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

This issue includes research on the incidence and predictors of emergence delirium in adults who have received general anaesthetics. There is also an interesting context-specific meta-analysis and systematic review of liberal versus restrictive blood transfusion strategies in surgical and critically ill patients. Authors from the US have analysed RCT data to answer the question – who benefits most from CBT (cognitive behavioural therapy) for chronic pain? This issue concludes with a report suggesting that nurses are generally less receptive to the use of oral PCA than patients.

We hope these regular updates in anaesthesia and pain management research are proving informative and helpful in your everyday practice. Please keep your feedback and suggestions coming.

Kind regards,
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Effect of regional versus local anaesthesia on outcome after arteriovenous fistula creation

Authors: Aitken E et al.

Summary: Adults scheduled for primary radiocephalic or brachiocephalic arteriovenous fistula creation were randomised to receive local anaesthesia with 0.5% L-bupivacaine and 1% lidocaine injected subcutaneously (n=63) or regional brachial plexus blockade with 0.5% L-bupivacaine and 1.5% lidocaine with adrenaline (epinephrine; n=63). Compared with the local anaesthetic group, a greater proportion of the brachial plexus blockade group exhibited arteriovenous fistula patency at 3 months (primary endpoint; 84% vs. 62%; odds ratio 3.6 [95% CI 1.4, 7.6]); this was greater in radiocephalic fistulae (77% vs. 48%; 3.6 [1.4, 3.6]). No significant procedure-related adverse events were recorded.

Comment (JB): Here is a classic quote found in the discussion section of this article: “…one of the few studies in which anaesthetic technique affects surgical outcome”. In most of our research the chosen endpoints relate to the quality of the anaesthesia or the rate of complications, and it always feels a little ‘holy grail-ish’ when a specific anaesthesia technique improves surgical outcome. The comparison was between local infiltration and regional block rather than the more usual general versus regional anaesthesia comparison. There was an absence of side effects in either group and postoperative pain relief was equally excellent in each group. The downside to the brachial plexus block was the need for skilled anaesthesia and the extra time taken to achieve an adequate block. Supravacular block was the primary technique used in the block arm of this study (lol). Where I work this approach to the brachial plexus has also had something of a resurgence reflecting the availability of ultrasound and that reassuring in-plane view of the block needle. The papers discussion focused on the importance of adequate initial flow rates in the fistula and the potential role of sympathetic blockade in optimising this flow. One of the subtle observations was that in two patients the vasodilatation caused by the plexus block meant the surgeons changed their preoperative plan of a brachiocephalic fistula to the more distal radiocephalic fistula. The distal arteriovenous fistula carries a lower risk of significant steal phenomena. Being published in the Lancet means the paper was written for a more general audience than an anaesthesia journal, and it was enjoyable learning a little about the technicalities of creating a successful arterovenous shunt.

Reference: Lancet 2016;388(10,049):1067–74
Abstract

Independent commentary by Gwyn Lewis
Assoc Prof Gwyn Lewis works in the Health and Rehabilitation Research Institute at Auckland University of Technology. She is a neuroscientist and is an active pain researcher and educator. For full bio CLICK HERE

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
Post-anaesthetic emergence delirium in adults: incidence, predictors and consequences

Authors: Munk L et al.

Summary: This prospective, observational cohort study assessed emergence delirium (RASS [Richmond Agitation-Sedation Scale] score ≥1) and its clinical consequences in 1970 adults who had received general anaesthesia in an operating room. Signs of emergence delirium were evident in 73 patients (3.7%), but this had decreased to 25 (1.3%) on subsequent PACU reassessment. Predictors of emergence delirium were male sex, ET (endotracheal tube) use and volatile anaesthetic use. Additional staff had to be called in 20 cases, and there was a single case of accidental IV access removal. No harm came to any patient or staff member.

