Welcome to the fifth issue of Anaesthesia and Pain Management Research Review.

We welcome Dr David Rice who has contributed to the commentaries for this issue while Assoc Prof Gwyn Lewis is unavailable. Anaesthesia papers for this issue include PCA versus epidurals for labour, always a challenging comparison to evaluate, and a comparison of volumes and doses of local anaesthetic for wound infiltration following Caesarean section. There is also interesting research reporting encouraging results looking into the feasibility of a BIS-guided dual closed-looped system for titrating propofol and remifentanil in children undergoing elective surgery. tDCS (transcranial direct current stimulation) was found to be useful for treating phantom limb pain, but cannot be routinely recommended for nonspecific chronic low back pain. The issue concludes with observations suggesting long-term opioid therapy for chronic pain in the community increases hyperalgesia independent of other factors known to affect heat pain perception.

Thank you for your comments, questions and suggestions – we enjoy receiving them.

Kind regards,

Dr John Barnard
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Patient controlled analgesia with remifentanil versus epidural analgesia in labour

Authors: Freeman LM et al.

Summary: Intermediate-to-high obstetric risk pregnant women who intended vaginal delivery were randomised to receive remifentanil PCA (n=709) or epidural analgesia (n=705) on request during labour. The proportion of women ultimately receiving pain relief was significantly higher in the PCA group than the epidural group (65% and 52%; relative risk 1.32 [95% CI 1.18, 1.48]); 13% of women primarily treated with PCA converted to epidural analgesia, and 1% of those primarily treated with epidural analgesia converted to PCA. There was no significant between-group difference for the area under the curve for total satisfaction with pain relief, but the value was lower in the PCA group for women who actually received pain relief (mean difference –10.4 [95% CI –13.9, –7.0]). The PCA group had significantly lower oxygen saturation than the epidural group, whereas Caesarean section and maternal and neonatal outcomes were similar.

Comment (JB): On the basis of this large multicentre RCT, epidural analgesia in labour remains the gold standard among the available pain relief options. For those thinking of a research project involving labouring women, this study is a must read. They are a difficult group to study and this fact is ably demonstrated by the quantity of missing data from the period in labour. Also once a mother is holding her newborn baby, deficiencies in their labour analgesia tend to become a thing of the past, so overall satisfaction with analgesia scores are generally high. There are other more subtle confounders; e.g. deciding to have an epidural seemed to be a ‘bigger’ step than deciding to have a PCA – of the women randomised to PCA on request for analgesia, 62% requested PCA, whereas of the women randomised to receive an epidural on request for analgesia, 52% actually requested an epidural. The investigators had to find ways to cope with all these problems. Proving nonequivalence between labour analgesia techniques is a real challenge. While the quality of epidural analgesia was better than PCA, the duration of analgesia was longer in the epidural group – in other words an apparent association with a longer labour. In the discussion the authors develop a worthwhile analysis of this finding. The other side of the coin is that PCA with remifentanil is a simple and reasonably effective technique. In this study the starting parameters were dose 30µg and lockout 3 minutes. The dose could be increased or decreased by 10µg depending on the woman’s response.


Abstract
Effect of sedative premedication on patient experience after general anaesthesia

Authors: Maurice-Szamburski A et al., for the PremedX Study Investigators

Summary: Adults scheduled for various elective surgeries under general anaesthesia were randomised to receive lorazepam 2.5mg, no premedication or placebo (n=354 for each group). No significant difference was seen between the lorazepam and no premedication or placebo groups for EVAN-G (Evaluation du Vécu de l’Anesthésie Generale) mean global index patient satisfaction scores, even in the prespecified subgroup of participants with heightened preoperative anxiety. Lorazepam premedication was associated with a longer time to extubation than the respective no premedication and placebo groups (17 vs. 12 and 13 minutes [p<0.001]) and a lower early cognitive recovery rate (51% vs. 71% and 64% [p<0.001]).

Comment (JB): Even if you don’t regularly offer premedication, this is an interesting article. It is a large and rigorously designed RCT. The active substance, lorazepam 2.5mg, is compared with two control groups; one given a sham capsule (identical looking to the lorazepam one) and one group not given a capsule at all. Also the authors had previously designed and validated the six-domain patient experience based measure of the quality of recovery after general anaesthesia (EVAN-G) used as the primary outcome measure in this study (available as an appendix with the electronic version of the article).

