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Abbreviations used in this issue:

- CRPS = complex regional pain syndrome
- QOL = quality of life
- RCT = randomised clinical trial
- REM = rapid eye movement
- RT = radiotherapy
- SCS = spinal cord stimulator
- TKR = total knee replacement

Welcome to issue 58 of Pain Management Research Review.

There is a lack of consensus regarding the optimal RT (radiotherapy) dose and fractionation schedule for alleviating pain associated with bone metastases, which the first paper selected for this issue has attempted to address. We also present data on the impact an opioid safety intervention for US veterans has had on pain and opioid prescriptions following TKR (total knee replacement). PaedPPOC (Paediatric electronic Persistent Pain Outcomes Collaboration) is an outcome measurement centre for measuring, benchmarking and improving children’s specialist pain services across Australasia, and its successful integration has been described along with early outcome data. This issue concludes with research in rats showing that sleep deprivation increases pain by increasing adenosinergic A1 activity and decreasing dopaminergic D2 activity in the nucleus accumbens.

We hope you enjoy this issue, and we welcome your comments and feedback.

Kind Regards,

Dr Tim Ho

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Single-fraction stereotactic vs conventional multifraction radiotherapy for pain relief in patients with predominantly nonspine bone metastases

Authors: Nguyen O-N et al.

Summary: Cancer patients with radiologically confirmed painful bone metastases were randomised to receive single-fraction stereotactic body RT 125Gy for ≥4cm lesions or 165Gy for <4cm lesions (n=81) or multifraction RT 30Gy in ten fractions (n=79) in this phase 2 noninferiority trial. Compared with multifraction RT, single-fraction RT was associated with a greater proportion of participants with a complete or partial pain response (combination of pain score and daily morphine-equivalent dose analgesic use; primary endpoint) at 2 weeks (62% vs. 36% [p=0.01]), 3 months (72% vs. 49% [p=0.03]) and 9 months (77% vs. 46% [p=0.03]), with no between-group differences for treatment-related toxic effects or QOL scores; local 1- and 2-year control rates were greater in the single-fraction RT arm.

Comment: This is a prospective, randomised, single-centre, phase 2 noninferiority trial (n=160, mostly nonspine bone lesions) showing that pain response rates (complete or partial response) and local disease control (local progression free survival) were higher at 2 weeks, 3 months and 9 months for high-dose single-fraction stereotactic RT (12 or 165Gy) as compared with standard multifraction RT (10×35Gy). Attrition was expected with increasing follow-up due to the natural history of metastatic disease. The inclusion of different cancer types and size may make it difficult to interpret differential responses in specific tumour subtypes and tumour sizes. I look forward to the larger phase 3 study.

Reference: JAMA Oncol 2019;5:872–8

Abstract

Ketamine infusions for chronic pain

Authors: Orhurhu V et al.

Summary: This systematic review and meta-analysis included seven RCTs, of which six were at high risk of bias, comparing intravenous ketamine with placebo for neuropathic, mixed and non-neuropathic (nociceptive or nociceptive) pain. Three studies reported that ketamine provided a significant but small analgesic effect assessed using a 10-point numerical rating scale for up to 2 weeks postinfusion (mean difference –1.83 points [p<0.0001]), and three studies reported higher responder rates (proportion with a positive outcome) among ketamine recipients compared with placebo recipients (51.3% vs. 19.4% [p=0.029]). There were no differences based on pain classification or condition.

Comment: This is a systematic review and meta-analysis of seven RCTs (n=211, with neuropathic, mixed or nociceptive/nociceptive pain) from 2002–2011 showing short-term benefit of intravenous ketamine (~2 weeks) when high-dose regimens were used. The median duration of ketamine infusion was 5 hours (range 0.5–100). A high-dose regimen was defined as a cumulative dose exceeding 400mg. This indicates that high-concentration blockade of NMDA (N-methyl-D-aspartate) may be needed to reverse wind up. Hence low-dose transdermal administration or as-needed sublingual ketamine (bioavailability ~24%) is unlikely to achieve this. Interestingly, in subgroup analyses, the neuropathic pain group did not have a superior outcome to the nociceptive/nociceptive group. Further research looking at better patient and dose selection is warranted. It will be important to look at outcome measures to assess medication use, function and long-term side effects.


