful pain reduction in 77% of the cases, regardless of surgical technique. This study result was consistent with previous study showing that 20–30% of neuroma is refractory, regardless of the type of surgery. Previous study has reported a re-operation rate of 65%. Previous study also theorised changing the microenvironment such as placing cut nerve in muscle or under vascularised flap to avoid external stimuli and prevent regeneration to the skin. One limitation of the study is the lack of key data reporting, which limits the ability to draw conclusions. Further improvement in quality data reporting is warranted in future studies.

Reference: Pain 2018;159:214–23
Abstract

Effect of opioid vs nonopioid medications on pain-related function in patients with chronic back pain or hip or knee osteoarthritis pain

Authors: Krebs EE et al.

Summary: The SPACE trial randomised 240 patients with moderate-to-severe pain despite analgesic use to treatment with opioids or nonopioids for 12 months. Each intervention had its own prescribing strategy that included multiple medication options in three steps. In the opioid group, the first step was immediate-release morphine, oxycodone or hydrocodone/paracetamol (acetaminophen). In the nonopioid group, the first step was paracetamol or a nonsteroidal anti-inflammatory drug. Medications were adjusted within the assigned treatment group according to individual patient response. Over a 12-month period, the groups did not differ significantly in pain-related function, but pain intensity was significantly lower in the nonopioid group (p=0.03). Adverse events were more common in the opioid group over 12 months (p=0.03).

Comment: There is a lack of high-quality data on the benefit of long-term opioid therapy for chronic musculoskeletal pain. This is an RCT that included 240 patients showing that opioid medication (maximum 100mg oral morphine equivalent daily dose) did not result in significantly better pain-related functional improvement compared with nonopioid medication (simple analgesia and adjuvants) at 12 months (BPI [Brief Pain Inventory] interference scale scores changed from 5.4 to 3.4 and from 5.5 to 3.3, respectively). There was no significant difference between changes in BPI pain severity scale scores (from 5.4 to 4.0 for the opioid group and from 5.4 to 3.5 for the nonopioid group). I note that for the nonopioid prescribing strategy, tramadol was included in step 3, which is interesting. Interestingly, this study also suggests that the poor pain outcome associated with long-term opioids in observational studies may be related to overprescribing and lack of pain management resources, rather than due to the opioid itself.

Reference: JAMA 2018;319:872–82
Abstract

Antisense oligonucleotides selectively suppress target RNA in nociceptive neurons of the pain system and can ameliorate mechanical pain

Authors: Mohan A et al.

Summary: The pharmacodynamic activity of antisense oligonucleotides in the spinal cord and dorsal root ganglia was characterised, showing activity that lasts for ≤2 months following a single intrathecal bolus dose. Comparisons of subcutaneous, intracerebroventricular and intrathecal antisense oligonucleotide administration showed that dorsal root ganglia were targetable by systemic and central delivery methods, while target reduction in the spinal cord was achieved only after direct central delivery. Detailed experiments of antisense oligonucleotide activity in individual cell populations in dorsal root ganglia revealed strong target suppression in all neuronal populations, confirming that these agents are effective in cell populations involved in pain propagation. The research also confirmed that antisense oligonucleotides are selective, with no modulation of basal pain sensation. It was also shown that antisense oligonucleotides targeting the sodium channel $Na_V1.7$ induced sustained analgesia for ≤4 weeks.

Comment: There was recent approval of antisense oligonucleotides for the treatment of spinal muscular atrophy by the US FDA. This is an animal study showing delivery of antisense oligonucleotides to dorsal root ganglion and lumbar spinal cord at 2 weeks postdose, using polymerase chain reaction data. The study also demonstrated suppression of target RNA in dorsal root ganglia and the lumbar spinal cord in a dose-dependent manner, using immunoassays and fluorescence *in situ* hybridisation. Mohan *et al.* also demonstrated sustained analgesia to mechanical pain using antisense oligonucleotides to suppress rat $Na_V1.7$ mRNA, with a rat pain behavioural model, which was sustained at 8 weeks after single intrathecal delivery. Antisense oligonucleotides also had the potential to upregulate protein expression if the upstream open reading frames were targeted. We may need to be prepared for arrival of genomic medicine at the horizon.

Reference: Pain 2018;159:139–49
Abstract

Social learning pathways in the relation between parental chronic pain and daily pain severity and functional impairment in adolescents with functional abdominal pain

Authors: Stone AL et al.

Summary: These researchers tested a model based on 7-day pain diaries for 154 paediatric patients with functional abdominal chronic pain. In the model, parental chronic pain predicted adolescents' daily average chronic pain severity and functional impairment, via parental modelling of pain behaviours and parental reinforcement of adolescents' pain behaviours, and adolescents' cognitive appraisals of pain threat. Significance was reached for indirect pathways from parental chronic pain status to adolescent average daily pain severity and functional impairment (p=0.03 for both) over the 7-day diary period via the adolescents' observations of parental pain behaviours and adolescent pain threat appraisal, but significance was not reached for the indirect pathway through parental reinforcing responses to adolescents' pain for either adolescent pain severity or functional impairment.

