Pain Management Research Review™

Making Education Easy

Issue 11 - 2013

In this issue:

Abbreviations used in this issue

IT = intrathecal
SCS = spinal cord stimulation
TAP = transversus abdominis plane

Welcome to the eleventh issue of Pain Management Research Review.

In the first issue for 2013, an exploratory study from Dutch researchers showed that SCS appears to be an effective and feasible treatment for intractable painful diabetic polyneuropathy, while a randomised trial from the US demonstrated that topical clonidine was effective for painful diabetic neuropathy in patients with functional, and possibly sensitised, nociceptors in the affected skin. Swedish researchers looked at patterns of slow-release strong opioid use for chronic pain diagnoses.

I hope you find this edition stimulating reading, and I welcome your comments and feedback.

Kind Regards,

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A prospective cohort study comparing early opioid requirement between Chinese from Hong Kong and Caucasian Australians after major abdominal surgery

Authors: Konstantatos AH et al

Summary: These researchers prospectively compared opioid consumption following major abdominal surgery between 68 Chinese patients (from Hong Kong) and 68 matched Caucasian patients (from Australia). While Chinese patients consumed significantly less opioids during the first 72 postsurgical hours than Caucasian patients (average 86.8 vs. 130.6mg; p<0.0005), they had significantly higher numerical rating scale pain score (5.3 vs. 4.4; p=0.029), more pruritus at 24–48 hours and 48–72 hours (p=0.001 for both), were more likely to report a strong preference for their pain to be managed by others, and their nurse carers were more likely to expect severe postsurgical pain.

Comment: This is an interesting study evaluating the effect of ethnicity as compared with race in the use, efficacy and adverse events with postoperative opioids. Previous studies and beliefs had indicated that Asians tend to use less opioids after major surgery, are more passive and stoical, and more anxious about the use of opioids. In this study, the Asians used less opioids (even after adjusting for body mass index), but had higher pain scores on coughing and more pruritus. There were also differences between the patients and nurses in the attitude to pain relief, which may also impact on opioid use. The increased incidence of pruritus (due to μ-1 opioid receptor OPRM1 polymorphism?) may contribute to the reduced opioid intake, despite higher pain scores. We should be aware of these aspects in our management of Asian patients.

Reference: Br J Anaesth 2012;109(5):797–803
http://bja.oxfordjournals.org/content/109/5/797.abstract

Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy

Authors: van Gulik L et al

Summary: Predictors for chronic thoracic poststernotomy pain were identified in 90 participants from a clinical trial who responded to a questionnaire 1 year postsurgery; 20% reported chronic thoracic pain. A multivariable regression model showed that chronic thoracic pain was independently predicted by remifentanil use during cardiac surgery (odds ratio 8.9 [95% CI 1.6–49.0]), age <69 years (7.0 [1.6–31.7]) and body mass index >28 kg/m² (9.1 [2.1–39.1]); the association with remifentanil appeared to be dependent on both total dose and dose corrected for kilogram of lean body mass and duration of surgery (respective p values <0.01 and <0.005 for trend).

Comment: Looking for predictors of chronic postsurgical pain is an important step in reducing this potentially preventable complication. Remifentanil has been implicated in the development of acute opioid tolerance and opioid-induced hyperalgesia, and although this analysis identified remifentanil as a predictor, the mechanism was not elucidated. However, like the studies on opioid-induced hyperalgesia, there was a correlation with the dose received during surgery and the incidence of chronic pain at 1 year. In this study, the use of nitrous oxide was optional, and although not identified as a variant, further investigations could elucidate if its use had any protective role.

