Welcome to issue 18 of Anaesthesia Research Review.

We begin this issue with an interesting study investigating the perineural administration of dexamethasone combined with ropivacaine for interscalene brachial plexus block, and discover that the clinical effect of the addition of dexamethasone wasn’t really all that impressive. Following on, we review a study investigating the effect of anaesthetic agent on outcomes in patients undergoing hepatectomy for hepatocellular carcinoma and receiving desflurane or propofol. Other topics covered in this issue include recovery after reversal of NMB with sugammadex or neostigmine, neuraxial versus general anaesthesia and hospital admission, dexmedetomidine for shivering during neuraxial anaesthesia, and deep NMB during gastric bypass surgery.

I wish you an enjoyable reading experience of our selected literature.

Kind Regards,
Professor Thomas Ledowski
thomas.ledowski@researchreview.com.au

Dose-response relationship of perineural dexamethasone for interscalene brachial plexus block: a randomised, controlled, triple-blind trial

Authors: Albrecht E et al.

Summary: This randomised, placebo-controlled triple-blind trial tested whether perineural dexamethasone doses 1-4 mg could dose-dependently prolong analgesia duration in 80 patients with an ASA physical status of 1-2 undergoing shoulder arthroscopy under general anaesthesia with ultrasound-guided interscalene brachial plexus block. Median duration of analgesia (time between block and first analgesic request) was dose-dependently prolonged (placebo 685 min; dexamethasone 1 mg 835 min; 2 mg 904 min; 3 mg 965 min; 4 mg 1023 min; p = 0.03).

Comment: This is an excellent and very interesting study comparing different low doses of perineural dexamethasone with a control group. While the authors’ main conclusion is that increasing doses of dexamethasone increased the clinical duration of analgesia achieved by the nerve block, it may also be interesting to note that at no time were any differences in postoperative pain scores found between placebo and the different doses of dexamethasone. Considering the fact that the addition of dexamethasone to a local anaesthetic is clearly off-label use, I personally find it reassuring that the clinical effect of the addition wasn’t really all that great. Yes, the overall increase in block analgesia was observed… but with a rather wide range of confidence intervals and a p-value relatively close to 0.05. So, my personal conclusion – why actually bother with the risk? But this is my opinion, of course.

Reference: Anaesthesia 2019;74(8):1001-8

Propofol-based total intravenous anaesthesia is associated with better survival than desflurane anaesthesia in hepatectomy for hepatocellular carcinoma: a retrospective cohort study

Authors: Lai H-C et al.

Summary: This single-centre, retrospective cohort study examined the effect of anaesthetic agent on outcomes in patients receiving desflurane (n = 492) or propofol (n = 452) undergoing hepatectomy for hepatocellular carcinoma. In total there were 369 deaths (75.0%) with desflurane versus 139 deaths (30.8%) with propofol anaesthesia. Propensity matching of 335 patients in each group indicated that propofol had a better survival with a hazard ratio (HR) of 0.47 (95% CI 0.38-0.59; p < 0.001). Subgroup analyses also suggested greater survival in the absence of distant metastasis (HR 0.47; 95% CI 0.37-0.60; p < 0.001) or local recurrence (HR 0.22; 95% CI 0.14-0.34; p < 0.001).

Comment: Yet another study showing what has been strongly debated at the last ANZCA ASM in Kuala Lumpur – propofol-based anaesthesia may cause/coincide with better survival rates after oncology surgery. Though a recent meta-analysis by Yap A et al., 2019 may be somewhat more valuable in a scientific manner, it may be valuable to all members of the anaesthesia community to “rub it in” again and again that there may at least be a problem with volatiles in cancer surgery. Personally, I have now converted to propofol TCI maintenance for almost all such cases. This may be seen as premature by some, since most evidence from controlled trials stems from animal research. However, after all, our specialty is at least a little bit like cooking, using some intuition and “gut feeling” may not be entirely wrong, and I am yet to find strong contraindications for propofol in otherwise normal subjects.


Abstract
The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period

Authors: Cravero JP et al.

