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Welcome to issue 24 of Anaesthesia and Pain Management Research Review.

This issue’s research begins with a systematic review reporting a large number of differing definitions that have been used in observational studies to define persistent opioid use. This is followed by a large cohort study reporting the impact of CUD (cannabis-use disorder) on perioperative outcomes following a range of major elective surgeries. We’ve also included a rapid review from NZ on the evidence (or lack thereof) for the use of cannabis-based medicinal products for managing arthritic pain. The issue concludes with a systematic review reporting that evidence regarding the benefits and harms of PRF (pulsed radiofrequency) of the dorsal root ganglion for treating non-neuropathic pain is of poor quality and obtained from few participants.

We hope you find the research selected for this issue enlightening and useful for everyday practice. We look forward to your comments and feedback.

Kind regards,

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Persistent postoperative opioid use

Authors: Jivraj NK et al.

Summary: This systematic review of 39 population-based cohort studies identified 29 different definitions of ‘persistent opioid use’, which when applied to a cohort of 162,830 opioid-naïve surgical patients, returned incidences within 1 year of surgery of 0.01–14.7% (median 0.7%). Opioid-related overdose or an opioid-use-disorder-associated diagnosis over 1 year of follow-up was recorded for 1 per 1000 operations. The respective ranges for the sensitivity and specificity values of each definition for identifying patients with opioid-use disorder or opioid-related toxicity were 0.01–0.36 and 0.86–1.00.

Comment (JB): Inherent in any kind of systematic review is the need to differentiate apples from oranges. These authors performed something like the converse of a systematic review exploring persistent postoperative opioid use. They even excluded RCTs as these would introduce unacceptable bias. From 39 studies they identified a fruit bowl of 29 postoperative opioid use definitions. When they applied these 29 definitions to the postoperative opioid dispensing data from a large cohort (n=162,830) of opioid-naïve elective surgery patients from Ontario, Canada, they found a 100-fold variation in the estimate of postoperative opioid use between the definition that was the least stringent and the definition that was the most stringent. The authors highlighted that the risk of postoperative opioid use, both in terms of the incidence and the danger, is probably overstated in some publications if the definition of postoperative opioid use applied was not stringent enough. They supported the application of definitions that imply continuous or near continuous opioid use over a period of months rather than a single dispensing in a time window a few months after surgery. The timbre of the article is that patients, prescribers and policymakers are currently all running a bit too scared. The cohort studied had their surgery sometime during the years 2014–2016, and the patients were followed for 12 months postoperatively. In this follow-up period, 20 members of the cohort suffered an opioid overdose and 146 developed an opioid use-disorder. When applied in a two-by-two table as ‘test’ for opioid-related adverse effects (overdose or diagnosis of opioid use disorder), none of the postoperative opioid use definitions demonstrated a sensitivity of more than 0.36 and the more stringent postoperative opioid use definitions demonstrated a particularly low sensitivity (<0.1), with the inference that the overlap between postoperative opioid use and opioid abuse was not large in this cohort. One of the throwaway lines from the study’s discussion was “Moreover, as nearly 14% of Ontario residents fill a prescription for opioids in a given year, it is possible that some definitions of persistent use approximate the baseline rate of use in the general population”. What would your prediction be for New Zealanders filling prescriptions for strong opioids?

Reference: Anesthesiology 2020;132:1528–39

Abstract
Thank you frontline workers.

No matter the alert level, we want to be there for you online.

At MSD New Zealand, we’re grateful to all who worked to keep our communities safe.

Now when you stay-in, why not tune-in to the most recent Networks in Anaesthesia and Surgery webcast, ‘The Obese Patient,’ playing on demand.

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Sphenopalatine ganglion block for the treatment of postdural puncture headache

Authors: Jespersen MS et al.

Summary: Forty adults meeting the criteria for an epidural blood patch for PDPH (postdural puncture headache) were randomised to bilateral sphenopalatine ganglion block with 1mL of 4% lidocaine plus 0.5% ropivacaine or saline. No significant difference was seen between the local anaesthetic and placebo groups for estimated median difference in visual analogue scale pain score change while upright 30 minutes after the block was administered (primary outcome; difference, 5mm [p=0.53]) or for the proportion who required epidural blood patch (50% vs. 45% [p=0.76]).

