MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS YEAR BOOK 2012/2013

MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS

Year Book 2012/2013

CELEBRATING GOLDEN ANNIVERSARY

50

1963 - 2013

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Foreword

I am indeed honored and delighted to write the foreword for the fifth edition of the Malaysian Society of Anaesthesiologists (MSA) Year Book 2012/2013 which coincides with the 50th Anniversary of the Society. The MSA Year Book is intended to keep members updated and abreast with recent developments in anaesthesia, intensive care and pain medicine. It is one of the many commitments of the Society to continuing medical education for its members.

The Year Book 2012/2013 is an excellent compilation of topics which are strongly debated today such as the effects of anaesthesia on the paediatric brain, the point-of-care ultrasound in the 21st century, reversal of neuromuscular blockade with Sugammadex and many more relevant topics. Clinical research and ethics is an important topic as anaesthesiologists in Malaysia are strongly encouraged to do research and publish but must abide by the good clinical practice guidelines. It may be the 'smallest' Year Book thus far but it is rich with current information for our day-to-day professional work.

When I was informed that Dr Tan It and Professor Dr Lim Thiam Aun had graciously accepted to be the editors for the Year Book 2012/2013, I was confident that it would be of a high standard especially coming from two prominent academicians. The Year Book has surpassed my expectations. Congratulations and Thank You!

I thank all the authors for their well researched and written contributions. I know this is not an easy task especially with our hectic schedules and daunting deadlines.

I hope our members will not only benefit from the Year Book 2012/2013 but will be inspired to be contributors to the future Year Books.

Happy 50 years MSA!

Sushila Sivasubramaianm
President
Malaysian Society of Anesthesiologists

Preface

This is the fifth edition of our Year Book. We hereby continue the tradition that was started in 2006/2007 to have a collection of articles which include updates on recent developments in anaesthesia and also some interesting write-ups.

It is the smallest Year Book so far, but we hope that there is something interesting for all anaesthesiologists, from the trainee to the most experienced anaesthesiologist. Perhaps some surgeons and even non-medical people may be interested in some of the articles.

The editors would like to thank all who have contributed articles and helped in other ways in the production of this book.

Happy reading!

Dr Tan It
Professor Dr Lim Thiam Aun
Editors
MSA Year Book 2012/2013

Reversal of Neuromuscular Blockade with Sugammadex

Lim Wee Leong
Consultant Anaesthesiologist, Hospital Sungai Buloh

INTRODUCTION

Occasionally, a new anaesthetic drug appears in the horizon which has the potential to drastically change the way we practice anaesthesia. However, like everything new, there are questions that need to be asked and issues that need to be resolved. Sugammadex, a reversal agent for neuromuscular blocking agents (NMBA), is certainly one of them and this article highlights some of the issues we need to consider as it is being introduced into our clinical practice.

Firstly, do we really need a selective NMBA reversal agent? Currently, we are using cholinesterase inhibitors as NMBA reversal agents. They act by increasing the concentration of acetylcholine at the neuromuscular junction thus displacing the NMBA molecules at the receptors by its competitive action. In addition, we also need to add an anticholinergic agent at the time of reversal to counteract the muscarinic effects of the cholinesterase inhibitors.

The limitations of cholinesterase inhibitors as NMBA reversal agents are as follows:

- Relatively slow in reversing neuromuscular blockade
- Inadequate reversal of deep blockade
- Require concomitant administration of anticholinergics
- Cardio-respiratory side effects.[1,2,3]

Sugammadex is a selective muscle relaxant binding agent that provides rapid reversal from neuromuscular blockade induced by the non-depolarising NMBA's rocuronium and vecuronium.[4,5] It is a modified gamma-cyclodextrin compound, marketed by MSD under the trade name Bridion and was licensed for use in Malaysia in 2010. In addition, it offers a new alternative to suxamethonium for rapid sequence induction because of its ability to reverse the effects of an intubating dose of rocuronium immediately.[6,7,8]

MODE OF ACTION

Sugammadex rapidly reverses neuromuscular blockade caused by rocuronium and vecuronium by encapsulating and inactivating the NMBA, forming a complex in the plasma. This reduces their ability to bind to nicotinic receptors in the neuromuscular junction, thereby reversing neuromuscular blockade.[4,5] Sugammadex is ineffective against succinylcholine and benzylisoquinolinium neuromuscular blockers such as mivacurium, atracurium and cisatracurium, because it cannot form inclusion complexes with these drugs.