Some of the results seemed predictable, e.g. lorazepam reduced preoperative anxiety, delayed wake-up in PACU, and caused some postoperative amnesia and cognitive impairment in the first 24 hours postoperatively. Other results were surprising, e.g. the placebo group had higher levels of anxiety than the no capsule group – an apparent nocebo effect. Some results were intriguing, e.g. having lorazepam worsened patients’ perceptions of staff attentiveness to their postoperative care and resulted in worse quality of sleep during the first postoperative night. There was no difference in the primary endpoint, the EVAN-G index, between the groups, and this lack of difference remained even if the analysis was restricted to the patients who had higher anxiety scores in their preoperative screening for anxiety.

But what if the dose of lorazepam was lower, or if they had used midazolam instead?

Reference: JAMA 2015;313(9):916–25

Abstract

Effect of high-volume systematic local infiltration analgesia in Caesarean section

Authors: Larsen KR et al.

Summary: Ninety patients scheduled for elective Caesarean section were randomised to receive infiltration with 0.5% ropivacaine 50mL, 0.2% ropivacaine 125mL or 0.9% saline 50mL during surgery under lumbar spinal anaesthesia. Postoperative pain did not differ significantly among the groups, but compared with placebo, 0.5% ropivacaine was associated with a significantly greater time until maximum pain score (p=0.0493) and significantly less 24-hour postoperative ketobemidone administration (p=0.029), which was also significantly less than with 0.2% ropivacaine (p=0.044). There were no significant between-group differences for time spent in the PACU, time to first mobilisation or maternal nausea/vomiting, and there were no ropivacaine-related complications.

Comment (JB): In this study sufentanil 2.5µg was given intrathecally with spinal 0.5% bupivacaine 2.2mL (11mg). Nearly all the patients were comfortable at the 2-hour post surgery mark. This degree of comfort will have contributed to the lack of significant differences between the groups. The authors attempted to address the large inter-individual variation in pain-related endpoints and the need for multiple comparisons by using a longitudinal linear mixed effects model. Unfortunately missing data meant this model was only applied to the rest VAS pain scores. The high volume group had 125mL of 0.2% ropivacaine injected and the low volume group 50mL of 0.5%; i.e. the dose of ropivacaine infiltrated was 250mg in each group. Serum concentrations of local anaesthetic were not done and there were no reported symptoms or signs of systemic local anaesthetic toxicity. The average weight of the patients was 70kg and the weight range quite narrow. The time to reach a maximum pain score was longest in the 0.5% ropivacaine group. The suggestion made was that the more concentrated local anaesthetic infiltration lasts longer, and that is probably the take home message. If you are going to give a single shot injection of local anaesthetic for postoperative analgesia, higher concentrations of smaller volumes will probably last better.


Abstract

Independent commentary by Dr John Barnard

Dr John Barnard works as an anaesthetist at Waikato Hospital with a part time academic component. In addition to his role in the operating theatres, four years ago he became the Clinical Director of the Hospital Pharmacy and Chairman of the hospital’s Medicines and Therapeutics Committee.

For full bio CLICK HERE

CONGRATULATIONS TO Jacqui Adair

who won the iPad mini 3 by taking part in our recent Subscriptions Update promotion. Jacqui is a Clinical Nurse Specialist at Middlemore Hospital in Auckland.

Granirex

Granirex (Granisetron) is a newly funded oral 5-HT3 antagonist¹
For the prevention of Chemo and Radiotherapy induced Nausea and Vomiting²
Granisetron has been recently reviewed by Radiation Oncologist Dr John Childs CLICK HERE to read.

References: 1 Pharmac Schedule 2 Granirex datasheet
Before prescribing Granirex click here or read the datasheet (available at www.medsafe.govt.nz) for information on dosage, contraindications, precautions, interactions and adverse effects.
Marketed by REX Medical Ltd, Auckland. TAPS NA 7548
Immediate and sustained effects of 5-day transcranial direct current stimulation of the motor cortex in phantom limb pain

Authors: Bolognini N et al.

Summary: Eight patients with unilateral lower or upper limb amputation and chronic phantom limb pain received 15 minutes of anodal tDCS 1.5mA over the motor cortex or a sham procedure for 5 consecutive days. Compared with the sham procedure, active tDCS was associated with a sustained decrease in background phantom limb pain and a reduced frequency of phantom limb pain paroxysms, and these effects persisted for 1 week post-treatment. Each day of active tDCS was also associated with immediate relief of phantom limb pain and an increased ability to move the phantom limb, whereas immediate responses to the sham procedure were variable with both increases and decreases in baseline phantom limb pain reported.