Reference: Br J Anaesth 2012;109(4):616–22
http://bja.oxfordjournals.org/content/109/4/616.abstract

Pain relief and quality-of-life improvement after spinal cord stimulation in painful diabetic polyneuropathy

Authors: Pluijms WA et al

Summary: This exploratory pilot study investigated the feasibility of SCS for the treatment of painful diabetic polyneuropathy. Fifteen patients with intractable painful diabetic polyneuropathy in the lower limbs had a neurostimulator implanted. Pain intensity was assessed using an 11-point scale and patients' global impression of change scale. Neuropathic pain characteristics, quality of life, sleep quality and mood were also assessed. Ten patients had clinically relevant pain relief 1 year after implantation. Quality of life was significantly improved at 2 weeks and at 3 months, and several neuropathic pain characteristics and quality of sleep were improved at 2 weeks and at 12 months. Preoperative clinical sensory testing did not predict treatment outcomes.

Comment: This is a small study with an initial cohort of 27 of whom 19 were eligible patients, 15 of whom had a trial SCS and 11 progressed to full implantation. The authors felt it was important to exclude peripheral arterial disease, which can coexist with diabetic neuropathy in this selection of patients. However, they could not predict with their sensory testing the positive outcomes. Large fibre dysfunction did not affect the outcomes of SCS in this group, which have been found to be a factor in other SCS studies. This study includes other parameters than just pain relief, which adds to the weight of the positive outcomes.

Reference: Br J Anaesth 2012;109(4):623–9
http://bja.oxfordjournals.org/content/109/4/623.abstract

Randomized control trial of topical clonidine for treatment of painful diabetic neuropathy

Authors: Campbell CM et al

Summary: Patients with painful diabetic neuropathy were randomised to receive topical 0.1% clonidine or placebo applied to their feet three times daily for 12 weeks; topical 0.1% capsaicin was applied to the pretibial area at baseline to assess nociceptor function. Compared with placebo, clonidine was associated with a trend towards less foot pain on a 0–10 numerical rating scale (primary endpoint; p=0.07), with the difference significant among participants who reported any level of pain to the capsaicin challenge (p<0.05). The mean decrease in foot pain was significantly greater in the clonidine arm than the placebo arm among participants with a capsaicin pain rating ≥2 (p=0.01).

Comment: Applying topical clonidine is effective in some patients with diabetic neuropathy, with the benefit of nearly no adverse reactions and being relatively inexpensive compared with the other article reviewed here using SCS. However, the effect was not clinically great, with 48% achieving a 30% reduction in pain in the clonidine group compared with 40% in the placebo group. The interesting component of this study was the pretesting of subjects with capsaicin. If this test was positive indicating the presence of TRPV1 receptors, then there was a response to clonidine. This provides a mechanistic approach to the cause of neuropathic pain and is an initial step in tailoring treatment.

Reference: Pain 2012;153(9):1815–23
http://www.painjournalonline.com/article/S0304-3959(12)00242-4/abstract

A pilot cohort study of the determinants of longitudinal opioid use after surgery

Authors: Carroll I et al

Summary: These researchers conducted a prospective, longitudinal inception cohort study of 109 patients undergoing surgery (mastectomy, lumpectomy, thoracotomy, total knee replacement, total hip replacement) to explore the effects of preoperative psychological distress and substance abuse on postsurgical opioid consumption. New opioid use for 150 days postsurgery was seen in 6% of patients. Opioid cessation postsurgery was reduced by: i) 73% in patients with preoperatively prescribed opioids (p=0.0009); ii) 53% with each 1-point increase of self-perceived risk of addiction (p=0.003); and iii) 42% with each 10-point increase in preoperative Beck Depression Inventory II score (p=0.002). Preoperatively prescribed opioid use, self-perceived risk of addiction and depressive symptoms were better predictors of variance in postoperative opioid use duration than postoperative pain duration or severity.

Comment: Often the commencement of prolonged opioid use originates after an acute hospital event. This study monitored patients' opioid intake following discharge until they had five consecutive days without opioids or ceased taking extra opioids above their preoperative level. In assessing the postoperative use for pain, the authors used the Brief Pain Inventory separately for the surgical pain and also any other pre-existing pain. They identified that the continuing prolonged use of opioids for surgical pain was not related to ongoing pain but other factors in the patient. Patients can be identified who would be at risk and would benefit from closer monitoring for the need for ongoing opioids following a surgical event.