Comment (JB): Either ET (endotracheal tube) management of the airway or the use of a volatile anaesthetic could have been kept as one of the three significant predictors. ET (endotracheal tube) use accounted for a fraction more of the variance than NMB use, so the authors kept this predictive factor in favour of relaxant use. If the authors had attempted to create a predictive model based on the three factors, the specificity would have been very poor (i.e. lots of false-positives; patients predicted to have emergence delirium who had smooth recoveries). This is definitely one of those studies that prompts questions rather than giving answers, e.g. why predominantly males? Also the rate of emergence delirium in this study is relatively low and it is worthwhile considering why that might be. One piece of clinical practice detail that stood out for me was the requirement for the TOFR (train-of-four ratio) to be greater or equal to 0.92 before each ET (endotracheal tube) patient was extubated. This is quite a stringent level of NMB recovery and the two likely ways to achieve this level would be to slow the emergence or to give sugammadex in place of neostigmine (or an alternative acetylcholinesterase inhibitor). Either approach might influence the rate of emergence delirium.


Physiotherapy for pain

Authors: Ginnerup-Nielsen E et al.

Summary: This was a meta-epidemiological study of 174 randomised trials reporting on 224 comparisons of physiotherapeutic interventions for self-reported pain in adults. The authors identified an overall moderate effect of physiotherapy on pain of 0.65 SD units with moderate inconsistency (I²=51%), with therapeutic exercises for musculoskeletal diseases providing greater benefit than multimodal interventions (p=0.03). The effect size associated with physiotherapy was greater in trials with a ‘no intervention’ comparator than those with a sham comparator (p=0.004). The authors stated that performance bias and between-study heterogeneity meant their confidence in the estimates was generally low.

Comment (GL): This was a mammoth review – I guess that’s why they call it a meta-epidemiological study – that attempted to identify if physiotherapy was effective for pain. It only included studies that had a control group who received no intervention or a sham intervention. Given the obvious difficulty in delivering sham physiotherapy, the study probably much said that physiotherapy has a moderate effect on pain compared with doing nothing. While this probably makes physiotherapists feel quite useful, I am not entirely convinced of its clinical relevance. With the inclusion of interventions that ranged from days to years, and with only the first follow-up measurement included in the analysis, it makes it difficult to know if a few bouts of exercise will reduce pain for months, or if 6 months of manipulative therapy will make you feel better for a few days.


For more information, please go to http://www.medsafe.govt.nz/
Intrathecal hydromorphone and morphine for postcesarean delivery analgesia: determination of the ED90 using a sequential allocation biased-coin method

Authors: Svigum HP et al.

Summary: Eighty women requiring spinal anaesthesia for caesarean delivery were randomised to receive intrathecal morphine or intrathecal hydromorphone with the doses determined using up-down sequential allocation with a biased-coin design to determine ED_{90} (effective doses for 90% of patients) in this dose-finding trial; participants received standardised postoperative multimodal analgesia as well. The respective ED_{90} for intrathecal morphine and hydromorphone, based on 12-hours postinjection numerical rating scale scores of <3, were 75μg and 150μg. Exploratory findings revealed no differences in the incidences of nausea and pruritus among the most commonly used intrathecal hydromorphone and intrathecal morphine doses. The patients’ analgesia satisfaction rates for intrathecal hydromorphone and intrathecal morphine at ED_{90} or higher doses were 100% and 95%, respectively.

Comment (JB): As the authors note, knowing that the dose ratio of morphine:hydromorphone via the intrathecal route is 2:1 compared with the 5:1 ratio if the two medications are given intravenously is useful, at least in countries where both of these opioids are available. Given the absence of hydromorphone in NZ, the aspect that caught my interest was the decision to structure the study to produce an ED_{90} (using a biased-coin toss technique), rather than the more classical ED_{50}. This decision reflected the value that the authors placed on analgesia and their relative acceptance of side effects. It would have been interesting to ask the women whether they would trade a bit less nausea or itch for a bit more pain. In most postoperative pain settings, anaesthetists deliberately structure the opioid prescribing so that much if not all the available opioid is given to patients. Thus, they would trade a bit more pain for less nausea or itch. By aiming for an ED_{90}, the authors are searching for a fixed dose that meets almost all the patient’s opioid requirements. At the 6-hour mark, 30–50% of subjects had moderate-to-severe nausea, and a similar percentage had moderate-to-severe pruritus. Intrathecal morphine and hydromorphone behaved similarly with regard to these two common side effects. Yet more than 90% of the subjects were very satisfied with their analgesia. Mothers with newborn infants must be a bit like part 2 candidates who have just passed the exam. You can give these successful candidates any undesirable list or a stretch of night shifts, and they will still be highly satisfied.