Comment (DR): tDCS is a form of noninvasive brain stimulation that delivers low-intensity electrical stimulation to the cortex. Clinically, tDCS is more attractive than traditional invasive brain stimulation techniques, as it appears safe with few side effects and is very cheap. Several small RCTs have observed a significant decrease in pain with tDCS in a range of chronic pain populations, including those with mixed neuropathic pain, pain after spinal cord injury and multiple sclerosis. In this study, background phantom limb pain and paroxysmal pain decreased by an average of 41% and 33%, respectively, after active brain stimulation. Remarkably, one patient with a 19-month pain duration reported 100% relief of both background and paroxysmal pain. While promising, major limitations of this (n=8) and other RCTs investigating tDCS have been their small sample sizes and limited follow-up periods.

Reference: BMJ 2015;350:h1640

Effectiveness of transcranial direct current stimulation preceding cognitive behavioural management for chronic low back pain

Authors: Luedtke K et al.

Summary: Patients with nonspecific chronic low back pain of >12 weeks duration (n=135) received 20 minutes of anodal tDCS 2mA over the motor cortex or a sham procedure for 5 consecutive days immediately before CBT in this RCT. There was no significant difference between tDCS and the sham procedure for reductions in VAS pain scores (p=0.68), disability scores (p=0.86) or CBT outcomes. tDCS was associated with minimal transitory adverse events.

Comment (DR): Recent systematic reviews and meta-analyses examining the effects of tDCS on chronic pain have cautioned that while early findings show some promise, the small sample sizes employed in all studies almost certainly increase the risk of bias and inflated effect sizes. This study is important for two reasons. One, it is the first trial of tDCS in a large sample (n≥100) of chronic pain patients. Second, it is the first trial to exclusively investigate the effects of tDCS in a population with nonspecific chronic low back pain. It cannot be sure whether the negative results of this trial reflect the more robust sample size or the specific population included in this study. Inflated effect sizes. This study is important for two reasons. One, this is the first trial to exclusively investigate the effects of tDCS in a population with nonspecific chronic low back pain. Second, it is the first trial of tDCS in a large sample (n=100) of chronic pain patients. We cannot be sure whether the negative results of this trial reflect the more robust sample size or the specific population included (i.e. nonspecific low back pain). It certainly brings into question the validity of earlier findings and highlights the need for larger RCTs of tDCS in other chronic pain populations (e.g. peripheral neuropathic pain).

Reference: BMJ 2015;350:h1640
A comparison of single-dose dexmedetomidine or propofol on the incidence of emergence delirium in children undergoing general anaesthesia for magnetic resonance imaging

Authors: Bong CL et al.

Summary: Patients requiring general anaesthesia following an MRI (magnetic resonance imaging) scan (n=120) were randomised to receive a single intravenous dose of dexmedetomidine 0.3 μg/kg, propofol 1 mg/kg or 0.9% saline 10mL before emergence. There was no significant difference among the groups for emergence delirium (p=0.671) or need for pharmacological intervention for emergence delirium (p=0.202). Time to awaken from general anaesthesia was the only significant predictor for emergence delirium.

Comment (JB): These authors have provided another reason to avoid paediatric MRI anaesthesia lists. A 40% emergence delirium incidence following anaesthesia with sevoflurane is not at all inviting (especially so for PACU nurses). This high rate is curious and by virtue of the high turnover of these lists, it does present an excellent model for demonstrating ways to reduce the frequency of this complication. The investigators compared three strategies – dexmedetomidine 0.3 μg/kg given just after induction, and either propofol 1 mg/kg or saline 10mL given at the end of the scan. All patients had sevoflurane/N₂O (nitrous oxide) induction then sevoflurane maintenance. The overall incidence of emergence delirium in the study was 39% and there was no significant difference in this incidence among the groups. Calmness at induction did not correlate with a calm wake up. The only significant predictor of emergence delirium was the speed of wake up in PACU. For each minute longer before return of consciousness, there was a 7% reduction in the incidence of delirium. This finding may interest researchers exploring the overlap of sleep mechanics and anaesthesia. The results of this study were quite sensitive to what value of PAED (Paediatric Anaesthetic Emergence Delirium) score was chosen as the threshold for detection of delirium. In the discussion the authors noted that if a more stringent threshold had been used, e.g. a score of 16 instead of a score of 10, then a significant difference among the groups might have been found, with the lowest rates in the propofol group. In a pilot study the authors tried giving dexmedetomidine at the end of the scan, but this seemed to delay recovery, hence the decision to give this drug just after induction.

Reference: Anaesthesia 2015;70(4):393–9

Regional versus general anesthesia in surgical patients with chronic obstructive pulmonary disease: does avoiding general anesthesia reduce the risk of postoperative complications?

Authors: Hausman MS et al.