The main advantage of Sugammadex over traditional reversal agents is that it enables rapid reversal from any depth of neuromuscular blockade, thus minimizing the risk of residual paralysis. It also has no effect on the parasympathetic nervous system. By itself, it has no pharmacologic effects on the body, does not bind to plasma proteins, and appears to be safe and well tolerated.[9-12]

PHARMACOKINETIC PROPERTIES OF SUGAMMADEX

i) Distribution
Sugammadex has a steady-state volume of distribution of approximately 11-14 litres. Neither sugammadex nor the complex of sugammadex and rocuronium binds to plasma proteins or erythrocytes. When given as an intravenous bolus dose of 1-16 mg/kg, sugammadex exhibits linear kinetics.[4]

ii) Metabolism
In preclinical and clinical studies, no metabolites of sugammadex have been observed and only renal excretion of the unchanged drug was observed as the route of elimination.[4]

iii) Elimination
The elimination half-life of sugammadex is

1.8 hours and the estimated rate of clearance from the plasma is 88 ml/min. Almost all (>90%) sugammadex is excreted within 24 hours of administration.[4]

RECOMMENDED DOSES OF SUGAMMADEX

The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed.[4]

Adult dosage guides

i) For reversal of moderate neuromuscular blockade (TOF of 1-2) induced by rocuronium, sugammadex at 2 mg/kg will be adequate for full reversal (i.e. TOF ratio>90%) within 1.2 to 1.5 minutes.

ii) For reversal of profound neuromuscular blockade (TOF of zero and post-tetanic count 1-2) induced by rocuronium, the recommended dose of sugammadex is 4 mg/kg (full reversal within 2.3 to 3.3 minutes).

iii) For immediate reversal of neuromuscular blockade induced by an intubating dose of rocuronium (both TOF and post-tetanic count of zero), sugammadex at a dose of 16 mg/kg will achieve full reversal within 5.7 to 6.7 minutes.

QUESTIONS WE NEED TO ASK:

1) Do we still need to use a neuromuscular function monitor with sugammadex?

We use the neuromuscular monitor to assess depth of block before giving the reversal (i.e. TOF count should be at least 1) and to measure the adequacy of reversal (i.e. achieve a TOF ratio >90%). We can argue that with the predictable effects of such a selective NMBA reversal agent, neuromuscular monitoring would not be necessary anymore. However, without knowing the depth of the rocuronium-induced neuromuscular blockade, it would be difficult to know the dose of sugammadex needed.

The better question to consider is, do we routinely monitor neuromuscular block using the TOF count? If one feels that he can confidently give a NMBA and reverse its effects with a cholinesterase inhibitor in a patient without the use of a neuromuscular function monitor, then the same must hold true with the use of sugammadex. However, in patients where one feels that a neuromuscular function monitor is needed for specific reasons (e.g. patient with myasthenia gravis), then the availability of sugammadex should not alter the monitoring requirements at all.

The recommendations for safety standards and monitoring during anaesthesia and recovery published by the College of Anaesthesiologists, AMM (2008) states that "where muscle relaxants are used, a device to monitor neuromuscular function such as a peripheral nerve stimulator should be available".

Some have suggested that a conventional nerve stimulator to determine the presence or absence of the twitch response would be sufficient as the appropriate dose of sugammadex could be administered accordingly. However, even in such circumstances, objective neuromuscular monitoring (i.e. train-of-four ratio) may still be needed to demonstrate complete reversal.[13]

2) Does sugammadex make a difference in post-operative outcome?

Using sugammadex will reduce the temporary but troublesome side-effects of inadequate NMBA reversal such as patients complaining of dyspnoea, inability to hold their head up, feeling of weakness and difficulty in swallowing.[14] In a review article by Paton[15], studies had shown that there were reductions in recovery time associated with sugammadex, thus saving time and costs in the operation theatre. What is more important is that we need to know if the use of sugammadex has made a difference in decreasing critical airway events like aspiration, post-operative hypoxaemia, airway obstruction and re-intubation in the immediate post-operative period. Studies like these are difficult to perform as these post-operative adverse events are usually due to a combination of factors. To date, there are still no large randomized studies to show that the routine use of sugammadex has improved patient safety and outcomes in the immediate post-operative period.