Reference: Anesth Analg 2012;115(3):694–702
http://www.anesthesia-analgesia.org/content/115/3/694.abstract

Pharmaceutical treatment patterns for patients with a diagnosis related to chronic pain initiating a slow-release strong opioid treatment in Sweden

Authors: Gustavsson A et al

Summary: These researchers analysed registry data to explore prescription patterns of slow-release strong opioids among 840,000 Swedish patients with chronic pain-related diagnoses; 16,257 started treatment with a slow-release strong opioid during the 2-year study period. The average age of slow-release strong opioid recipients was 71 years, 60% were female and 34% had cancer. Oxycodone was the agent most commonly prescribed first (54%), followed by fentanyl (19%), buprenorphine (14%) and then morphine (13%). Most patients (63%) refilled their prescription within 6 months, while 12% switched to another slow-release strong opioid, usually fentanyl. Around half (51%) of cancer and a quarter (27%) of noncancer patients were still receiving a slow-release strong opioid at 3 years. Concomitant selective serotonin reuptake inhibitor or benzodiazepine therapy was received by 35% of noncancer patients.

Comment: This population study showed a high dropout rate of patients started on extended-release opioids at 3 years, despite ongoing pain, with only 27% for noncancer pain. Only just over half the cancer pain patients continued on opioids. The main reasons cited were insufficient efficacy and severe side effects. These authors also noted that those who did remain on opioids had a higher incidence of psychiatric comorbidities. Much has been written about improving the management of chronic pain, but this study shows that opioids, despite their previous promotion, have only a limited long-term role. We need to find other treatment regimens that better serve our patients. Also, an article by Kurita GP (Pain 2012;153[12]:2332–8) and commentary by Ballantyne JC (Pain 2012;153[12]:2303–4) are in the same journal.

Reference: Pain 2012;153(12):2325–31
http://www.painjournalonline.com/article/S0304-3959%2812%2900422-8/abstract

Prospective study of 3-year follow-up of low-dose intrathecal opioids in the management of chronic nonmalignant pain

Authors: Hamza M et al

Summary: This long-term follow-up study investigated the administration of low-dose opioids via an IT drug delivery system for the treatment of intractable, severe chronic nonmalignant pain. Sixty-one consecutive patients with a mean duration of symptoms of 6.2 years were referred for drug delivery system implantation. All patients underwent a trial with IT opioids; three participants failed the trial. The worst pain score decreased from 8.91 at baseline to 4.02 at 36 months ($p=0.012$) and the mean pain score decreased from 7.47 to 3.41 ($p<0.001$). These decreases in pain scores were accompanied by a significant reduction in oral opioid consumption and significant improvements in physical and behavioural function. The dose of IT opioids remained low and stable during follow-up (1.4 and 1.48 morphine equivalents/day at 6 and 36 months, respectively).

Comment: This is one of the very few studies of IT morphine that has shown a positive long-term result (at 3 years). The authors attributed the key to their success as withdrawal from oral opioids before implantation (but not prior to the trial) and the use of small doses of IT morphine (<1.5 mg/day). In this cohort, there was minimal escalation of dose and minimal use of oral opioids, which have been seen in so many other studies. Their programme included a strong reliance on rehabilitation to improve and maintain function. Unfortunately, only the Brief Pain Inventory was used to assess change in function and mood. Hopefully this group will continue to be monitored to assess if these changes are maintained at 5 years and beyond.

Reference: Pain Med 2012;13(10):1304–13
http://onlinelibrary.wiley.com/doi/10.1111/j.1526-4637.2012.01451.x/abstract

The beneficial effect of transversus abdominis plane block after laparoscopic cholecystectomy in day-case surgery

Authors: Petersen PL et al

Summary: Patients undergoing laparoscopic cholecystectomy were randomly allocated to bilateral ultrasound-guided posterior TAP blocks with 0.5% ropivacaine 20mL or placebo; postoperative pain treatment was paracetamol (acetaminophen), ibuprofen and IV morphine within 2 hours and ketobemidone thereafter. Compared with placebo, TAP was associated with significantly lower visual analogue scale pain scores while coughing (primary outcome; 26 vs. 34mm; $p=0.04$) and significantly lower morphine consumption within 2 postoperative hours (5 vs. 7.5mg; $p<0.001$). No significant between-group differences were seen for visual analogue scale scores at rest, total postoperative ketobemidone consumption, nausea and sedation levels, number of patients vomiting and ondansetron consumption.