Abstract

Restrictive versus liberal transfusion strategy in the perioperative and acute care settings

Authors: Hovaguimian F & Myles PS

Summary: This was a context-specific systematic review and meta-analysis of 31 RCTs comparing restrictive versus liberal blood transfusion strategies applied at >24 hours in adults who were critically ill or had undergone surgery. Compared with liberal strategies, restrictive strategies in patients undergoing cardiac or vascular procedures and in elderly orthopaedic patients were associated with (significant and non-significantly) increases in the risks of inadequate oxygen supply (respective risk ratios 1.09 [95% CI 1.07–1.12] and 1.24 [1.00–1.54]), no difference was evident for infections alone, and there were no differences for any of the outcomes in critically ill patients.

Comment (JB): To my mind the authors of this paper have set a benchmark for how to design and present a meta-analysis examining the effect of transfusion threshold on outcome after anaesthesia and surgery. The authors have taken a pragmatic and logical approach to the issues of methodological and clinical heterogeneity, and in doing this they have balanced the power of pooled data with their own clinical insight. The stratification of clinical trial populations increases the likelihood that true signals from the data will not be overlooked, and the stratification matches how clinicians think about the patient in front of them. Past parturient patients and elderly orthopaedic patients are very different, so combining their transfusion related data is unlikely to improve the signal-to-noise ratio. Likewise combining a study aiming for a haemoglobin level of 70 g/L in the restricted threshold group with another study using a level of 100 g/L in the restricted group is unlikely to help define a real therapeutic effect. My only quibble is the inclusion of some studies that predated the routine use of white-cell filters as part of the processing of donated blood. There are a number of other recent advances in transfusion medicine and fluid management that may influence outcomes: using point-of-care testing of coagulation to drive transfusion of blood components, giving IV iron pre- or postoperatively, using less synthetic colloid solutions, and earlier use of low-dose vasoressor infusions; all of which make the inclusion of older studies questionable. In the ideal world the data would allow much stronger conclusions; conclusions that matched the effort required to produce this well-constructed systematic review. Frustratingly the data do not allow this. Yet there is enough of a signal to be very wary of sending that elderly revision hip patient up to the ward with a haemoglobin level of 79 g/L.

Reference: Anesthesiology 2016;125(1):46–61

Abstract

Gabapentin for the hemodynamic response to intubation

Authors: Doelman B et al.

Summary: This systematic review and meta-analysis included 29 randomised trials comparing gabapentin with controls, fentanyl, clonidine or β-blockers for attenuating haemodynamic response to intubation; only two studies had low risk of bias. No studies included high-risk patients and there were no differences in the hemodynamic response between the different interventions. Compared with liberal strategies, restrictive strategies in patients undergoing cardiac or vascular procedures and in elderly orthopaedic patients were associated with (significant and non-significantly) increases in the risks of inadequate oxygen supply (respective risk ratios 1.09 [95% CI 1.07–1.12] and 1.24 [1.00–1.54]), no difference was evident for infections alone, and there were no differences for any of the outcomes in critically ill patients.