Abstract
Impact of an opioid safety initiative on patients undergoing total knee arthroplasty

Authors: Chen Q et al.

Summary: This time series analysis examined the impact of the Opioid Safety Initiative, which was designed to decrease high-dose prescriptions among US veterans, on pain scores and opioid prescriptions for TKR, using group-level data for 700–850 patients per month over 72 consecutive months covering periods before and after the initiative was implemented. After the initiative was introduced, the patients were slightly older and sicker, but had lower mortality rates. Postoperative pain scores were slightly higher and 871 fewer patients received chronic postoperative opioid prescriptions. Time series analyses revealed that the mean postoperative minus preoperative pain score increased from 0.65 to 0.81. The respective proportions of patients with chronic postoperative and chronic preoperative opioid prescriptions declined by 20% and 13%, and nonopioid analgesia prescriptions increased. These findings were confirmed in sensitivity analyses.

Comment: The Opioid Safety Initiative was rolled out in 2013 using an academic detailing approach (face-to-face tutorial with prescribers), guideline dissemination and dashboard audit. TKR was used as an exemplar due to it being the most frequent major surgery and commonly associated with persistent postsurgical pain. This is an ecological study (retrospective observational study at the population level) of patients undergoing TKR (n=60,000, 700–850 per month from 2010 to 2015) showing a lower mortality rate, a significant decrease in opioid use, fewer chronic postoperative prescriptions and slightly higher pain scores after the rollout of the Opioid Safety Initiative. This study supports a provider-focused feedback approach.

Reference: Anesthesiology 2019;131:369–80

Can a brief psychological expectancy intervention improve postoperative pain?

Authors: Benson S et al.

Summary: In this study, 96 women undergoing breast cancer surgery were randomised at two stages as follows: presurgery, anesthesiologists delivered either positive or neutral verbal suggestions regarding the benefits of acupuncture needling on postoperative pain, then sham acupuncture or no sham acupuncture during postoperative care. Participants who were exposed to positive treatment-related suggestions had significantly lower postoperative pain ratings (p=0.038), and those who received an intervention aimed at optimised treatment expectations indicated significantly greater analgesia satisfaction (p=0.030).

Comment: This is a prospective RCT in women undergoing breast cancer surgery (n=96) showing that positive expectation reduced pain intensity and greater satisfaction with analgesia at 24 hours, but the effect size is small. Verbal positive or neutral suggestion was given for sham acupuncture. Interestingly, sham acupuncture alone had no effect on pain intensity and did not enhance the effect of positive verbal suggestions. Clinically, apart from positive verbal suggestion, clinician-patient interactions including empathy, trust, optimism and caring attitude may also optimise the expectancy effect.

Reference: Pain 2019;160:1562–71

The Paediatric electronic Persistent Pain Outcomes Collaboration (PaedePPOC): establishment of a binational system for benchmarking children’s persistent pain services

Authors: Lord SM et al.

Summary: The PaedePPOC is an outcome measurement centre with the purposes of measuring, benchmarking and improving specialist pain services for children across Australasia. These authors documented its establishment and reported baseline and initial outcome data. As at June 2018, seven of ten services had provided data on 1432 enrolled patients. The patients were aged 12.4 ±3.0 years at baseline, 68% were female, 93% were born in Australia and 5% were Aboriginal and/or Torres Strait Islander people. Most patients had presented with moderate-to-severe functional disability and impaired QOL, and their pain was affecting their attendance at school and employment. Sixteen percent of the patients were taking opioid-containing medicines often or daily. Clinically significant improvements in pain intensity were seen in 49% of patients who had completed outcome measures at treatment end, 59% showed improvements in functional ability and 69% had better QOL.

Comment: This is a foundation paper describing the process of the establishment of PaedePPOC 2014–2018. With seed-funding catalysing the process, a consensus document on the dataset, rollout, software and training was achieved. A national reference group refined the ePPOC minimum dataset and developed the protocol, with the supervision of a paediatric reference group. Individual services own their data and, every 6 months, send unidentified extracted data to PaedePPOC. The statistical linkage key and software allow automatic computation of data at the time of entry. Data from seven Australasian services (n=1432) were presented, capturing demographics, pain-related disability, QOL, school attendance, employment and opioid medication utilisation.