Comment (JB): These researchers have demonstrated that a single sphenopalatine ganglion block markedly reduces the pain intensity from PDPH (measured when standing 30 minutes after the block). While the block was curative in only a minority of patients, approximately 50% of the subjects avoided having an epidural blood patch. The authors describe a straightforward low-risk technique for performing the block, and only one out of the 40 subjects could not tolerate the procedure. So far so good. Unfortunately, they achieved similarly positive results with their sham blocks, performed with saline rather than a mixture of lidocaine and ropivacaine. A powerful placebo then? Seventy-five percent of the study patients developed their PDPH following diagnostic lumbar puncture, and the remainder developed PDPH after neuraxial anaesthesia with spinal (5%) or epidural techniques (20%). This shouldn’t have been a cause of bias in this study as the treatment and the control groups had near-identical numbers of each PDPH cause. It could provide added variability though and reduce the chances of finding a true benefit from local anaesthetic over saline. Numerically, pretty much all the results were “better” in the treatment group, and perhaps if the study had been larger, the differences would have reached statistical significance. Are you a purist or a pragmatist? On the basis of the study, would you advocate for sphenopalatine block because 50% of the enrolled women at risk of postpartum haemorrhage. Giving tranexamic acid early reduced the chance of death due to haemorrhage by almost 30% without increasing the thrombosis-related deaths. The magnitude of this net benefit was not altered when patients were stratified by the predicted risk of death from haemorrhage. The outstanding questions are: would the positive impact of tranexamic acid found in this study translate to other common clinical scenarios where there is an appreciable risk of bleeding; and does this meta-analysis provide convincing evidence that the risk of harm from tranexamic acid is extremely low? The answers are maybe and probably not. I need to confess that my assessment of this paper was turned on its head somewhat by the accompanying editorial, aptly named “Tranexamic acid: the king is dead, long live the king!”. I read the paper first and thought it made a strong case for tranexamic acid, even when the risk of severe haemorrhage is not particularly high. I then read the editorial and felt much more uncertain. The role of a chief editor must be interesting. Apparently, you receive a high-quality paper from an established research group, then ask for an editorial based on this paper from authors who then pick it to pieces. It is entertaining, but probably not likely to encourage future collaboration. I would strongly recommend reading both, and if you want to maximise your feelings of inadequacy, read the original paper before the editorial.

Reference: Br J Anaesth 2020;124:739–47

Abstract

Effect of tranexamic acid by baseline risk of death in acute bleeding patients

Authors: Ageron F-X et al., for the Antifibrinolytics Trials Collaboration

Summary: This was a meta-analysis of individual participant-level data (n=28,333) from two RCTs of tranexamic acid given ≤3 hours of acute bleeding onset. The risk of bleeding-associated death at baseline was low (0–5%) for 81% of the participants. Bleeding-associated deaths occurred in 1%, 8%, 14% and 30% of participants with low, intermediate (6–10%), high (11–20%) and very high (>20%) baseline risks, respectively. Tranexamic acid effectiveness did not vary according to baseline risk when given within 3 hours after bleeding onset (p=0.51 for interaction), and its administration was not associated with an increased risk of vascular occlusive events overall or according to baseline risk (p=0.26).

Comment (JB): Most of us have probably wondered, what is the threshold of bleeding risk below which giving tranexamic acid causes more problems with clotting (or seizures) than it prevents problems with bleeding? The authors of this paper believe that the threshold is low. Two large RCTs contributed data for meta-analysis: CRASH-2 (n=13,485) and WOMAN (n=14,848). As the names of the trials suggest, one enrolled trauma patients and the other enrolled women at risk of postpartum haemorrhage. Giving tranexamic acid early reduced the chance of death due to haemorrhage by almost 30% without increasing the thrombosis-related deaths. The magnitude of this net benefit was not altered when patients were stratified by the predicted risk of death from haemorrhage. The outstanding questions are: would the positive impact of tranexamic acid found in this study translate to other common clinical scenarios where there is an appreciable risk of bleeding; and does this meta-analysis provide convincing evidence that the risk of harm from tranexamic acid is extremely low? The answers are maybe and probably not. I need to confess that my assessment of this paper was turned on its head somewhat by the accompanying editorial, aptly named “Tranexamic acid: the king is dead, long live the king!”. I read the paper first and thought it made a strong case for tranexamic acid, even when the risk of severe haemorrhage is not particularly high. I then read the editorial and felt much more uncertain. The role of a chief editor must be interesting. Apparently, you receive a high-quality paper from an established research group, then ask for an editorial based on this paper from authors who then pick it to pieces. It is entertaining, but probably not likely to encourage future collaboration. I would strongly recommend reading both, and if you want to maximise your feelings of inadequacy, read the original paper before the editorial.