3) Should I use sugammadex as a routine reversal agent?

The issue is one that is related to *the cost-benefit ratio*.[16] Compared to cholinesterase inhibitors, sugammadex will appear to be costly. In countries where the cost of surgery is relatively higher, the impact of increased anaesthetic costs due to the use of sugammadex will not be felt. However, the case is different for many Asian countries including Malaysia. In non-public institutions where the cost of anaesthesia is borne by the patient or insurance companies, justification for usage will probably need to be agreed upon by the patient or the healthcare institution. In the case of public institutions or non-paying patients where cost is a major issue, it is useful to establish some sort of guide or advisory as to when it can be used. It is the author's opinion that the use of sugammadex in selected groups of patients will improve patient safety by reducing the incidence of adverse airway events in the immediate post-operative period as well as reduce the length of stay in the post-operative care unit.

For example, the need for early return of airway reflexes and pharyngeal muscle tone will be an important concern in obese patients with obstructive sleep apnoea, who are prone to develop upper airway obstruction and run the risk hypoxic events. An advisory board consisting of members of the College of Anaesthesiologists, AMM, was convened in April 2012, during which recommendations for the use of sugammadex based on the likelihood of benefits on patient groups was suggested. The advisory statement should be available in the near future.

4) If a patient requires a second anaesthetic within 24 hours after sugammadex was used as reversal agent, can we still use recuronium to paralyse the patient?

Based on pharmacokinetic studies, it is advisable that we avoid the use of rocuronium or vecuronium and choose other NMBAs instead. This is because residual molecules of sugammadex in the blood stream may bind to rocuronium given thus rendering it ineffective.[4]

5) Are there any limitations in using Sugammadex?

The safety of sugammadex in patients with end-stage renal failure has not yet been established.[17] Likewise, there are limited studies on the use of sugammadex in children less than 2 years old. In a phase IIIa study, Plaud demonstrated similar times to reversal to TOF ratio > 0.9 after sugammadex 2 mg/kg was given at reappearance of T2 of TOF in infants, children, adolescents and adults.[18]

6) Should I still use the recommended 2 mg/kg dose of sugammadex (for neuromuscular blockade with TOF count of 1-2) in morbidly obese patients?

For morbidly obese patients, the recommended dose of NMBA is calculated according to ideal body weight rather than actual weight. Hence, the dose of sugammadex is also calculated according to ideal body weight rather than actual body weight. However, it is best to use a neuromuscular function monitor to determine the depth of neuromuscular block and use an appropriate dose of sugammadex to reverse the effects of the NMBA in patients who are morbidly obese. A recent paper by Llauradó demonstrated that for morbidly obese patients undergoing laparoscopic bariatric surgery, the sugammadex requirements was higher than predicted.[19]

Summary

Sugammadex has come and is here to stay in our clinical anaesthetic practice. It has not only increased our options when managing our patients across a wide range of clinical situations but will probably change the way we use NMBA's in the future. However, current pharmaco-economic barriers will limit the widespread introduction of sugammadex and further clinical trials will contribute more data to the debate concerning cost-effectiveness.

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Update on Perioperative Hypertension

Tan It
Consultant Anaesthesiologist, Sunway Medical Centre

CASE STUDY

A 21 year old primigravida at 36 weeks gestation presented with a history of headache for 3 days and left hemiparesis for 1 day.[1]

On examination, she was found to be drowsy, irritable, with peripheral pitting oedema. Her heart rate was 104/min, and BP 170/110 mmHg. She was found to be aphasic, her pupils were equal and reactive to light, and she was hemiparetic on the left.

Blood tests showed that her Hb was 9.2 g/dl, proteinuria 4+ was present in the urine, her coagulation profile was normal, and liver function was normal.

Ultrasound showed a live foetus with cephalic presentation, estimated weight 2.5 kg and gestational age 35 weeks.

Computed tomography of the brain showed a right temporo-parietal intracerebral haematoma with midline shift.

How would you manage this patient?

(The case report resumes at the end of the article.)

