Research in anaesthesia update

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The ANZCA Clinical Trials Network (CTN) has run a busy programme of clinical outcomes research since its inception 12 years ago. Projects have centred around re-evaluating commonly used anaesthetic drugs and procedures where a diversity of strongly held views are expressed, but good quality evidence as to what is best is lacking. I will review some of the programmes of clinical research we have been involved with and where they are heading. There are a number of current major studies that are in their early stages that hospital departments with keen anaesthetists are welcome to join.

ENIGMA 1 & 2 Eliminating nitrous oxide in the gas mixture for anaesthesia. PI Paul Myles, Melbourne.

These studies kicked of the CTN. Nitrous was under attack, but had never undergone a formal safety evaluation, in fact its use pre-dated the existence of both the FDA and Fisherian statistics. The Enigma 1 study of 2050 patients gave a strong hint that the theoretical issue of cardiac toxicity causing MI and death may also be a clinical problem. The 7112 patient Enigma 2 study definitively nailed the answer and found that short term use in our setting did not increase complication rates, and the well-known issue of nausea was transient and easily treated. Long-live nitrous oxide!

Relief . Restrictive versus liberal fluid therapy for major abdominal surgery. PI Paul Myles

This ended up as a 2983 patient comparison of 3.7L with 6.1L of IV fluids within 24 h of surgery in patients having major procedures. There was no difference in the primary outcome of disability free survival at 1 year or how long patients stayed in hospital. However patients in the restrictive group had a higher incidence of acute kidney injury. The study ended a trend in anaesthetic practice that was based on opinion, good ideas and optimism, but lacked evidence.

Balanced 1 & 2. Anaesthetic depth and complications after major surgery: an international randomised controlled trial. PI Timothy Short, Auckland.

Balanced was a 6644 patient study comparing BIS 35 with BIS 50 anaesthesia in sick elderly patients having major surgery. This was the first large anaesthesic outcome study run out of New Zealand, and we offer a further special thanks to all the anaesthetists from 12 NZ hospitals who helped us recruit 1358 patients into it. We found no difference in 1 year mortality or serious complications. A 600 patient substudy of delirium however found significantly more delirium in the deep patients and also longer hospital stays and more cognitive dysfunction. Metaanalysis including this result tilts the balance toward unnecessary depth causing more delirium and possibly worse neurocognitive outcomes. More evidence is needed.

Balanced 2 (PI Carolyn Deng) is now planned and we have approached possible funders. The study will be of 2766 sick elderly patients presenting for major surgery and randomised to deep or light anaesthesia. Both volatile and intravenous anaesthesia will be acceptable and all brands of depth monitor may be used. The primary outcome will be the incidence of post-operative delirium. Secondary outcomes will include neurocognitive function, days alive out of hospital, all-cause mortality and awareness at 90 days.

PADDI Perioperative administration of dexamethasone and infection. PI Tomas Corcoran, Perth.

PADDI was an 8880 patient non-inferiority study of whether dexamethasone increases perioperative surgical-site infection. Patients received 8mg of dexamethasone or placebo and were followed up for 30 days after surgery. The incidence of infection was similar in each group at 8.1% for dexamethasone and 9.1% for placebo (CI95 –2.1 to 0.3) -a result close to the border for superiority of dexamethasone!

There was also no difference in the incidence of infection in the 1154 diabetic patients in the study, but a 0.4% increase in the incidence of hyperglycaemia in diabetics.