Reference: Pain 2019;160:1572–85

Explantation of percutaneous spinal cord stimulator devices

Authors: Simopoulos T et al.

Summary: Reasons for SCS (spinal cord stimulator) device explantation were assessed in this retrospective descriptive analysis of patients from a single-centre over a 15-year period. Among 356 patients trialled, 252 underwent percutaneous SCS device implantation with a permanent-to-trial ratio of 71%. Among patients with permanent SCS implantation, 50% had failed back surgery syndrome, 25% had CRPS and 25% had other diagnoses. The explantation rate at study end was 30%, for which the reasons provided were biological complications in 26.6%, paraesthesia limitations or side effects in 26.6%, hardware complications in 13.3%, ineffective pain control in 28% and no ongoing need for stimulation therapy 5.3%.

Comment: This is a single-centre retrospective chart analysis (n=356) from 2002 to 2015 showing the long-term probability of explantation of percutaneous SCS devices as 30% on a Kaplan-Meier graph. The study is confined to traditional low-frequency SCS and does not represent the new waveform. Potential modifiable factors to reduce the risk of explantation were loss of efficacy/habituation, paraesthesia and side effects, coverage mismatch, MRI requirement and hardware design. It will be interesting to see long-term explantation data of the newer waveform, high-frequency, paraesthesia-free and MRI-compatible SCS system for comparison.


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.
Known hypersensitivity to tapentadol or any component of PALEXIA SR; conditions in which mu-opioid receptor agonist activity is contraindicated

Care should be taken when combining with mixed opioid agonist/antagonists or partial mu-opioid agonists; additive CNS depression

ADVERSE EFFECTS: Very common (≥ 1/1): dizziness, somnolence, headache, nausea, constipation; Common (≥ 1/10 to <1/10): decreased appetite, anxiety, depressed mood, sleep disturbance, nausea, appetite decreased, dry mouth, vomiting, diaphoresis, dyspepsia, pruritus, hypertension, rash, asthenia, fatigue, feeling of body temperature change, mucosal dryness, oedema. Postmarketing suicidal ideation, angioedema, anaphylaxis and anaphylactic shock. Dosage and Administration: to be taken orally twice daily with sufficient liquid, approximately every twelve hours, with or without food. Initiation of therapy in patients currently not taking opioid analgesics: start with 50 mg PALEXIA SR twice daily. Initiation of therapy in patients currently taking opioid analgesics: follow advice under close supervision of prescribing physician. Titration regimen in increments of 50 mg twice daily every 3 days shown to be appropriate in most patients in clinical trials. Total daily doses > 500 mg not recommended. Discontinuation of treatment: taper dose gradually to prevent symptoms of withdrawal. Renal Impairment: not recommended in severe renal impairment. Hepatic Impairment: initiate at 50 mg once daily in moderate hepatic impairment; not recommended in severe hepatic impairment. Elderly patients more likely to have decreased renal and hepatic function—care in dose selection. Not recommended for use in children <18 years old.

MINIMUM PRODUCT INFORMATION: PALEXIA SR (Tapentadol hydrochloride) INDICATION: Moderate to severe chronic pain unresponsive to non-narcotic analgesics. CONTRAINDICATIONS: Known hypersensitivity to tapentadol or any component of PALEXIA SR; conditions in which mu-opioid receptor agonist activity is contraindicated. Known hypersensitivity to opioids, centrally acting analgesics or psychoactive drugs; patients who are receiving MAO inhibitors or who have taken them within the last 14 days. PRECAUTIONS: Monitor for signs of abuse and addiction; repeated administration may lead to tolerance; withdrawal symptoms could occur after abrupt discontinuation; not recommended in patients with increased intracranial pressure, impaired consciousness, or coma and severe renal or severe hepatic impairment; caution in patients with impaired respiratory function; patients with head injury brain tumours, a history of seizures or any condition that increases risk of seizures, moderate hepatic impairment or biliary tract disease, including acute pancreatitis. Use in pregnancy (Category C). Should not be used during breastfeeding. Not recommended for children <18 years old. May impair ability to drive or operate machinery. INTERACTIONS: Care should be taken when combining with mixed opioid agonist/antagonists or partial mu-opioid agonists; additive CNS depression with concomitant administration of other mu-opioid receptor agonist analgesics, general anaesthetics, phenothiazines, other tranquilisers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs). Reduction of dose of one or both agents should be considered contraindicated in patients who are receiving MAO inhibitors or who have taken them within the last 14 days. Isolated case reports of serotonin syndrome when used in combination with serotonergic drugs (see full PI). Opioids, centrally acting analgesics or psychotropic drugs; patients who are receiving MAO inhibitors or who have taken them within the last 14 days; isolated case reports of serotonin syndrome when used in combination with serotonergic drugs (see full PI).