HYPERTENSION

1. Definition
Hypertension has traditionally been defined as a blood pressure (BP) of over 140/90 mmHg in adults.

However, recently it has been found that death from ischaemic heart disease and stroke increases as blood pressure increases from as low as 115 systolic and 75 mmHg diastolic.[2]

In 2003, the National Heart, Lung and Blood Institute of the US in Bethesda, Maryland published new clinical guidelines for hypertension.[3]

Categories for Blood Pressure Levels in Adults (mmHg)

Category	Systolic		Diastolic
Normal	< 120	and	< 80
Prehypertension	120 - 139	or	80 - 89
High blood pressure			
Mild (Stage 1)	140 - 159	or	90 - 99
Moderate (Stage 2)	160 - 179	or	100 - 109
Severe (Stage 3)	>180	or	>110

- The ranges in the table apply to most adults (aged 18 years and older) who do not have short-term serious illnesses.

2. History
In 1905, Nicolai Sergeivich Korotkoff described the measurement of blood pressure using a Riva-Rocci cuff and stethoscope.

55 years ago, hypertension was first treated, with the emphasis on diastolic hypertension.

3. Incidence and Prevalence
Hypertension affects 1 billion people around the world and is responsible for 7.1 million deaths per year.[4]

4. Complications
The complications of hypertension include coronary artery disease, stroke, renal failure, retinopathy, peripheral vascular disease and death.

67% of an international cohort undergoing coronary artery surgery have current or past history of hypertension.[5]

Medical treatment of hypertension reduces the lifetime risk of stroke, congestive heart failure and renal failure.[6,7]

PERIOPERATIVE HYPERTENSION

1. Risk of Perioperative Hypertension
In the 1960's, unstable BP intraoperatively and some cases of profound hypotension and cardiovascular collapse was found to be associated with anaesthetic induction in hypertensive patients.[8,9]

2. Questions and Suggested Answers regarding Perioperative Hypertension:

Questions that need to be answered:-

i. Should elective surgery be postponed in patients with uncontrolled hypertension?
   Does inadequate control of hypertension result in complications that can be prevented with better control?
   How much control is needed and for how long?
ii. Does overzealous control cause unnecessary postponements of surgery and predispose the patient to risk of hypotensive episodes perioperatively?
iii. Should antihypertensives be continued up to the morning of surgery?
iv. What is the goal of intraoperative BP control?

Suggested answers:-

In 1971, Prys-Roberts[8,9] found that poorly controlled hypertension was associated with greater haemodynamic lability and an increased risk of perioperative myocardial ischaemia, and recommended that antihypertensives should not be withdrawn prior to anaesthesia without compelling reason.

In 1977, Goldman[10] studied outcome in 4 groups undergoing non-cardiac surgery (normotensive, adequately treated hypertensives, poorly treated, and untreated) and concluded that:

- Those with diastolic BP < 110 mmHg behaved similar to the normotensives.
- Mild to moderate hypertension did not increase perioperative risk.
- Intraoperative management was the principal factor in lowering risks.
- Hypertensives having other cardiovascular risks were at highest risk for mortality.

Howell[11] in a meta-analysis of 30 observational studies concluded that hypertensive patients are 1.31 times (95% CI 1.13 – 1.51) more likely to experience adverse perioperative cardiac events than normotensives.

In 2002, Eagle[12] drew up the following ACC/AHA (American College of Cardiology/American Heart Association) guidelines:

- Mild to moderate hypertension (SBP < 180 mmHg, DBP < 110 mmHg) is not an independent risk factor for perioperative cardiovascular complications.
- Elective surgery should be postponed in severely hypertensive patients (SBP > 180 mmHg or DBP > 110 mmHg) to control BP before surgery.

Spahn[13], however, found little evidence to support the above recommendations.

Weksler[14] studied patients with DBP between 110-130 mmHg on arrival at the OT, excluding patients with target organ damage. He randomized them into 2 groups: those in one group were given intranasal nifedipine to reduce DBP acutely to < 110 mmHg, in the control group surgery was delayed > 3 days until DBP < 110 mmHg. There was no major difference in perioperative cardiac events; hence he concluded that there is no benefit in delaying surgery.