Paracetamol and pain modulation by TRPV1, UGT2B15, SULT1A1 genotypes

Authors: Pickering G et al.

Summary: Healthy volunteers received oral paracetamol (acetaminophen) and placebo separately, with a 1-week break in between, in this randomised, crossover pilot study with the aim of investigating the impact of the genetic polymorphisms of 23 enzymes and receptors involved in paracetamol metabolism and its mechanism of action. Compared with placebo, paracetamol was antinociceptive (222 vs. 23 kPa/min [p=0.0047]). Thirty participants reported a response and 17 no response with paracetamol. Responders had genetic polymorphisms that confirm the involvement of a specific TRPV1 (transient receptor potential vanilloid type 1 receptor) rs224534 variant in paracetamol antinociception, as well as a new antinociceptive role for specific variants of hepatic phase 2 enzymes involved in paracetamol metabolism.

Comment (JB): Despite it being the most commonly used analgesic worldwide, there remains a fair bit of mystery about paracetamol. This experimental pain study demonstrated a new and unexpected rule of thirds. The applied pain stimulus was a point pressure pain caused by a von Frey hair apparatus. Of the 52 young male volunteers taking part, one third were strong responders, one third were moderate responders, and one third were nonresponders to the analgesic effects of a single 2g dose of our favouriteinline dye derivative. The authors went on a focussed genotypic fishing trip looking for a signature that would identify responders versus nonresponders, and their targets were specific polymorphisms of a key receptor (TRPV1), and two of the enzymes that play a role in paracetamol phase 2 metabolism (glucuronidase [UGT] and sulfotransferase [SULT]). While there were some statistically significant associations, the major importance of this paper is that a third of well adult men were nonresponders to the analgesic effects of paracetamol using a mechanical pain stimulus model. The most interesting part of the study was the brief description of putative sites of drug action, including the potential that a phase 1 metabolite linked to a fatty acid chain may be responsible for some of paracetamol’s central action (AM404). The TRPV1 receptor exists both peripherally on nociceptive neurons and in some key ‘pain’ areas centrally, like the periaqueductal grey zone, and AM404 is a potent agonist of the TRPV1 receptor. A failure to relieve experimental pain may not imply failure in the clinical context, but it is certainly worth bearing in mind when a patient says “paracetamol doesn’t work for me”.


Abstract

Cannabis-based medicinal products in arthritis, a painful conundrum

Authors: Van den Berg M et al.

Summary: These NZ authors performed a rapid medical literature review on cannabis-based medicinal products for arthritis. Data from animal studies have indicated that arthritis involves endocannabinoid pain pathways that are potentially amenable to intervention. The cannabis-based product Sativex® was associated with some improvements in pain in one randomised placebo-controlled trial of adults with rheumatoid arthritis, but not when compared with a standardised pharmacological regimen. Systematic reviews have failed to identify sufficient evidence to recommend cannabis-based medicines for arthritis in routine clinical practice. At the time of the review, five registered clinical trials of cannabis-based products in arthritis were ongoing.