Summary: A Society for Pediatric Anesthesia taskforce examined literature and developed recommendations for perioperative opioid administration in children. The recommendations address vital issues about opioid administration in children after surgery, including appropriate pain assessment, monitoring, dosing considerations, adverse events, strategies for delivery, and analgesic efficacy assessment.

Comment: Pain therapy in children can certainly be a daunting task, especially for those of us like myself who do not regularly anaesthetise children. This consensus paper may be a worthwhile read as it offers a brief overview of the actual level of evidence for recommended pain treatment strategies. What do I make of it? Well, we all know that kids aren’t simply small adults, but to my surprise it appears that in many ways the recommended treatment pathways are not so dissimilar from the ones in adults. PCA is favourable for stronger pain and regular pain assessment and monitoring for potential side effects of opioids are vital. Importantly, the doses for most synthetic opioids, but not for remifentanil, need to be carefully age-adjusted, especially in neonates. And of course, multimodal pain concepts are the gold standard. Still worth a read as the actual level of study-derived knowledge is at times remarkably weak.


Abstract

HTX-011 reduced pain intensity and opioid consumption versus bupivacaine HCl in bunionectomy: phase III results from the randomized EPOCH 1 study

Authors: Viscusi E et al.

Summary: This randomised placebo- and active-controlled phase III trial tested an extended-release, dual-acting local anaesthetic HTX-011 (bupivacaine plus meloxicam in a bio polymer) and postoperative opioid use versus bupivacaine hydrochloride (HCl) for postoperative pain in 412 patients undergoing primary unilateral, distal, first metatarsal bunionectomy. HTX-011 was superior to both saline placebo and bupivacaine HCl in producing sustained pain reduction over 72 hours and reducing opioid consumption and more opioid-free subjects. Safety profiles did not differ across groups and there were fewer opioid-related adverse events in HTX-011 recipients.

Comment: We frequently utilise off-label adjuncts such as clonidine or dexamethasone in order to extend the duration of action of local anaesthetics when performing nerve blocks. Firstly, the evidence for doing so isn’t really very strong and secondly, does such practice expose its user to the risk of litigation. Thus, I read with great pleasure that a novel extended-release combination of bupivacaine and meloxicam has shown some promise in significantly reducing pain when compared with placebo or standard bupivacaine even 72 hours after surgery. HTX-011 may hence improve pain treatment where it currently frequently fails, i.e. talking about nerve blocks prematurely wearing off in the middle of the first postoperative night. At present, nerve catheters may offer a solution. However, this comes with the price tag of a somewhat reduced mobilisation and the risk presented by the catheter itself. A single injection with a long-lasting local anaesthetic is thus certainly tempting.

Reference: Reg Anesth Pain Med. 2019;May 21 [Epub ahead of print]

Abstract

Influence of reversal of neuromuscular blockade with sugammadex or neostigmine on postoperative quality of recovery following a single bolus dose of rocuronium: A prospective, randomized, double-blinded, controlled study

Authors: Kim NY et al.

Summary: This prospective, double-blind, randomised, active-controlled trial examined the reversal of NMB with sugammadex (n = 40) or neostigmine (n = 44) on postoperative quality of recovery following a single bolus dose of rocuronium in 84 ASA grade 1-2 patients undergoing pars plana vitrectomy under general anaesthesia. Fifteen minutes after surgery the recovery rate in the physiological domain was greater in sugammadex than neostigmine recipients (p = 0.020). There were no differences in the overall cognitive recovery domain, although sugammadex recipients could recall more numbers in reverse order. There were no differences in the other domains of the cognitive scale.

Comment: I am known to love sugammadex, hence, this study showing some early benefits for reversal of rocuronium with sugammadex is just what I like to report on. However, considering the significant differences in associated costs (neostigmine vs sugammadex) as well as the hypothetical benefits of sugammadex-based reversal beyond the recovery room (i.e. decreased pulmonary complications), the reported results are almost a bit disappointing. If one actually reads the paper, it becomes pretty clear why: in both groups reversal was only given when the TOF ratio was at least 0.7. This pretty much excludes the most severe cases of residual lock and may explain why the differences between the reversal strategies found in this paper were so tiny.


Abstract

The association of neuraxial versus general anesthesia with inpatient admission following arthroscopic knee surgery

Authors: Padwal JA et al.