POISE 1,2 & 3 Perioperative ischaemia evaluations. PJ Devereaux, Canada

Poise-1 studied 8351 patients at risk of atherosclerotic disease randomized to metoprolol or placebo. There was a 1.5% absolute reduction in cardiac events, but a 0.8% increase in mortality, mostly due to a doubling of the incidence of stroke, this has led to a reduction of use of betablockers in the perioperative period.
Poise-2 studied aspirin and clonidine in 10,010 patients at risk of atherosclerotic disease. Clonidine was also found to not decrease the incidence of cardiac events or death. There was a 0.2% increase in the incidence of non-fatal cardiac arrest in the clonidine group. Continuation of aspirin did not decrease myocardial events but led to a 0.8% increase in major bleeding. The conclusion was with-hold aspirin.
Poise-3 was designed firstly to determine if tranexamic acid reduces the incidence of life-threatening, major, and critical organ bleeding, and whether it increases major arterial and venous thrombotic events; and secondly to determine the impact of a hypotension-avoidance strategy (stop most antihypertensives, aim MAP>80) versus a hypertension-avoidance strategy (continue all antihypertensives, aim MAP>60) on the risk of vascular death and major vascular events within 30 days of noncardiac surgery. Patients were over 45 and either undergoing major surgery or with a history of IHD.
The study stopped at 9507 patients due to a lack of funds, but an event rate above that predicted, which maintains study power. TXA significantly reduced major bleeding, HR 0.76 absolute reduction from 11.7% to 9.1%. Cardiovascular events occurred in 14.2% after TXA and 13.9% after placebo. This is a very small questionably relevant increase in cardiac thrombotic events. The hypertension and hypotension avoidance studies were bedevilled by a high non-compliance rate with the protocol, but showed no evidence of harm from continuing ace inhibitors and calcium antagonists during the perioperative period.

The Cogpoise substudy of post-operative delirium and cognitive dysfunction recruited 2816 patients and the NT-proBNP substudy of using BNP as a predictor of badness at 1071 patients. Results are awaited.

ROCKET Reduction of chronic post-surgical pain with ketamine. A multicentre double-blind parallel-group placebo controlled, randomised trial of the effect of perioperative ketamine on the risk of development of chronic post-surgical pain. PI Phil Peyton, Melbourne.
This 4884 patient study gained a large NHMRC grant in Australia, where patient recruitment started over 18 months ago. We finally have our approvals in place and the study has commenced in NZ. The target group are patients undergoing surgery with an incision over 8cm long with a post-operative opioid plan for analgesia. The ketamine arm receives an infusion of ketamine from before surgical incision to at least 24h post op. The primary outcome is the incidence of chronic post-surgical pain at 3 months. Other outcomes include 12-month outcome, perioperative pain severity, incidence of delirium, hospital stay etc. We hope this study will answer our questions about the place of ketamine in anaesthetic practice.

VAPOR-C Volatile anaesthesia and perioperative outcomes related to cancer. PI Bernhard Riedel, Melbourne.
This is a 5736 patient international, multicentre, randomised trial of inhalational versus intravenous

propofol anaesthesia and also intravenous lignocaine/placebo to improve disease-free survival after cancer surgery that has been funded by NHMRC in Australia with supplementary funding from AMRF in NZ. All cancer surgery done with an intention of cure is included. We hope to start recruitment this year. This study should answer a lot of questions about the relative merits of TIVA versus volatile anaesthesia and also about some of the theoretical advantages of lignocaine in these patients.

LOLIPOP Long-term outcomes after lignocaine infusions for postoperative pain. PI Tomas Corcoran, Perth.
This is a 4400 patient international, multicentre, randomised trial of lignocaine infusion for the reduction of chronic post-surgical pain following operations with a high incidence of this complication. It is funded by NHMRC. This study should provide good quality patient centred outcome data on the effectiveness and safety of lignocaine infusion as a post-operative analgesic. There will also be a pharmacokinetic substudy as the narrow therapeutic index and lack of good PK data in the elderly means varied results from past studies may be a result of inconsistent plasma concentrations. We will be going through the compliance process later this year for NZ.

