



Pain Management Research Review™

Incl. Anaesthesia

HONG KONG

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Welcome to the latest issue of Pain Management Research Review.

As always I hope that this review saves you time in keeping up to date with recent Pain Management scientific research. I have selected twelve studies, and commented on why they are of interest to the practicing profession. Highlights this time include administration of CFA after epidural analgesia following total knee replacement, and an article reviewing the ideas of the WHO analgesic ladder and proposing its extension to a platform model for pain management. For this issue I have also decided to include a few anaesthesiology studies.

I hope you find the selected studies interesting and look forward to hearing your comments and feedback.

Kind regards

Professor Michael Irwin

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The prevention of chronic postsurgical pain using gabapentin and pregabalin: a combined systematic review and meta-analysis

Authors: Clarke H et al

Summary: This systematic review and meta-analysis investigated the perioperative use of gabapentin and pregabalin for the prevention of chronic postsurgical pain (CPSP). A search of electronic databases identified 11 suitable studies (8 gabapentin and 3 pregabalin) that evaluated perioperative administration of the drugs for the prevention of CPSP (≥ 2 months after surgery). Four of the gabapentin studies (50%) and all 3 of the pregabalin studies found that perioperative administration of the drug decreased the incidence of CPSP. Meta-analysis of pooled data from 6 gabapentin and 2 pregabalin trials found a moderate-to-large reduction in the development of CPSP with gabapentin (pooled odds ratio 0.52; $p=0.04$), and a very large reduction in the development of CPSP with pregabalin (pooled odds ratio 0.09; $p=0.007$). In conclusion, perioperative administration of gabapentin and pregabalin effectively reduce the incidence of CPSP.

Comment: CPSP is now recognised as a significant problem. As it is notoriously difficult to treat, the focus has switched to prevention as there is increasing evidence that the management of pain both intra and postoperatively has a significant influence in subsequent development. A number of drugs have shown efficacy in this regard including ketamine and gabapentanoids.

Reference: *Anesth Analg* 2012;115(2):428-42

<http://tinyurl.com/967vp2l>

Pain Management Research Review

Independent commentary by Professor Michael Irwin

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Research Review publications are intended for Hong Kong health professionals.

Exercise training attenuates neuropathic pain and cytokine expression after chronic constriction injury in rat sciatic nerves

Authors: Chen Y et al

Summary: To elucidate the underlying mechanism of exercise on neuropathic pain, this study investigated whether physical exercise regulates functional recovery and heat shock protein 72 (Hsp72), tumour necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β) expression after chronic constriction injury (CCI) of the sciatic nerve in rats. Male Sprague-Dawley rats were divided into 7 groups: control, sham operated (SO), SO with swimming or treadmill exercise (SOSE or SOTE), CCI, CCI with swimming or treadmill exercise (CCISE or CCITE). CCI rats with swimming or treadmill exercise had greater increases in thermal withdrawal latency and mechanical withdrawal threshold than CCI rats without exercise on day 21 after CCI. Both CCISE and CCITE groups demonstrated greater Hsp72 expression and lower TNF- α and IL-1 β levels in sciatic nerve than the CCI group on day 21 after CCI. In conclusion, progressive exercise training decreases peripheral neuropathic pain as well as TNF- α and IL-1 β overproduction and increases Hsp72 expression after CCI of the sciatic nerve.

Comment: Again, neuropathic pain is notoriously difficult to control and many of the drugs used have significant side effects. Although this is just an animal study, the findings are encouraging for potential and relatively simple clinical application. An area worthy of translational research.