Summary: Data from matched patients with chronic obstructive pulmonary disease who had undergone surgery under general (n=2644) and regional (n=2644) anaesthesia were analysed. Compared with regional anaesthesia, general anaesthesia was associated with higher rates of postoperative pneumonia (3.3% vs. 2.3% [p=0.0384]), prolonged ventilator dependence (2.1% vs. 0.9% [p=0.0008]), unplanned postoperative intubation (2.6% vs. 1.8% [p=0.0487]) and composite morbidity overall (15.4% vs. 12.6% [p=0.0038]) and excluding pulmonary complications (13.0% vs. 11.1% [p=0.0312]), but similar 30-day mortality (2.7% vs. 0.9% [p=0.0384]). There was no significant difference for propofol or remifentanil consumption during induction, but more maintenance remifentanil consumption with the closed-loop system (0.39 vs. 0.22 μg/kg/min [p=0.003]). No significant difference was found in perioperative adverse events or PACU length of stay.

Comment (JB): In the garden of anaesthesia there aren’t many chestnuts older than the general versus regional anaesthesia debate. There is a bit of a pattern in the published trials. The large RCTs have tended to show no benefit and the even larger meta-analyses or retrospective matched case series, like this one, tend to show better outcomes with regional anaesthesia. Little has changed for the practising clinician except the frequency of which the pumps could made automated dose rate adjustments was based on the effect site kinetics of the two drugs. Remifentanil has faster effect site kinetics, so this pump was able to make automated dose adjustments more frequently. The system was driven by the BIS error term (the actual BIS number minus 50), and this error term was used to modify the target effect site concentration. The pump then had to respond by changing dose rates to achieve the new target. Effectively the remifentanil was the fine tune and the propofol was the coarse tune to achieve the perfect BIS of 50. The article is worth a glance just to see the frequency of dose adjustments made by the remifentanil pump. Overall the automated system kept the BIS in range much better than the skilled manual control and the automated system gave significantly more remifentanil. There were no other significant differences between the two groups. A single dose of ephedrine was given to one patient in the automated group, but at no point were the automated infusions manually adjusted during the maintenance of anaesthesia.


Feasibility of closed-loop titration of propofol and remifentanil guided by the bispectral monitor in pediatric and adolescent patients

Authors: Orilaquet GA et al.

Summary: Children scheduled for elective surgery were randomised to dual closed-loop titration of propofol and remifentanil guided by BIS (n=23) or a manual titration group (n=19). Compared with the manual group, the closed-loop group was associated with a significantly greater percentage of time with BIS values of 40–60 (87% vs. 72% [p=0.002]) and a lower percentage of BIS values <40 (7% vs. 21% [p=0.002]), with no significant difference for propofol or remifentanil consumption during induction, but more maintenance remifentanil consumption with the closed-loop system (0.39 vs. 0.22 μg/kg/min [p=0.003]).

Comment (JB): Automated closed-loop control of anaesthesia is probably not all that far off large-scale clinical trials rather than smaller feasibility studies like this one in children. At least part of the justification for this study was the knowledge that the pharmacokinetic and effect site kinetic models used in TCI (target controlled infusion) devices were developed using adult subjects, so using these pumps for children may risk relative overdose or underdose, more likely the latter. The closed-loop feedback system should reduce the chance of getting the depth of anaesthesia wrong. The system used in this study had both the remifentanil and the propofol infusion rates determined by closed-loop feedback algorithms driving TCI pumps with the aim to keep the BIS between 40 and 60. The frequency with which the pumps could make automated dose rate adjustments was based on the effect site kinetics of the two drugs. Remifentanil has faster effect site kinetics, so this pump was able to make automated dose adjustments more frequently. The system was driven by the BIS error term (the actual BIS number minus 50), and this error term was used to modify the target effect site concentration. The pump then had to respond by changing dose rates to achieve the new target. Effectively the remifentanil was the fine tune and the propofol was the coarse tune to achieve the perfect BIS of 50. The article is worth a glance just to see the frequency of dose adjustments made by the remifentanil pump. Overall the automated system kept the BIS in range much better than the skilled manual control and the automated system gave significantly more remifentanil. There were no other significant differences between the two groups. A single dose of ephedrine was given to one patient in the automated group, but at no point were the automated infusions manually adjusted during the maintenance of anaesthesia.