Comment (GL): The title of this paper is rather misleading — it’s not really a conundrum when the evidence, or lack of it, is fairly clear. I found the lack of human trials in this area surprising, although there are several currently ongoing (a quick check for an update confirmed most are suspended due to COVID-19). The article itself is a rapid review, so it’s not quite as pristine as a full systematic review, and it doesn’t really add to the literature on cannabis-based products given the only two human studies found had already been included in two previous systematic reviews. However, it does portray the topic in a clinically friendly manner and clearly outlines the lack of good evidence for beneficial effects of cannabis products for arthritic conditions. The authors did make one point that long-term osteoarthritis should be associated with central sensitisation, and that there is some evidence for positive effects of cannabis products for neuropathic pain. However, central sensitisation is not neuropathic, but rather nociceplastic in nature. Nociceplastic pain is due to dysfunction of the nociceptive system rather than neural damage, which implicates separate mechanisms and management approaches.


Abstract

Apps for older people’s pain self-management: perspectives of primary care and allied health clinicians

Authors: Bhattarai P et al.

Summary: These researchers conducted semistructured interviews of 17 primary care and allied health clinicians in Australia to gauge their perspectives on the use of pain self-management apps to improve arthritic pain management in older individuals. There was an overarching theme that integration of such apps for the self-management strategies of older people with pain was idealistic but uniquely challenging. The following four subthemes were identified: i) self-management apps have potential, although careful consideration is required; ii) the involvement of clinicians is necessary yet potentially onerous; iii) there is no single app that is ideal for every older person with arthritic pain; and iv) while patient data access is beneficial, there is need for caution regarding real-time access.

Comment (GL): This study is even more relevant since the enforced switch to video and phone consultations during lockdown, and the likely persistence of this in the future. I think the authors summed things up rather well with the phrase “idealistic but uniquely challenging”. It seems somewhat similar to “great in theory, but...’’. One of the noteworthy points raised was in relation to clinicians’ time – it takes extra time to become familiar with apps, check patient entries and provide ongoing technical support for patients. What seems to be a simple solution can rapidly become more complex. It is not dissimilar to online teaching – I find it takes more time to prepare and deliver courses online than teaching in person, and it is far more tiring. There are definitely unique benefits of apps that are worth pursuing, such as an ability to provide information or instructional videos on demand or to capture data over long periods that can be automatically summarised and made available to clinicians, but I don’t think they are a one-stop solution. Certainly, we should make the most of the benefits they offer, but perhaps not try to fit them into the aspects of management in which they don’t do well.


Abstract

The New Zealand Society of Anaesthetists will be hosting a conference this year

Anaesthesia 2020

Emerge, Reflect and Reconnect

SAVE THE DATES: 16-17 Oct 2020
(with optional pre-conference workshops on 15 Oct 2020)
WHERE: Wellington
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(a virtual option will also be offered)

Our organising committee is now busy working on the details – scientific and social programs, workshops and more. More information to come soon, including a conference website so you can register.

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Do decision aids benefit patients with chronic musculoskeletal pain?

Authors: Bowen E et al.

Summary: This was a systematic review of RCTs assessing decision aids to make treatment decisions for chronic musculoskeletal pain (including osteoarthritis of the hip, knee or trapeziometacarpal joint and back pain) in adult outpatients; 13 RCTs evaluated the use of decision aids for deciding between surgical and nonsurgical management, and four evaluated decision aids for nonsurgical treatment options. There were mixed effects of decision aids on decision-making outcomes. In five studies that examined knowledge scores, decision aids improved patient knowledge compared with usual care. Of four RCTs that evaluated satisfaction with the decision-making process, none found the decision aid made any difference. Data on other decision-related outcomes were limited and inconsistent. Seven of eight studies that evaluated surgical utilisation reported no difference in surgery rates with decision aid use. Among the five RCTs that compared different types of decision aids, no format was identified that was better than the others.

Comment (GL): One of the drivers for this study was previous research showing that patients’ choices of treatment differed from usual care when they were given full information about treatment efficacy and risks of side effects. While all the theory was there, the evidence from the review findings pointed to a minimal impact of decision aids for patients in terms of their outcomes and the actual decisions made, with the exception that they felt better informed. There were some limitations in the studies included in the review, particularly the relatively young age of the participants and the focus on decision aids regarding surgery rather than conservative management options, so I guess there is always the potential that more research would have different findings. I think that’s a slim chance though. It was nice to know that the platform for delivering information didn’t really matter, in that simple paper-based information and decision aids had the same effect as more technological aids. Perhaps it is just that managing chronic musculoskeletal pain is rather complex and it takes more than factual information to guide decisions about management and the outcomes of this. Certainly, factoring in the emotional and social aspects of long-term pain would be tricky, and may explain why the findings were different from other conditions where decision aids have been shown to be useful. There is also the possibility that patients are already pretty set in how they think their condition should be managed, so that decision aids do not do any additional aiding.