Summary: This retrospective cohort analysis of data from the US National Surgical Quality Improvement Program (2007-16) examined differences in complications between general (n = 55,257) and neuraxial (n = 23,374) primary anaesthesia in patients undergoing arthroscopic knee procedures. In matched cohorts, neuraxial anaesthesia recipients were more likely to require postoperative hospital admission (p < 0.001). This was confirmed in a multivariate regression model (OR 5.93; 95% CI 4.90-7.21). Additional predictors of hospital admission were Asian race (OR 6.47; 95% CI 4.90-8.56), history of bleeding disorder (OR 5.44; 95% CI 2.14-12.76), COPD (OR 3.10; 95% CI 1.94-4.82), increased operation time (OR 3.01; 95% CI 2.69-3.37), and diabetes (OR 1.90; 95% CI 1.43-2.49).

Comment: The paper describes data of no less than 57,000 patients! The authors describe a higher risk for inpatient admission after neuraxial versus general anaesthesia. Interestingly, the reported number of neuraxial anaesthesia patients was only about 4% of the general anaesthesia population. One does wonder whether the somewhat rare cases of neuraxial anaesthesia may have been a specifically bad sub-selection of patients with possible contraindications to receive a general anaesthesia, hence more prone for problems and un-planned admission. Though the authors present a regression model identifying neuraxial anaesthesia as an independent predictor for hospital admission, their conclusion is that the association between the higher rate of hospital admission and neuraxial anaesthesia needs further evaluation. Even with big data, ultimately more questions than answers, but the clear hint that neuraxial anaesthesia may certainly not be safer in each and everybody.


Abstract
Anaesthesia

IMMEDIATE RELEASE

ATYPICAL OPIOID

PALEXIA® IR PROVIDES:

• Strong pain relief as effective as oxycodone IR

• Significantly less constipation, nausea and vomiting vs. oxycodone IR

∗Analgesia not solely derived from opioid agonism.  †S8 analgesic.

†Non-inferior efficacy (5-day Sum of Pain Intensity Difference); secondary endpoint, primary endpoint was met. Significantly lower incidence of nausea, vomiting, and constipation (nominal p<0.001 for all events); PALEXIA® IR 50mg vs. oxycodone IR 10mg.

MINIMUM PRODUCT INFORMATION: PALEXIA® IR (tapentadol hydrochloride) INDICATION: Moderate to severe pain. CONTRAINDICATIONS: Known hypersensitivity to tapentadol or any component of PALEXIA IR; conditions in which mu-opioid receptor agonist activity is contraindicated e.g. significant respiratory depression and acute or severe bronchial asthma or hypercyanotic congenital heart disease; acetate intake with alcohol; hypotonic, centrally acting analgesics or psychotropic drugs; patients who are receiving MAO inhibitors or who have taken them within the last 14 days. PRECAUTIONS: Monitor for signs of abuse and addiction; repeated administration may lead to tolerance; withdrawal symptoms could occur after abrupt discontinuation, not recommended in patients with increased intracranial pressure, impaired consciousness, or coma and severe renal or severe hepatic impairment; caution in patients with impaired respiratory function, patients with head injury, brain tumours, a history of seizures or any condition that increases risk of seizures, severe renal impairment, moderate or severe hepatic impairment or biliary tract disease, including acute pancreatitis. Use in pregnancy (Category C). Should not be used during breastfeeding. Not recommended for children <18 years old. May impair ability to drive or operate machinery. INTERACTIONS: Care should be taken when combining with mixed opioid agonist/antagonists or partial mu-opioid agents, add or C/D depression with concomitant administration of other mu-opioid receptor agonist analgesics, general anaesthetics, phenothiazines, other tranquillizers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs)- reduction of dose of one or both agents should be considered, contraindicated in patients who are receiving MAO inhibitors or who have taken them within the last 14 days; isolated case reports of serotonin syndrome when used in combination with serotonergic drugs (see full PI). ADVERSE EFFECTS: Very common (≥1/10): dizziness, somnolence, headache, nausea, vomiting; common (≥1/100 to <1/10): Decreased appetite, anxiety, confusion, drowsiness, dry mouth, pruritus, hyperesthesia, rash, muscle spasms, asthenia, fatigue, feeling of body temperature change. DOSAGE AND ADMINISTRATION: To be taken orally, whole with sufficient fluid, approximately every 4 to 6 hours, with or without food. Usual recommended dose 50 to 100 mg every 4 to 6 hours and should be adjusted to maintain adequate analgesia with acceptable tolerability. Total daily doses >600 mg not recommended. Discontinuation of treatment: taper dose gradually to prevent symptoms of withdrawal. Renal Impairment: not recommended in severe renal impairment. Elderly patients more likely to have decreased renal and hepatic function – care in dose selection. Not recommended for use in children <18 years old. Based on Approved Product Information. References: 1. PALEXIA IR Approved Product Information. 2. Schug S. ANZCA Bulletin 2018 Not all opioids are the same. 3. Raffa RB. Curr Med Res Opin 2014; 30(12):2579–2584. 4. Perigall J et al. NEMA Research Group. Naples, Florida, USA 2017. 5. Hartrick C et al. Clin Ther 2009; 31(2):260–271. PALEXIA® IR is registered trademark of Grünenthal Pty Ltd and distributed by Seqirus (Australia) Pty Ltd under licence from Grünenthal GmbH. PBS Information: This product is not listed on the PBS.
Effect of iloprost inhalation on postoperative outcome in high-risk cardiac surgical patients: a prospective randomized-controlled multicentre trial (LOCARD)