Reference: *Anesth Analg* 2012;114(6):1330-1337

<http://www.anesthesia-analgesia.org/content/114/6/1330.abstract>



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A randomized trial of epidural analgesia followed by continuous femoral analgesia compared with oral opioid analgesia on short- and long-term functional recovery after total knee replacement

Authors: Nader A et al

Summary: This study compared the effects of continuous femoral nerve analgesia (CFA) after epidural analgesia with those of oral opioid analgesics on functional recovery following total knee replacement. 62 patients were randomised 1:1 to receive either oral analgesics or CFA (ropivacaine 25mg bolus and 5 mg/h infusion) after discontinuation of epidural analgesia on the morning after surgery. Catheters were removed after 24 hours. All patients received oral opioid analgesics as needed. The median difference in the change in knee flexion from baseline was 7.5° greater in CFA than non-CFA groups at 1 month ($p=0.04$). Patients receiving CFA had better compliance with physical therapy, lower pain scores and lower opioid requirements during hospitalisation. Thromboembolic events occurred in more non-CFA than CFA recipients (4 vs 0; $p=0.04$). In conclusion, administration of CFA for 24 hours after epidural analgesia was associated with less pain, greater compliance with physical therapy, increased range of motion and reduced opioid requirements.

Comment: There are a number of options for pain management after TKR. CFA is a relatively straightforward and effective technique. The use of epidural and CFA seems a little extreme, however, as CFA can be instituted after induction of anaesthesia (either GA or SA) and used straight away. This avoids the problems of using and removing an epidural catheter in patients receiving anti-DVT prophylaxis. Patients may also require supplementary oral analgesics as the femoral nerve does not solely innervate the knee.

Reference: *Pain Med* 2012;13(7):937-47

<http://dx.doi.org/10.1111/j.1526-4637.2012.01409.x>

Effect of perioperative systemic alpha 2-agonists on postoperative morphine consumption and pain intensity - systematic review of randomized controlled trials

Authors: Blaudszun G et al

Summary: This systematic review evaluated the effects of perioperative administration of alpha 2 agonists on postoperative opioid requirements and pain intensity. A literature search identified 30 randomised trials ($n=1792$) of systemic alpha 2 agonists administered before, during or after surgery in adults undergoing non-cardiac surgery under general anaesthesia, that reported postoperative opioid consumption or pain intensity. The alpha 2 agonist regimens varied widely across trials. Their opioid-sparing effect increased over time, and they significantly decreased pain intensity at 30min and at 2h but not at 24h. They also significantly decreased nausea at 8h and 48h, and vomiting at 48h. Alpha 2 agonists increased the risk of postoperative bradycardia, and intraoperative and postoperative arterial hypotension. Recovery times were not prolonged. In conclusion, perioperative systemic alpha 2 agonists have a weak postoperative opioid-sparing effect and a short lived effect on pain intensity.

Comment: Alpha-2 agonists are potentially useful adjuncts to anaesthesia but their effects on pain are somewhat controversial. This review shows only minor benefit in analgesia and avoidance of opioid related side effects.

Reference: *Eur J Anaesthesiol* 2012;28:196

<http://tinyurl.com/8e9n4qh>

From ladder to platform: a new concept for pain management

Author: Leung L

Summary: The World Health Organization (WHO) analgesic ladder was proposed in 1986 and has been the cornerstone of pain management. It provides guidelines for choosing analgesic agents but is often inadequate in daily practice because of the diversity of various pain conditions. This article reviewed the ideas of the WHO analgesic ladder and proposed its extension to a platform model for pain management. Incorporating the latest paradigm of neuromatrix theory, both acute and chronic pain should be best managed by combining multimodal non-pharmacological and supportive treatments. Different levels of pain severity and chronicity necessitate different analgesic platforms of management. The clinician should move up or down the appropriate platform to explore the various treatment options according to the status and needs of the patient.

Comment: Although the analgesic ladder has served a useful purpose, a lot has happened in pain management since 1986. An interesting proposal.