Comment: Whilst TAP blocks have been shown to be helpful in lower abdominal surgery for reducing opioid requirements and reducing pain, especially on coughing, previous studies on upper abdominal surgery have been of poor quality. The primary outcome in this study was pain on coughing. There was no clinical difference between the groups for pain scores on coughing, but there was a slight reduction in opioid consumption that was not sufficient to recommend adding this technique to the procedure.

Reference: Anesth Analg 2012;115(3):527–33
http://www.anesthesia-analgesia.org/content/115/3/527.abstract

Paclitaxel-induced neuropathic pain is age dependent and devolves on glial response

Authors: Ruiz-Medina J et al

Summary: These researchers looked at the severity of paclitaxel-induced neuropathy and the inflammatory reaction in the spinal cord dorsal horn in young, adult and aged male CD1 mice. Paclitaxel administration was associated with increased nociceptive reaction to thermal noxious (hyperalgesia) and mechanical non-noxious (allodynia) stimuli in all mice, but the signs of neuropathy were greatest in young mice, followed by in aged mice. Marked microglial and astrocytic response seen in the spinal cords of young and aged mice following paclitaxel administration was less important in adult mice; good correlation was seen between the most severe glial activation with major signs of neuropathy in young mice.

Comment: The mechanism of the peripheral neuropathic pain induced by paclitaxel has been shown to be due to glial cell activation in some studies but not others. This study demonstrated that age is an important variable in this mechanism. There was a correlation between the degree of glial inflammation and the severity of neuropathy in the young mice (juvenile) window of susceptibility. Whilst in the aged animals the glial cells were in a primed state, microglial cells became less ramified and more active, also increasing their susceptibility to developing neuropathy. This study helps develop our understanding of the chemotherapeutic effects in developing neuropathy, and hopefully will lead to some protective measure that can reduce this adverse effect.

Reference: Eur J Pain 2013;17(1):75–85
http://onlinelibrary.wiley.com/doi/10.1002/j.1532-2149.2012.00172.x/abstract

The correlation between pain-related behaviour and spinal microgliosis in four distinct models of peripheral neuropathy

Authors: Blackbeard J et al

Summary: The associations between spinal microgliosis and behavioural measures of neuropathic hypersensitivity and pain-related anxiety behaviour were explored in the following four rat models of peripheral neuropathic pain: i) traumatic neuropathy (L5 spinal nerve transection); ii–iii) HIV-related neuropathies (treatment with zalcitabine with or without perineural exposure to the HIV-gp120 protein); and iv) varicella zoster virus infection. While all neuropathic rat models developed persistent mechanical hypersensitivity, spinal microgliosis was seen in the spinal nerve transection and, to a lesser extent, the HIV neuropathy models, but not the varicella virus infection model. The authors commented that their results suggest that *"behavioural hypersensitivity and thigmotaxis can only be linked to a microglial response in certain models of neuropathy"*.

Comment: This article supplements the previous paper by demonstrating that not all neuropathies are associated with glial inflammation leading to activation. The previous models of studying neuropathic pain have been with traumatic injury, e.g. the Chung model. By comparing nontraumatic injuries, the authors have shown varying degrees of glial activation. In the varicella zoster virus model there was no glial activation (perhaps somewhat surprising), ranging through to maximal activation in the traumatic model. These findings help to explain the different responses to treatment in various neuropathic pain states.

Reference: Eur J Pain 2012;16(10):1357–67
http://onlinelibrary.wiley.com/doi/10.1002/j.1532-2149.2012.00140.x/abstract