ATACAS and TRIGS Tranexamic acid to reduce Infection after gastrointestinal surgery. PI Paul Myles, Melbourne.
Atacas was a 4662 patient study of the hazards of using aspirin and tranexamic acid in cardiac surgery. Aspirin neither increased bleeding nor prevented thrombotic events. TxA was associated with a 1.4% lower absolute risk of bleeding without increasing thrombotic complications in this setting, however there was a signal of increased seizures. A substudy of 613 patients found a 5% absolute risk reduction in infection rates.
Trigs is another large, multicentre clinical trial of TxA, funded by NHMRC. The aim is to study 3300 patients and determine whether TxA: reduces surgical site infection and other healthcare-associated infections such as pneumonia and sepsis; reduce red cell transfusion in GI surgery; reduce a composite of any serious postoperative complications, and so increase "days alive and at home up to 30 days after surgery"; and to evaluate the temporal effect of TxA on perioperative immune and inflammatory responses. We are nearly ready to start recruitment in NZ.

Masterstroke. Management of systolic blood pressure during thrombectomy by endovascular route for acute ischaemic stroke: a randomized clinical trial. PI Doug Campbell, Auckland.
Thrombectomy for ischaemic stroke done within, preferably, 6 hours of onset is associated with a profound reduction in long term disability and is significantly more effective as a treatment than thrombolysis. Surprisingly there is very little guidance on BP management in these patients, or indeed in stroke patients in general. This study compares a target systolic pressure of 140mmHg with 170 mmHg in 550 patients. The primary outcome is modified Rankin score of disability at 90 days and secondary outcomes are functional outcome and days at home in the first 90 days post stroke. The study is a milestone in developing lean outcome studies as all the postoperative data come from service databases. The study is only relevant to the three NZ centres that do clot retrieval, but the result will have much broader applicability.

SNAP Sugammadex or neostigmine and pulmonary complications. PI Kate Leslie, Melbourne
Sugammadex is a more effective reversal agent for some muscle relaxants than neostigmine, but expensive. Reliable complete reversal of neuromuscular block may reduce respiratory and other complications of anaesthesia but has not been adequately evaluated and the relative risks of the two agents are unknown. This is a 3500 patient study, we have applied for funding, here's hoping…

Further use of CTN trial data

Inclusion characteristics and outcomes of male and female participants in large international

perioperative studies. PI Kate Leslie, Melbourne. Kate has combined data from 11 large outcome studies that the CTN has been involved with, totalling ~55,000 patients to investigate whether there are disparities in outcomes between male and female patients that would indicate gender bias in their treatment. No differences were found that were not accounted for by underlying patient pathology. It was noted that selection bias in who surgeons choose to treat could not be ruled out.

Quality of Recovery-15 Scores An analysis of use of the QoR-15 score in various anaesthetic trials found that it was a strong predictor of poor post-operative outcome. We are now looking at seeing whether it is a useful in the recovery room to discriminate patients in which escalation of care is indicated.

Maori Health Outcomes. We are required to gather data on ethnicity but numbers are not sufficient to analyse from the point of view of outcome. Combining all the studies above we have sufficient Maori recruited to determine if there are disparities in perioperative outcomes that need to be addressed.

Midazolam. We have sufficient data from high quality prospective studies of delirium to answer the observation that midazolam may be associated with an increased incidence of post operative delirium.

Future Directions

These big studies are expensive and future funding is uncertain. We are looking at simplified randomized study designs, for instance by using the National Minimum Data Set (NMDS), which is Health Department data for all operations in NZ, for the outcome data. This database includes days in hospital, days alive out of hospital and mortality. Doug Campbell's Masterstroke study is our flagship for this approach.

The results have often been controversial, and it is always interesting to hear what anaesthetists make of them, but they form a strong body of evidence from which to tailor our anaesthetics to individual patients. We thank all hospital departments and their research leaders who have been involved in these studies and invite all departments in NZ to get involved in studies that seem relevant to their case mix and interests. The studies are interesting to do, and the outcomes are more relevant to us if we recruit actively into them. **Rocket, Vapor-C, Trigs** and **Lollipop** are all open for business.

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