Authors: Winterhalter M et al.

Summary: This multicentre, randomised, double-blind, placebo-controlled phase III trial tested whether prophylactic iloprost inhalation would reduce post-operative ventilation time after cardiac surgery \( (n = 235) \). Iloprost had no effect on median duration of postoperative ventilation (primary endpoint) versus placebo \( (720 \text{ vs } 778 \text{ min}; \text{median decrease } 65 \text{ min}; 95\% \text{ CI } -77 \text{ to } 210) \). Nebulisation of iloprost decreased right ventricular afterload and improved cardiac index, but did not affect secondary endpoints including perioperative haemodynamics, intensive care unit or hospital length of stay and 90-day mortality \( (14\% \text{ vs } 14\%; \text{HR } 0.97; 95\% \text{ CI } 0.50-1.89) \).

Comment: Patients with a high risk for right ventricular failure were exposed to intraoperative (before and during weaning from bypass) iloprost inhalation in this double-blinded, randomised controlled study. And while iloprost nebulisation certainly delivered the assumed benefits of lower right ventricular afterload and increased cardiac index, none of the tested primary endpoints describing patient outcome were affected. The conclusion clearly is that a prophylactic administration may not be useful. However, I wonder whether discontinuation after successful weaning may have been too early. One could assume that the reduction in right ventricular afterload might have been of significant benefit even after the weaning, as the right ventricular strain from (probably not yet fully atelectasis-free) re-perfusion of the lungs might have been longer lasting than iloprost was provided. Just a thought \( (\text{of only a long-time ex-cardiac anaesthetist, of course}) \).


Intravenous dexmedetomidine for the treatment of shivering during Cesarean delivery under neuraxial anesthesia: a randomized-controlled trial

Authors: Lamontagne C et al.

Summary: This prospective, randomised, placebo-controlled, double-blind trial in 80 parturients undergoing Cesarean delivery and experiencing shivering under neuraxial anesthesia, tested whether the alpha 2-adrenergic agonist dexmedetomidine would reduce duration of shivering. Dexmedetomidine reduced mean shivering duration from 17.3 to placebo to 2.6 min \( (\text{difference } -15.3 \text{ min}; 95\% \text{ CI } -11.2 \text{ to } -19.4) \). The effect persisted for 15 min after dexmedetomidine was administered, with shivering completely reduced mean shivering duration from 17.9 with placebo to 2.6 min \( (\text{difference } -15.3 \text{ min}; 95\% \text{ CI } -11.2 \text{ to } -19.4) \). The effect persisted for 15 min after dexmedetomidine was administered, with shivering completely reduced.