Abstract

Centralized pain and pain catastrophizing mediate the association between lifetime abuse history and self-reported pain medication side effects

Authors: Pierce J et al.

Summary: The impact of physical or sexual abuse history on self-reported pain medication side effects was explored in this cross-sectional analysis of 3118 outpatients presenting to a tertiary-care pain clinic. A history of abuse was reported by 479 (~15%) of the patients. Compared with patients reporting no history of abuse, those who did, particularly those who experienced abuse during both childhood and adulthood, reported more side effects associated with their pain medication. Furthermore, a path analysis revealed that the association between lifetime abuse history and the sum of pain medication side effects was mediated by a centralised pain phenotype and pain catastrophising.

Comment (GL): It is known that a history of abuse is a risk factor for chronic pain, that catastrophising is also associated with a higher risk of developing chronic pain as well as having poorer outcomes from treatment, and that the presence of central sensitisation indicates a need for a more holistic approach to pain management. So how do all these factors relate to pain medication side effects? This was a novel and clinically relevant question, as the findings had the potential to impact decision-making regarding the prescription and presentation of pain medication to patients. The study design did suffer from the problem of being retrospective, using previously collected clinical data, which means that it gains in terms of participant numbers, but is rather limited by a lack of detailed information and, more importantly, a clear temporal relationship between taking medication and the (presumably) associated side effects. A major problem with the main findings of this paper is that the potential side effects of medication are also some of the factors defining central sensitisation, so it was obvious from the start that these two aspects were going to be linked. This limits the relevance of the findings somewhat. More meaningful for me is the (further) evidence provided that a history of abuse is so markedly associated with adverse physical and mental health outcomes. It highlights why a multidisciplinary approach to pain management is so important for people presenting with features of central sensitisation.

Reference: Reg Anesth Pain Med 2020;45:293–300
Abstract

Efficacy and safety of pulsed radiofrequency as a method of dorsal root ganglia stimulation for treatment of non-neuropathic pain

Authors: Vuka I et al.

Summary: This systematic review included 17 studies (n=599) comparing targeted PRF of the dorsal root ganglion with any comparator for treating a variety of non-neuropathic pain syndromes. Two RCTs included participants with lower back pain, and nonrandomised studies included participants with lower back pain, postsurgical pain, pain associated with herpes zoster, cervicogenic headache, complex regional pain syndrome type 1, intractable vertebral metastatic pain, chronic sacral and inguinal pain, occipital radiating pain in rheumatoid arthritis and chronic migraine. Targeted PRF was usually started after other treatments had failed. Positive conclusive statements regarding efficacy were reported in 11 of the studies, and the rest made positive inconclusive statements. Regarding safety, two studies provided positive conclusiveness of evidence statements, and one provided a positive inconclusive statement. The risk of bias was primarily unclear in the randomised studies, and was ‘serious’ in the nonrandomised studies.

Comment (GL): The same team of authors have published a similar review in neuropathic pain, and both of these reviews are well-conducted. While PRF can have direct neural effects that reduce nociception in neuropathic pain conditions, the rationale for its use in other chronic pain conditions is somewhat lacking. This is perhaps reflected in the heterogeneity of pain populations within the current review. Given the largely low-quality evidence presented, I think the rationale for use in these populations is still lacking. There were a huge range of stimulation parameters used across the studies (suggesting a fishing expedition), and like a lot of alternative treatments, only people who hadn’t responded to traditional treatment were included in most of the studies, indicating some selection bias. While the majority of studies did report results favouring PRF, the low quality of the evidence presented means I’d hold off trying it as a treatment for non-neuropathic chronic pain conditions for now.

Reference: BMC Anesthesiol 2020;20:105
Abstract

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