Comment: Some CBT trials for paediatric chronic pain were unable to show persistent benefit with pain and functional impairment at 12 months, and new targets for treatment are needed. Social learning theory suggests that behaviour can be learnt through observation of behaviour models and operant reinforcement. This is a path analysis of 154 adolescents with chronic functional abdominal pain, showing adolescent observation of parent pain behaviour and adolescent pain threat demonstrated significant relationships with adolescent pain severity and function. Parental solicitousness was not significantly related to adolescents' pain threat appraisal, pain severity or functional impairment. Parental modelling of pain behaviour may be a target for family-based therapy for adolescents with chronic pain. Further study is warranted.

Reference: Pain 2018;159:298–305
Abstract

Increased pain sensitivity in accident-related chronic pain patients with comorbid posttraumatic stress

Authors: Vaegter HB et al.

Summary: Antinociceptive and pronociceptive pain mechanisms, pain intensity and psychological distress were evaluated in patients with accident-related chronic spinal pain with (n=44) versus without (n=64) PTSD characteristics. Compared with patients without PTSD, those with PTSD had increased pain intensity and psychological distress, as well as reduced warmth detection threshold and pressure pain tolerance on cuff algometry (p<0.05), with no significant difference in pressure pain threshold, heat pain threshold, temporal summation of pain or conditioning pain modulation. Pain catastrophising mediated the relationship between PTSD and pain intensity, and fear of movement mediated the association with pressure pain tolerance.

Comment: This is a cross-sectional study of 108 patients with accident-related spinal pain, showing increased pain intensity in patients with comorbid PTSD, mediated by pain catastrophising, using multiple mediation models. This is consistent with previous study. The PTSD subgroup also showed an increased warmth detection threshold, suggesting dissociation, and reduced pressure pain tolerance, suggesting increased pain perception above their pain threshold. Interestingly, temporal summation and controlled pain modulation were not significantly different in PTSD patients, suggesting PTSD does not further facilitate central pain mechanisms in addition to chronic pain. It will be interesting to see if treating PTSD would change pain intensity and sensory profiles.

Reference: Clin J Pain 2018;34:313–21
Abstract

Effect of transcranial direct current stimulation of the motor cortex on visceral pain in patients with hepatocellular carcinoma

Authors: Ibrahim NM et al.

Summary: Forty patients with visceral pain secondary to hepatocellular carcinoma were randomised to undergo 30-minute sessions of TDCS (transcranial direct current stimulation) at 2mA applied over the primary motor area for 10 consecutive days or a sham procedure. Compared with the sham procedure, TDCS was associated with significant reductions in pain on visual analogue and verbal descriptor scales as well as reduced depression on the Hamilton rating scale, with effects in the active treatment group becoming apparent from the fifth session and continuing for 1 month post-treatment; effects in the sham group lasted for 5 days only.

Comment: Pain management in patients with impaired liver function and altered pharmacokinetics presents a challenge. This is a randomised, controlled, double-blind trial involving 40 patients showing that TDCS, with anodal stimulation of the M1 motor cortex (EEG 10/20 map) at 2mA, 30 minutes daily for 10 days, induced a clinically significant reduction of pain at 5 days that persisted at 1 month. The sham group also showed pain reduction but the difference did not reach statistical significance, suggesting a strong placebo effect. TDCS was thought to induce motor cortex driven inhibition of somatosensory cortex and thalamic inhibition. Anodal stimulation increases excitability. It will be interesting to see a large crossover RCT.

Reference: Pain Med 2018;19:550–60
Abstract

Efficacy of intra-articular botulinum toxin in osteoarticular joint pain

Authors: Courseau M et al.

Summary: This meta-analysis of six of eight analysed RCTs (n=382) on intra-articular botulinum toxin injections for refractory joint pain found that: i) four of five trials measuring NRS outcomes reported a benefit at 1 or 2 months for botulinum toxin at any dose versus controls, with the remaining trial reporting no effect (overall weighted mean difference, –1.10 [95% CI –1.62 to –0.58]); ii) three of four trials evaluating botulinum toxin 100U reported a positive effect on NRS at 1 or 2 months versus controls, with the fourth reporting no effect (–0.95 [–0.02 to –1.88]); iii) two trials evaluating botulinum toxin 200U reported an almost zero effect on NRS at 1 or 2 months (0.13 [–0.55 to 0.81]); an iv) three trials reporting NRS at 6 months showed no significant effect in favour of botulinum toxin (–0.57 [–1.98 to 0.83]).

Comment: Botulinum toxin has been used for osteoarthritis pain and was thought to reduce central sensitisation via retrograde axonal transport to central sensory regions after peripheral injection. This is a meta-analysis of eight RCTs involving 382 patients showing statistically significant, clinically significant reductions of pain (on NRS) in the short term with 100U of botulinum toxin. This is consistent with a previous meta-analysis showing a weighted mean difference of 1.1 at 8 weeks. It is interesting that the trials using a dose of 200U of botulinum toxin showed no reduction of NRS. Three trials had 6 months of data but showed a nonsignificant reduction of 0.57 on NRS. Like many meta-analyses, the studies were single-centre and had small sample sizes, and key data were not consistently collected in all studies. Further evidence is warranted.

Reference: Clin J Pain 2018;34:383–9
Abstract

Independent commentary by Dr Tim Ho, who is a rehabilitation and pain specialist at Inner West Pain Centre. Tim also works in work capacity centre and addiction medicine. His interests are chronic musculoskeletal pain, neuropathic pain, visceral pain and headache. His research interests are management of comorbid chronic pain and addiction, return-to-work programmes, osseointegration and nursing home resident pain management.