Comment (JB): The authors of this paper have been somewhat disheartened after they had completed their search for RCTs to include in the meta-analysis. The quality of the studies was relatively good, with 29 of the original 95 studies screened then retained; the total number of subjects was also reassuring, but the subjects were all ASA 1 or 2, so the chance of finding a difference in MI rates or mortality rates was low (read nonexistent). Nevertheless, the authors battled on with the study knowing that they might find that gabapentin attenuates the increase in blood pressure and heart rate that follows intubation in relatively well patients. That is exactly what they did find. The trouble is then deciding what to do with this piece of information. The nub of the conundrum is that the studies pooled to create this meta-analysis were all aimed at defining the role of gabapentin as a perioperative analgesic, not as a cardioprotective agent. This aim drove the decisions around study populations and endpoints measured – no troponin levels, no careful examination of ST-segments, etc. Taking a step further back, where is the basic science? A quick Medline search looking for MI and gabapentin yielded neither animal model nor human studies directly examining the cardioprotective effects of gabapentin before or after MI. There are a few studies looking at gabapentinoid premedication prior to cardiac surgery. Even if the quality of these studies is poorer than the studies pooled in this meta-analysis, they may give a better signal about the potential cardioprotective effect of this class of medications.

Reference: Can J Anesth 2016;63(9):1042–58

Abstract
Cognitive behavioral therapy for chronic pain is effective, but for whom?

Authors: Broderick J E et al.

Summary: This paper reported moderator analyses for the post-treatment outcomes of CBT versus usual care for chronic hip/knee OA (osteoarthritis) pain in 256 RCT participants. The treatment effects of CBT were significant, but small, for several primary and secondary outcomes. Differential responses to CBT for subgroups of patients with chronic pain to guide clinical decision-making for treatment were examined. Demographics and several clinical variables (disease severity, body mass index, patient treatment expectations, depression and patient pain coping style) were specified as potential moderators. Trial outcome variables included pain, fatigue, self-efficacy, quality of life, catastrophising and pain medication use. Pain coping style, patient expectation, radiographically assessed disease severity, age and education were identified as moderators for post-treatment outcomes, whereas sex, race/ethnicity, body mass index and depression at baseline were not. In contrast, little treatment benefit was obtained among patients with interpersonal problems associated with pain coping. Most participants indicated that they had positive expectations for CBT prior to randomisation, but benefits were only evident in those with moderate-to-high expectations. The treatment effects were also greater in patients with moderate-to-severe OA, and also in older and more educated patients.

Comment (GL): I was astounded to read that there have been over 100 studies on the effects of CBT and self-management on chronic pain. This was an additional analysis of one of these studies that aimed to identify moderators that explained differential treatment responses in people with lower-limb OA. While some of the five moderators identified weren’t surprising (treatment expectation, coping style), it did raise my eyebrows that disease severity, measured using radiographs, had a marked influence on several outcomes, including pain. Traditionally, biomedical factors have little association with outcomes, and the authors themselves stated that they believed this was the first time a measure of disease severity had been shown to have a relationship with treatment efficacy. Does this suggest that those with more progressed disease severity have CBT before considering joint replacement?

Reference: Pain 2016;157(9):2115–23

Abstract

High correlation of VAS pain scores after 2 and 6 weeks of treatment with VAS pain scores at 12 weeks in randomised controlled trials in rheumatoid arthritis and osteoarthritis

Authors: Karabis A et al.

Summary: This meta-analysis of data from 50 RCTs (n=22,854) explored associations and predictive abilities of changes in baseline VAS pain scores at 2, 6 and 12 weeks during NSAID therapy for rheumatoid arthritis or OA. The respective weighted correlation coefficients between 2 and 6 weeks, 2 and 12 weeks and 6 and 12 weeks were 0.84, 0.79 and 0.96. Baseline VAS score change at 6 weeks was highly predictive and similar to the change at 12 weeks, with a regression coefficient of 0.9, and change at 2 weeks was significantly associated with changes at both 6 and 12 weeks with regression coefficients of 0.9 and 0.8, respectively.