SIDE EFFECTS: signs of abuse and addiction; repeated administration may lead to tolerance; withdrawal symptoms could occur after abrupt discontinuation; not recommended in patients with increased intracranial pressure, impaired consciousness, or coma and severe renal or severe hepatic impairment; caution in patients with impaired respiratory function; patients with head injury brain tumours, a history of seizures or any condition that increases risk of seizures, moderate hepatic impairment or biliary tract disease, including acute pancreatitis. Use in pregnancy (Category C). Should not be used during breastfeeding. Not recommended for children <18 years old. May impair ability to drive or operate machinery. INTERACTIONS: Care should be taken when combining with mixed opioid agonist/antagonists or partial mu-opioid agonists; additive CNS depression with concomitant administration of other mu-opioid receptor agonist analgesics, general anaesthetics, phenothiazines, other tranquilisers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs). Reduction of dose of one or both agents should be considered contraindicated in patients who are receiving MAO inhibitors or who have taken them within the last 14 days. Isolated case reports of serotonin syndrome when used in combination with serotonergic drugs (see full PI).

Before prescribing, please review the Product Information available at www.seqirus.com.au/PBS Information: Restricted benefit. Chronic severe disabling pain not responding to non-narcotic analgesics. Authority required for increased maximum quantities and/or repeats. Refer to PBS schedule for full restricted benefit and authority information.
The role of afferent input in postamputation pain

Authors: Buch NS et al.

Summary: Amputees experiencing constant postamputation pain received neural blockade with 2% lignocaine and adrenaline (epinephrine) or saline in a randomised crossover manner; 9 of 12 enrolled participants were included in the analysis. The difference between lignocaine and saline injections for median worst pain intensity score was −2.0 (p=0.02), with all participants reporting at least some pain relief after receiving lignocaine versus only two participants reporting this after receiving saline (p=0.04). Compared with saline, lignocaine was also associated with a significant reduction in phantom pain intensity (p=0.04), but not stump pain intensity (p=0.17). Evoked responses were eliminated for all nine participants after they received lignocaine.

Comment: Cortical reorganisation has been the main focus of research for postamputation pain. However, experimental studies also documented changes in sodium channels over axons, cell bodies and dendrites, which may also be drivers for postamputation pain. Vaso et al. showed benefit (n=11) with transforaminal block, suggesting primary functional changes in the peripheral nerve and spinal cord. This is a randomised double-blind, placebo-controlled, crossover trial (n=12) showing significant reductions in phantom limb pain and evoked pain at 30 minutes after peripheral nerve block with lignocaine when compared with placebo. There was significant heterogeneity in the study population with mixed types of amputation, pain (phantom/stump pain) and time since amputation (2–56 years). A larger study comparing blocks at different levels may further identify peripheral mechanism components of postamputation pain.

Reference: Pain 2019;160:1622–33

Abstract

Short-term efficiency and tolerance of ketoprofen and methylprednisolone in acute sciatica

Authors: Gastaldi R et al.

Summary: Patients with discogenic acute sciatica, without neurological deficit, were randomised to receive intravenous methylprednisolone 60 mg/day, ketoprofen 200 mg/day or placebo for 5 days added to standard care, which included paracetamol (acetaminophen), nefopam, tramadol and morphine; 50 of 54 enrolled participants completed the study. Leg pain over 5 days (primary outcome) did not differ significantly among the three groups, but methylprednisolone recipients had a higher rate of clinically relevant responses at day 3. There were no significant between-group differences for secondary efficacy outcomes or safety.