Fontes[5] found that in CABG, neither systolic nor diastolic BP was associated with postoperative cardiac events. However, a pulse pressure > 80 mmHg was a strong predictor of stroke, death, renal dysfunction and 50% increased risk of CHF. This may be due to a decrease in coronary perfusion pressure and mismatch between myocardial oxygen delivery and demand - low diastolic pressure results in low myocardial perfusion.

3. Preoperative Assessment of the Hypertensive Patient:
Do consider the possibility of 'white coat hypertension' - take multiple BP readings.

Assessment of the patient includes the assessment of exercise tolerance:

- 10 METS (metabolic equivalents): swimming, single tennis, badminton, football, basketball
- 4 METS: climb a flight of stairs, walk up hill, walk level ground at 6 kph, run short distance, golf, dancing, doubles tennis
- 1 MET: eat dress use toilet, walk indoors, walk on level ground at 3-4 kph

In the drug history, inquire if the patient is on antihypertensives, statins, aspirin, clopidogrel or other drugs. Check serum electrolytes if the patient is on diuretics. Ask about the use of herbal supplements some of which can impair platelet function.

The physical examination and simple laboratory tests can rule out some of the rare but important causes of hypertension. Further evaluation to exclude secondary hypertension is rarely warranted before necessary surgery. If pheochromocytoma is a serious possibility, surgery should be delayed to permit its exclusion. A loud abdominal bruit may suggest renal artery stenosis. A radial to femoral artery pulse delay may indicate coarctation of the aorta. Hypokalemia in the absence of diuretic therapy raises the possibility of hyperaldosteronism.

Hypertension has a known association with coronary artery disease, renal impairment, and carotid artery disease. Hence, assessment of these systems to detect previously unknown disease should be carried out:

- CNS - is there any history of previous stroke, carotid artery disease?
- CVS - ask for angina, previous MI (2002 AHA guideline - wait 6 weeks for 'low-risk' patients[12]), does the patient have a recent coronary artery stent?
- PVD (peripheral vascular disease) - is there lower limb claudication?
- Renal - look for renal dysfunction.

ECG - is there any evidence of ischaemia, left ventricular hypertrophy or strain, arrhythmias?

Referral to a cardiologist may be needed for exercise stress test, echocardiogram, imaging, or angiography.

4. To Postpone or to Proceed with Surgery?
If the initial evaluation establishes hypertension as mild or moderate, and there are no associated metabolic or cardiovascular abnormalities, there is no evidence that it is beneficial to delay surgery.[11,15,16]

To assess if the benefit of surgery justifies the risk, we may consider the following:-

i. Is the surgery an emergency - will delay cause more harm to the patient? Is there time to bring the BP down to more normal levels? Will a 'normal' BP be detrimental (e.g. in patients with carotid artery stenosis or with raised intracranial pressure)? If the BP is above 180/110 mmHg and the surgery is not an emergency, it should probably be postponed.[11,17]

ii. The degree of cardiac risk associated with surgery[11,15] - if the risk is high, it may be advisable to take more time to stabilize the patient pre-operatively:

- low cardiac risk - surface, cataract, breast, endoscopic surgery
- moderate risk - limbs, head / neck, intraperitoneal, thoracic, prostate, carotid surgery
- high risk - vascular and aortic surgery, long operations with large fluid shifts, emergency major operations particularly in elderly

iii. Will surgery be therapeutic? In cases where there is raised intracranial pressure or in pregnancy-induced hypertension (PIH), surgery may be necessary to treat the cause of the high blood pressure.

iv. Consider the anaesthetic plan - local, regional, or regional + general anaesthesia. If the operation is not major and can be done under local or regional anaesthesia (e.g. low spinal anaesthesia), the risk may not be excessive.

MANAGEMENT OF ANAESTHESIA

The patient whose BP is found to be high pre-operatively

There seems little logic to the concept of rapid, overnight reduction in blood pressure, as such a strategy will probably increase the risk of intraoperative haemodynamic instability. If the surgery can be delayed, joint management after discussion with the surgeon and physician may be appropriate.