Comment: Some may recall the days of pethidine being used to fight postoperative shivering and most will probably utilize it still. Probably not altogether surprising that another alpha-2-agonist \( (\text{dexmedetomidine}) \) can do the same trick. Interestingly, this nicely done double-blinded trial shows us that a single bolus rather than a continuous infusion was sufficient to abolish shivering in 90% of patients and shorten the total time of shivering by 11-19 min \( (\text{vs placebo}) \). Though the trial did not compare dexmedetomidine with clonidine, it would be interesting to see whether the duration of certain undesirable side effects \( (\text{i.e., hypotension and sedation}) \) may show an advantage for dexmedetomidine. Certainly, a matter for a follow-on study, I suggest.


The impact of a transversus abdominis plane block including clonidine vs. intrathecal morphine on nausea and vomiting after caesarean section

Authors: Dereu D et al.

Summary: This Swiss randomised, controlled, double-blinded study tested whether transversus abdominis plane \( (\text{TAP}) \) block with ropivacaine and clonidine would reduce postoperative nausea and vomiting \( (\text{PONV}) \) versus intrathecal morphine \( (\text{ITM}) \) in 182 pregnant women undergoing elective Cesarean section. There was no difference between TAP and ITM in incidence of PONV \( (18.5\%; 95\% \text{ CI } 11.1-27.9 \text{ vs } 30.7\%; 95\% \text{ CI } 21.3-41.4) \) after 24 hours. ITM recipients had lower pain scores at 6 hours and lower cumulative morphine consumption \( (p < 0.0001) \) at 24 hours. Hypotension incidence was higher with TAP \( (64.3 \text{ vs } 29.2\% ; p = 0.0006). \)

Comment: Yet again, a study about off-label adjuncts to nerve blocks, at least in part. This one showed that intrathecal morphine was superior for post-caesarean section pain when compared to a TAP block with ropivacaine and clonidine. I am not the greatest fan of intrathecal morphine, due to a fair bit of nausea and vomiting I have observed in my own ITM patients. Hence, a bit to my surprise, this study did not find a significant difference for PONV between the groups. However, I guess one might see a trend towards a higher rate in the ITM group. Possibly the effect of the clonidine, more hypotensive episodes were observed in the TAP group. Given the relatively weak evidence for this off-label use of clonidine, this may be a warning that using the drug in this context may still have significant systemic side effects – adding clonidine to block could hence be tricky to defend in case of a related serious adverse event.


Deep neuromuscular blockade improves surgical conditions during gastric bypass surgery for morbid obesity

Authors: Fuchs-Buder T et al.

Summary: This single-centre, randomised controlled study compared the effects of deep versus moderate NMB on surgical conditions in 85 obese patients undergoing laparoscopic gastric bypass surgery under general anaesthesia. At an initial evaluation under moderate NMB, the surgical rating \( (4\text{-point scale}) \) was 'excellent' in 20 patients, 'good' in 55, 'acceptable' in 18, and 'poor' in 12 patients. After excluding those rated as 'excellent', 65 patients were randomised to deep or moderate block. Re-evaluation after 10 minutes demonstrated an improvement of surgical conditions in 29/34 patients receiving deep block and in 4/31 receiving moderate block \( (p < 0.0001)\). Poor surgical conditions were associated with more frequent surgical complications \( (61.5\% \text{ vs } 15.3\%; p < 0.001). \)

Comment: This is another study from the team of Thomas Fuchs-Buder from Nancy. Like in several other publications within the last 5 years, deep NMB was associated with better surgical conditions. Deep NMB resulted in fewer conditions being rated as “poor” and, though the authors did not find a direct difference in post-surgical outcome between moderate and deep NMB, poor conditions were associated with a higher incidence of complications. The latter is at least suggestive of a potential benefit of deep NMB on postoperative patient outcome. However, we should not forget that deep NMB most certainly requires reversal with sugammadex. Though I am fortunate enough to only practice in hospitals that provide sugammadex, not properly reversed deep NMB is well-known to be still have significant systemic side effects – adding clonidine to block could hence be tricky to defend in case of a related serious adverse event.

Reference: Eur J Anaesthesiol. 2019;Apr 9 [Epub ahead of print]