Comment (GL): I found this a really interesting and clinically relevant study. Essentially, in trials of NSAIDs in arthritis populations, the change in pain from baseline to 2 weeks can predict pretty darn well the change in pain at 12 weeks. The statistical outcomes are so strong that it makes me wonder why this hasn’t been looked at previously. I liked the bold suggestions of both altering recommendations for clinical care, i.e. early assessment of efficacy and switching medication if indicated, and also for research, i.e. reducing the duration of clinical trials in this area (12 weeks follow-up is currently the regulatory requirement for trials of symptom-modifying drugs in OA). It makes me wonder which of these would be harder to implement.


Abstract

Genetic and environmental risk for chronic pain and the contribution of risk variants for major depressive disorder

Authors: McIntosh AM et al.

Summary: These researchers explored how genetics and shared family environment contribute to chronic pain by spouse, sibling and household relationships using a family-based mixed-model analysis. There were 23,960 individuals from the Scottish population included in whom the correlation between chronic pain and MDD (major depressive disorder) was evaluated and the contribution of genetic factors and shared environment estimated. Data from two independent genome-wide association studies were used to determine if a polygenic architecture exists for chronic pain, and to examine whether genomic psychiatric disorder risk predicts chronic pain and if genomic chronic pain risk predicts MDD. The analyses were repeated in 112,151 individuals from the UK with genotyping and phenotypic data. Chronic pain was found to be 38.4% heritable and significantly concordant in spouses (variance explained 18.7%). There was a significant positive correlation between chronic pain and depression (p=0.13) with a significant genetic correlation of 0.51. Polygenic risk profiles for pain (generated using independent genome-wide association study data) were significantly associated with chronic pain in both the Scottish and UK cohorts, as was genomic risk of MDD.

Comment (GL): Choose your partner carefully! I fully confess to glossing over much of the detail of this study as it was beyond my comprehension. One finding that stood out was that the combination of genetic factors and a spouse/partner contributed to over 50% of the variation in chronic pain. Notably, the findings also suggest that the presence of chronic pain in one partner increases the probability of MDD in the other partner. Partners of people with chronic pain may not be surprised by this. It is related to the burden of caring, the effect of a common environment and common stressors, or the attraction of a similar mate? There was also an interesting relationship in that chronic pain was associated with an increased risk for MDD, but not vice versa. I was excited that this might answer the chicken and egg question about these conditions until the authors provided a range of methodological reasons why we shouldn’t assume a directional association. Still, these findings highlight the very real importance of genetics in chronic pain.


Abstract

Nurses’ perceptions and attitudes toward use of oral patient-controlled analgesia

Authors: Riemondy S et al.

Summary: This institutional review board approved project sought to evaluate nurses’ perceptions and attitudes around the use of oral PCA devices for treating patients’ pain. In the 4-week study, nurses were educated about oral PCA device use and were asked to complete prestudy and poststudy surveys. The nurses and their patients also completed questionnaires regarding oral PCA device use. Compared with patients, nurses reported less favourable attitudes regarding oral PCA device use. Data from 37 nurses showed that overall knowledge and attitudes increased from 70.8% prestudy to 74.2% after the study, and although this did not reach statistical significance overall (p=0.1637), knowledge about the effectiveness of NSAIDs increased significantly from 27.5% to 60.0% (p=0.0028) as did understanding about opioid use in patients with a history of substance abuse (from 50% to 70% (p=0.0331)).

Comment (GL): A key finding of this study was that oral PCA was more acceptable to patients than to nurses, largely because it was easy for patients to use and they preferred using the device to having to call a nurse. It was interesting that almost all of the suggestions to improve the acceptability of the device centred on educating and training the nurses more, as though their knowledge and skills were the limiting factors. Given that the nurses were provided with step-by-step instructions in a classroom, one-on-one and/or in an online setting, as well as receiving the product instructional brochure, I am not sure how much extra education is needed without conceding it may have been a complex device to use and that the nurses had legitimate concerns about the concept of oral PCA. One limitation of the study is that they did not measure pain outcomes, and I wonder how much of an effect of the opioids is lost when they are administered by a device rather than a lovely, caring nurse.


Abstract