Preoperative Preparation and Preanaesthetic Medication

Once a hypertensive patient is accepted for anaesthesia, consideration must be given to the effects that the prescribed drugs may have on the anaesthesia. Withdrawal of antihypertensive medication is generally considered inadvisable, as many of these drugs may produce rebound effects when withdrawn. Continue beta-blockers and calcium channel blockers if the patient is already on them, but do not start for the first time just hours before operation.[18,19]

Anxiolysis: night sedation may reduce the likelihood that anxiety will further increase the high BP. A benzodiazepine premedication may be useful to reduce anxiety which may otherwise aggravate any pre-existing hypertension. Aspirin should be continued if there is a coronary stent in place or if there is known coronary artery disease.[15,20] Exceptions may be intracranial, intraspinal, middle ear or eye surgery - this should be discussed with the cardiologist before operation. Clopidogrel (or other potent antiplatelet agents) should normally be stopped 7 days prior to surgery (14 days in the case of ticlopidine which has a longer half-life). However, the discontinuation of anti-platelet agents may result in stent thrombosis especially if the stent is drug-eluting or has been recently placed, and should be discussed with the cardiologist. Clopidogrel and aspirin should normally be continued for at least a year after the placement of certain types of drug-eluting stents and non-emergency surgery postponed until after that time. The technology of stents continues to improve, however, and this should have been discussed with the cardiologist before listing the patient for surgery.

The use of beta-blockers perioperatively in patients at risk of coronary artery disease (CAD).

Mangano[21] in 1996 found that patients with a high risk of CAD have lower cardiac mortality if put on beta-blockers. As a result, in 2002, ACC/AHA guidelines gave a Class IIa recommendation to use perioperative beta-blocker in patients with preoperative untreated hypertension.[12]

However, in 2008, the POISE Study Group conducted a randomized controlled trial in more than 8000 patients undergoing non-cardiac surgery (who were not already on beta-blockers), randomized to either the beta-blocker **metoprolol** or placebo. The results showed that the beta-blocker reduced the risk of myocardial infarction (MI) but increased the

risk of severe stroke and overall death in patients undergoing non-cardiac surgery.[22] It suggested that for every 1000 patients treated, metoprolol would prevent 15 MI's, but there would be an excess of eight deaths and five severe disabling strokes.

Perioperative use of beta-blockers is a Class I indication only for those already on beta-blockers [who were not studied in POISE] for treatment of conditions with Class I indications. Beta-blockers titrated to heart rate and blood pressure is a Class IIA indication for patients with a high cardiac risk undergoing vascular surgery.[15,23] Routine administration of high dose beta-blockers in the absence of dose titration may be harmful to patients not currently taking beta-blockers who are undergoing non-cardiac surgery.

Angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin II Receptor blockers (ARB's).

There are several reports of intraoperative hypotension which is difficult to treat if the patient continued to receive these drugs up to the morning of surgery.[17,24-28] Some authors therefore suggest that ACEI's / ARB's be discontinued at least 10hr before anaesthesia.[17]

Induction - choice of tracheal tube vs. LMA

Insertion and subsequent removal of a Laryngeal Mask Airway may not cause as much cardiovascular changes as a tracheal tube.[29] If tracheal intubation is necessary, adequate depth of anaesthesia and / or the use of a small dose of a short acting beta-blocker or GTN may help to attenuate the hypertensive response.

Regional Anaesthesia

Epidural and intrathecal anaesthesia will also block sympathetic fibres and this may cause hypotension. A thoracic epidural block with local anaesthetics especially if combined with general anaesthesia can cause profound hypotension and bradycardia in hypertensive patients on drug treatment. This is especially so if the treatment was commenced for the first time just hours before surgery. If general anaesthesia plus a thoracic epidural is planned, one should be careful not to over-treat the hypertension preoperatively. Small doses of local anaesthetic should be given in a titrated manner, and atropine with vasopressors should be immediately available to treat any resultant hypotension.

Maintenance

What BP levels should one maintain during the operation? Goldman[30] found that postoperative cardiac death was associated with a 33% or greater fall in SBP for > 10min intraoperatively. Charlson[31] suggested that fluctuation in MAP > 20% in a high-risk population of hypertensive and diabetic patients is associated with perioperative complications. Hanada[32] proposed that haemodynamic stability is more important than absolute target values of BP.

Drugs that should be available immediately to treat intraoperative hypo- or hypertension include:

- Antihypertensives - beta-blockers, nitrates (GTN), CCBs, labetalol
- Vasopressors - phenylephrine
- Atropine
- Others - adrenaline, dopamine, noradrenaline, vasopressin.