Psychological predictors of recovery from low back pain
Authors: George S2 & Beneciuk JM
Summary: This was a secondary analysis of a prospective cohort of 111 patients receiving outpatient physical therapy for low back pain, who were assessed using the SBT (STarT Back Screening Tool), individual psychological measures, a numerical pain rating scale and the RMDQ (Roland Morris Disability Questionnaire) at baseline, 4 weeks and 6 months. The 6-month recovery rate (numerical pain rating scale 0 and RMDQ score ≤2) was 12.6%. Compared with recovered participants, those who had not recovered had SBT risk status (p=0.004), higher intake pain intensity scores (p=0.008) and more fear avoidance, kinesiophobia and depressive symptoms (p<0.001 for all). Discriminant function analyses were 87.2% and 86.4% accurate for predicting recovery at baseline and 6 months, respectively, with fear-avoidance, kinesiophobia and depressive symptoms providing unique contributions.

Comment (DR): Perhaps the most startling finding from this study was that only 12.6% of patients were considered ‘recovered’ 6 months after presentation for treatment of a back pain episode. This reflects the inclusion of chronic low back pain patients (47%) in the cohort and the strict composite criteria employed where patients had to report both 0/10 pain and a RMDQ score of ≤2/24. While seemingly stringent criteria, these reflect the scores obtained in a previous study where patients considered themselves ‘completely recovered’. The findings again highlight decades of research that show that amongst the most important predictors of recovery in patients with back pain is their cognitive and emotional response to their injury and/or pain. It is vitally important that these factors are assessed in primary care and an attempt is made to address unhelpful beliefs with robust patient education and/or referral for appropriate psychologically informed interventions.

Reference: BMC Musculoskel Dis 2015;16:49
Abstract

Effect of primary care-based education on reassurance in patients with acute low back pain
Authors: Traeger AC et al.
Summary: This was a systematic review and meta-analysis of 14 trials (n=4872) of primary care education interventions for low back pain that reported postintervention reassurance. Compared with usual care/control education, patient education was associated with greater short- and long-term reassurance (respective standardised mean differences −0.21 [95% CI −0.35, −0.06] and −0.15 [−0.27, −0.03]; moderate- to high-quality evidence) and fewer low back pain-related primary-care visits over 12 months follow-up (−0.14 [−0.28, −0.00]; moderate evidence; number needed to treat to prevent one visit, 17). Furthermore, reassurance was significantly better when the interventions were delivered by general practitioners rather than other primary-care practitioners.

Comment (DR): Providing appropriate reassurance and patient education (e.g. advice to stay active, imaging may not be useful, back pain is usually benign and self-limited) is surely one of the easiest and most cost-effective interventions we can provide in primary care. Interestingly, the results of this study suggest that such an intervention may be most effective for reducing measures of fear (e.g. fear avoidance beliefs) when compared with more general measures of concern (e.g. anxiety, worry, catastrophising). It is important to highlight that such a simple intervention appears effective in providing reassurance and decreasing low back pain-related healthcare utilisation for up to 12 months. It was interesting but not surprising that reassurance provided by a doctor was found to be more effective than that provided by a physiotherapist or nurse – never underestimate the power and authority of the (metaphorical) white coat!Alarmingly, a recent survey of Australian general practitioners found that only 20% reported giving this kind of advice and education to patients presenting with low back pain. Hopefully we do better than that in NZ.

Reference: JAMA Intern Med 2015;175(5):733–43
Abstract

Opioid-induced hyperalgesia in community-dwelling adults with chronic pain
Authors: Hooten WM et al.
Summary: Associations between opioid use and heat pain perception were explored in consecutive community-dwelling adults with chronic pain admitted to an outpatient interdisciplinary pain treatment programme, including 85 opioid-treated and 102 nonopioid-treated. Compared with the nonopioid group, opioid users had significantly lower nonstandardised and standardised heat pain 5–0.5 values (a measure of the slope of the line connecting heat pain threshold [0.5] and intermediate tolerance [5]). Univariable and multiple variable linear regression analyses revealed significant associations between opioid use and lower nonstandardised and standardised heat pain 5–0.5 values.

Comment (DR): There is convincing evidence in animals that opioids given in high doses or for long periods of time can paradoxically increase, rather than decrease, hyperalgesia and pain. This is supported by a handful of studies in healthy human volunteers that have shown that opioid infusions can increase secondary hyperalgesia. Far more controversial is the idea that long-term opioid use at relatively low doses may increase, rather than decrease, pain in patients with chronic pain. The findings of this study are an important step forward in the debate, suggesting that opioid-treated chronic pain patients demonstrate significantly greater hyperalgesia to standardised painful heat stimuli than nonopioid treated patients. A strength of this study was that these findings were apparent even after controlling for a host of other factors that may influence heat pain sensitivity, including age, gender, clinical pain severity, depression and pain catastrophising. However, a more convincing study design would be to examine clinical pain intensity and tests of pain sensitivity in a group of chronic pain patients before and after opioid use, compared with a control group of chronic pain patients who do not receive opioids.

Abstract

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