Reference: *J Prim Health Care* 2012;4(3):254-8

<http://www.ncbi.nlm.nih.gov/pubmed/22946077>

Development and validation of shortened, restructured Treatment Outcomes in Pain Survey instrument (the S-TOPS) for assessment of individual pain patients' health-related quality of life

Authors: Haroutiunian S et al

Summary: The Treatment Outcomes in Pain Survey (TOPS) is a validated health-related quality of life tool that has sufficient accuracy and sensitivity to monitor the overall pain experience of patients receiving multidisciplinary chronic pain management. However, the length of time needed to complete the 14-scale TOPS questionnaire limits its use. This study evaluated the validity of a shortened and restructured instrument, the S-TOPS, for monitoring individual patients receiving multidisciplinary chronic pain treatment. The reliability and validity of the S-TOPS were analysed using data from 964 patients with chronic pain who were treated in a single interdisciplinary pain clinic and completed >1 TOPS. The 7-scale S-TOPS was found to have excellent construct validity, high reliability, and improved sensitivity to change for monitoring individual patient outcomes. Patients found the S-TOPS acceptable and brief enough for routine repeated administration.

Comment: Audit of management is an important means to measure efficacy but many of the surveys are time consuming and complicated. This is a suggestion worthy of further clinical evaluation, perhaps also in different languages and cultures e.g. Chinese

Reference: *Pain* 2012;153(8):1593-601

<http://www.ncbi.nlm.nih.gov/pubmed/22503221>

Is spinal manipulation effective for pain?

Author: Posadzki P

Summary: This author systematically reviewed 22 systematic reviews with data relevant to the effectiveness of spinal manipulation for back pain (6 reviews), headache (5), neck pain (4), any medical problem (1), carpal tunnel syndrome (1), dysmenorrhoea (1), fibromyalgia (1), lateral epicondylitis (1), musculoskeletal conditions (1) and nonspinal pain (1). No positive conclusions (or unambiguously positive conclusions for multiple systematic reviews) could be drawn for any of these conditions, although the author noted that this review may have inherited publication bias from the source reviews.

Comment: Non pharmacologic interventions are attractive in pain management for obvious reasons. These data fail to demonstrate that spinal manipulation is an effective intervention for pain management. Safety of the technique was not evaluated.

Reference: *Pain Med* 2012;13(6):754-61

<http://tinyurl.com/d3yyq9s>

Ketamine as an adjunct to caudal block in neonates and infants: is it time to re-evaluate?

Authors: Lönnqvist P-A & Walker SM

Summary: These authors discussed the following two main issues associated with the use of ketamine as an adjunct to caudal block (to extend analgesia times) in neonates and infants: i) systemic exposure due to the dose used in this setting (which is similar to the dose used IV or IM for anaesthesia induction in children) and lipid solubility, resulting in rapid increases in plasma concentrations; and ii) significantly increased apoptosis seen in the dorsal horn of neonatal rats exposed to intrathecal ketamine at doses similar to those needed to produce an antihyperalgesic effect (toxic dose/analgesic dose ratio <1). They added that current data suggest that clonidine and morphine have less adverse effects on the developing spinal cord than ketamine, and this should be considered in the clinical choice of caudal block adjuvant agent in neonates and infants.

Comment: Just because a drug has systemic analgesic effects doesn't mean that local application will also be efficacious or, more importantly, safe. The idea often is actually to avoid systemic side effects and adding adjunct analgesic drugs to local anaesthetics for neuraxial block in children is common, especially with caudal blocks. However, systemic absorption is quite rapid from the caudal epidural space and, as can be seen above, these drugs may have direct neural tissue toxicity. This is a potentially dangerous practice. As a minimum these drugs must be preservative free and such a formulation of ketamine is not available in Hong Kong.

Reference: *Br J Anaesth* 2012;109(2):138-40

<http://bj.a.oxfordjournals.org/content/109/2/138>

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High intraoperative inspired oxygen does not increase postoperative supplemental oxygen requirements

Authors: Mackintosh N et al

Summary: This randomised trial with a 2x2 factorial design explored the effects of intraoperative FI_{O2} 0.3 vs. >0.9 with and without 3–5cm H₂O PEEP on postoperative supplemental oxygen requirements in 100 patients undergoing lower risk surgery. Supplemental oxygen was discontinued 30 minutes and 24 hours after extubation, and SaO₂ by pulse oximetry was recorded 15 minutes later. Supplemental oxygen, incrementally added to maintain saturation >90% if it dropped below this level, was needed for nearly all patients in the PACU. No statistically significant difference was seen between the groups for supplemental oxygen requirements at 45 minutes and 24 hours following tracheal extubation (p values 0.56 and 0.98, respectively).