Reversal

Tracheal extubation while the patient is still deep may minimize hypertensive changes. It may be useful to give a small dose of a beta-blocker or GTN just before extubation.

Postoperative Care

Epidural infusions postoperatively may help to control the BP especially if the patient is unable to take oral antihypertensives post-operatively. In cases of prolonged fasting in patients without an epidural, i.v. infusion of GTN or labetalol may be useful.

Sublingual nifedipine: The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC-VI], states that the use of immediate-release sublingual nifedipine is "unacceptable".[33] In 1985, the FDA concluded that the use of immediate release nifedipine for hypertensive emergencies is neither safe nor effective and therefore it should not be used.[34]

SPECIAL SITUATIONS

PIH (pregnancy-induced hypertension):
Assessment of the patient should include the blood pressure and its trend, the patient's conscious level, and the possible presence of coagulopathy, thrombocytopaenia and impaired liver function (HELLP syndrome). Consider a regional anaesthesia technique if there are no contraindications, e.g. thrombocytopaenia and coagulopathy.[35]

Raised intracranial pressure (ICP)
When the ICP is high in patients with an intracranial mass lesion, hypertension may be due to Cushing's reflex. Cerebral autoregulation may be impaired and the BP should not be brought down too low as this will compromise cerebral perfusion. Urgent surgery may be necessary to bring down the ICP and this may also bring down the high BP.

Phaeochromocytoma: this topic is outside the scope of this short article.

CONCLUSION

Previously undiagnosed hypertension, presenting for the first time at surgery, requires a basic investigation of target organ disease prior to anaesthesia, and appropriate subsequent follow-up referral for further management.

Delaying surgery only for the purpose of blood pressure control may not be necessary, especially in the case of mild to moderate hypertension (BP below 180/110 mmHg), if there is no significant end organ damage. Strict care should be taken to ensure perioperative haemodynamic stability because labile haemodynamics, rather than preoperative hypertension per se, appears to be more closely associated with adverse cardiovascular complications.

Delaying surgery in hypertensive patients may be justified if target organ damage exists that can be improved by such a delay or if there is suspected target organ damage that should be evaluated further before the operation.

In the emergency or semi-emergency situation, the relative risk of postponing surgery should always be considered. In some situations, e.g. in pregnancy-induced hypertension or raised intracranial pressure, surgery itself may bring down the blood pressure. Attempting to 'normalise' the blood pressure in some situations, e.g. carotid stenosis or raised intracranial pressure, may be detrimental and may result in end-organ ischaemia.

For very severe hypertension, the benefits of delaying surgery to establish adequate hypertensive control must be weighed against the risk of delayed surgery. Where a surgical delay is considered, adequate time to establish appropriate blood pressure control must be allowed, and there is no place for sudden "cosmetic" correction of blood pressure immediately prior to anaesthesia.

CASE STUDY, CONTINUED

Coming back to our case study[1]:
The patient: a 21 year old primigravida at 36 weeks gestation

- C/o: headache 3/7, L hemiparesis 1/7, aphasia 1/7
- O/E - Drowsy, irritable.
  - Peripheral pitting oedema present.
  - HR 104/min, BP 170/110mmHg.
  - Aphasic, PERL, left hemiplegia.
- Investigations: Hb 9.2 g/dl, proteinuria 4+, coagulation profile normal, liver function normal.
- U/S: live foetus - cephalic presentation, estimated weight 2.5 kg, gestational age 35/52.
  CT brain: R temporo-parietal intracerebral haematoma.

Management:

- Given: i.v. 20% mannitol 100ml, phenytoin 1000mg, ranitidine 50mg, metoclopramide 10mg.
- Team discussion: obstetrician, neurosurgeon, anaesthesiologist, paediatrician
- Decision: emergency LSCS followed by craniotomy

- Informed consent taken.
- Monitoring: HR 112/min, BP 160/114mmHg
- Rapid sequence induction: Pre-O_2, Fentanyl 150mcg, propofol 150mg, succinylcholine 75mg, cricoid pressure, cuffed ETT 6.5mm
- BP dropped to MAP 55mmHg – given ephedrine 6mg
- MAP maintained at 80 – 100 mmHg
- $ETCO_2$ maintained at 28 – 31 mmHg
- Maintenance of anaesthesia: O_2 / N_2O (50:50), Isoflurane 0.5 - 1%, vecuronium
- Female baby delivered - Apgar score 4 at 1 min, bag and mask with O_2; Apgar 8 at 5 min. Sent to NICU.
- Craniotomy and evacuation of haematoma performed.
- Given lignocaine 80mg, GTN 200mcg, extubated.