Comment: Use of NSAIDs (nonsteroidal anti-inflammatory drugs) and glucocorticoids in discogenic radiculopathy has been controversial and data were scarce based on previous meta-analyses. This is a multicentre, double blinded RCT (n=53) of discogenic radicular pain in hospitalised patients showing no significant benefit of intravenous prednisolone 60 mg/day or ketoprofen 200 mg/day for 6 days when compared with placebo. All patients received an oral analgesic protocol (paracetamol, nefopam, tramadol, morphine). When using categorical outcomes (dichotomous variable), methylprednisolone had a much more robust statistical difference at day 3. This highlighted that the way of expressing data when evaluating pain has a significant impact on the results and conclusions.


Abstract

Chronic exposure to insufficient sleep alters processes of pain habituation and sensitization

Authors: Simpson NS et al.

Summary: Seventeen healthy adults participated in 3 weeks of in-laboratory restricted sleep with limited recovery versus control sleep conditions; 14 participants completed both 3-week protocols. Mild but statistically significant increases in spontaneous pain were seen with the sleep- restricted protocol when compared against the control protocol. Following the first week of sleep restriction, significant decreases in heat-pain threshold were recorded, but these normalised with further exposure to sleep restriction. In contrast, chronic exposure to restricted sleep led to significantly decreased habituation and increased temporal summation in response to cold pain, although only during the prior 2 weeks of exposure to this protocol. These alterations in pain-modulatory processes did not completely resolve after limited recovery sleep.

Comment: This is an experimental study (n=17, healthy young volunteers) using a model of chronic insufficient sleep with limited recovery opportunity (5 nights of 4 hours sleep plus 2 nights of 8 hours sleep per week for 3 weeks) showing that markers of spontaneous pain and evoked pain increased significantly with sleep restriction. The changes in the heat pain threshold showed initial sensitisation and habituation (dysfunction of central inhibition) in the sleep-restricted group. The changes in the cold pain tolerance (measure of temporal summation) also suggest increased temporal summation and less habituation in the sleep-restricted group. This study suggests that the exposure to chronic insufficient sleep may result in alteration of pain modulatory processes that may increase vulnerability to chronic pain. Further study may look at how behaviour and pharmacological modification of sleep may change sensitisation and habituation.

Reference: Pain 2018;159:33–40

Abstract

Nucleus accumbens mediates the pronociceptive effect of sleep deprivation: the role of adenosine A2A and dopamine D2 receptors

Authors: Sardi NF et al.

Summary: These researchers conducted experiments in Wistar rats showing that REM sleep deprivation for 24 hours resulted in a pronounced nociceptive effect that decreased progressively over a sleep rebound period. An increase in faecal glucocorticoid metabolite levels was seen with sleep deprivation, but there was no difference between the sleep-deprived group and a control group. Excitotoxic lesion of the nucleus accumbens prevented the pronociceptive effect of REM sleep deprivation, whereas acute blockade reversed it. A2A receptor antagonist or D2 receptor antagonist administration into the nucleus accumbens led to an increase home-cage activity with blockade of the pronociceptive effect of REM sleep deprivation. Complementarily, A2A receptor agonist or D2 receptor antagonist administration decreased home-cage activity and impaired reversal of the pronociceptive effect. Expression of c-Fos protein in the nucleus accumbens was not affected by REM sleep deprivation.

Comment: Previous animal study showed that caffeine or modafinil normalised pain sensitivity in sleep-deprived animals. This is a rat experimental pain study showing that 24 hours of REM sleep deprivation induced a significant pronociceptive effect (decrease in mechanical nociceptive paw withdrawal threshold) that did not completely normalise with sleep rebound even at 48 hours. Local administration of an A2A antagonist or D2 agonist to the nucleus accumbens blocked the effect, suggesting that the pronociceptive effect depends on increased activity at adenosine A2A receptors and decreased dopamine D2 receptors in the nucleus accumbens. It will be interesting to see if caffeine (which induces dopamine release in the nucleus accumbens) changes pain sensitivity in the sleep-deprivation model.

Reference: Pain 2018;159:75–84

Abstract

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