Comment: Although a high fraction of inspired oxygen (FI_{O2}) may reduce surgical site infection, there is concern it could increase postoperative pulmonary complications. This study appears to refute such concerns, at least in relatively healthy patients. There are, however, other potential adverse effects of excessively high oxygen concentrations which are not explored in this study.

Reference: *Anesthesiology* 2012;117(2):271–9

<http://tinyurl.com/al7pzdvl>

Unintentional dural puncture with a Tuohy needle increases risk of chronic headache

Authors: Webb C A-J et al

Summary: This case-control study investigated the incidence of and risk factors for chronic headache and chronic back pain in 40 parturients who experienced unintentional dural puncture with a 17-gauge Tuohy needle, compared with 40 matched controls. Two validated questionnaires assessing headache and back pain symptoms 12–24 months postdelivery found that the cases were significantly more likely to report experiencing chronic headaches than the controls (28% vs. 5%; odds ratio 7; p=0.0129). Cases who received dural punctures were also more likely to report chronic back pain than controls (odds ratio 4; p=0.0250), while those who received epidural blood patches were not.

Comment: Headache can be a very debilitating consequence of dural puncture (even when intended, as with spinal anaesthesia). This study suggests that problems may persist longer than one might expect and also supports the use of epidural blood patch for treatment.

Reference: *Anesth Analg* 2012;115(1):124–32

<http://www.anesthesia-analgesia.org/content/115/1/124.abstract>

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Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Warmth is analgesic in healthy newborns

Authors: Gray L et al

Summary: This trial randomised 47 healthy full-term newborn infants into 1 of 3 groups prior to vaccination: warmth exposure, sucrose taste or pacifier suckling. Analyses of the babies' responses to the injection showed that those who were warmed cried significantly less than babies in the other groups. Nearly a quarter did not cry at all, whereas all the babies given sugar cried. In all groups, the babies' heart rates rapidly increased after the injection and then decreased at broadly the same speed for each treatment.

Comment: TLC. Turn down the air conditioning.

Reference: *Pain* 2012;153(5):960–6

<http://www.sciencedirect.com/science/article/pii/S030439591100772X>

Bayesian enhanced meta-analysis of postoperative analgesic efficacy of additives for caudal analgesia in children

Authors: Engelman E & Marsala C

Summary: These researchers performed a meta-analysis for the following three efficacy endpoints associated with adding clonidine, tramadol or neostigmine to postoperative analgesia: i) the time until analgesia administration; ii) analgesia requirements during the initial 24 postoperative hours; and iii) analgesia amount required. The duration of analgesia was increased by 9.96h with neostigmine, compared with 3.68h and 4.45h with clonidine and tramadol, respectively, and the respective durations of postoperative analgesia were increased by >8h, >2.8h and >3.5h with these agents versus local anaesthetics alone with 95% probability. The likelihood of requiring analgesic drugs was significantly reduced with clonidine and neostigmine (odds ratios 0.22 [95% CI 0.13, 0.37] and 0.28 [0.10, 0.75], respectively, but not tramadol. The amounts of postoperative analgesic drugs were reduced by all three agents. Neostigmine and tramadol were also associated with decreased odds of postoperative nausea or vomiting.

Comment: Certain adjuncts can significantly prolong caudal analgesia. However, as seen in one of my other reviews (ketamine), this may not be a safe practice. Safety was not evaluated in this meta-analysis.

Reference: *Acta Anaesthesiol Scand* 2012;56(7):817–32

<http://onlinelibrary.wiley.com/doi/10.1111/j.1399-6576.2012.02651.x/abstract>



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