Post-op ICU:

- Hb 7.9 g/dl - transfused 1 unit AB+ blood.
- Diastolic BP > 110 mmHg - i.v. GTN, oral amlodipine and labetalol given to bring DBP < 90 mmHg. 10 doses mannitol were given post-op.
- 12 hours post-op the patient was opening eyes and obeying simple commands, PERL.

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Anaesthetic Considerations in Laparoscopic Surgery in Neonates and Infants

Felicia S K Lim
Professor (Clinical Teaching) & Paediatric Anaesthesiologist, Universiti Kebangsaan Malaysia Medical Centre

Minimal invasive surgery (MIS) or key hole surgery in children is not a new development. In the early 70's, Gans[1] published his experience on peritoneoscopy in infants and children, well before the development of cholecystectomy in adults in 1987. Although adult laparoscopic surgery has undergone tremendous development since the late 80's, its application in children and infants had lagged behind until the mid 90's. With the increase in experience, advancement in technology, refinement in techniques and the development of fine laparoscopic instruments for neonates and small infants, minimally invasive surgery is increasingly being used.

BENEFITS OF LAPAROSCOPIC SURGERY

The benefits of minimally invasive surgery over traditional `open' operative techniques include the avoidance of large incisions, less fluid loss, heat loss and tissue trauma, and reduced postoperative pain. These benefits result in better cosmetic results, quicker recovery from surgery, earlier postoperative mobilization, and a shorter hospital stay compared to open procedures. In addition, the surgical field is magnified by the camera system, with improved visualization of some difficult areas like the pelvis, subphrenic spaces and thoracic apices.

LAPAROSCOPIC PROCEDURES IN NEONATES AND INFANTS

With the increase in experience and the refinement of miniaturized instruments, more and more surgery in neonates and infants are being done laparoscopically either for diagnostic or therapeutic purposes. Table 1 shows the types of laparoscopic procedures that have been done in paediatric patients in UKM Medical Centre from 2008-2012.

Contraindications include patients who have an unstable haemodynamic status, severe cardiac diseases, pulmonary insufficiency and bleeding disorders. Laparoscopy is more hazardous in patients with abdominal scars and adhesions resulting from repeated abdominal procedures. In patients with abdominal sepsis, laparoscopy increases the risk of spreading infection. Laparoscopic resection of malignant tumour is controversial as some believe that it can lead to tumour implantation at port sites.

PRINCIPLES OF LAPAROSCOPIC PROCEDURE

Laparoscopic procedure involves insertion of a telescope into the abdominal cavity for visualization. This is done through an incision around the umbilicus. The image is transmitted to 1 or more monitors. The peritoneal space is distended by insufflation of a gas. This produces an increase in intra-abdominal pressure (IAP), which is determined by the compliance of the abdominal cavity and the volume of gas insufflated. Insufflation is achieved either by direct insertion of a Verres needle through the skin into the peritoneal cavity (closed method) or by an open `cut down' technique. The latter is generally preferred because there is a less risk of perforation of abdominal viscera or vessels, particularly in neonates and infants where the liver lies partly below the rib cage and the bladder is intra-abdominal. The gas most commonly used for insufflation is carbon dioxide. It is not combustible and is highly soluble, which is a potential advantage in the event of intravascular embolization. Its main disadvantage is that it has physiological effects when absorbed. Adequate surgical access often requires that patients are positioned in steep head up, steep head down or lateral positions. The creation of a pneumoperitoneum and associated position changes may have significant effects on the cardiovascular and respiratory systems.

CHALLENGES OF LAPAROSCOPIC SURGERY

Laparoscopic surgery in neonates and infants presents different sets of problems compared to the traditional open technique. It is especially challenging in this age group because of smaller size and smaller working space.

PHYSIOLOGICAL CHANGES ASSOCIATED WITH LAPAROSCOPIC SURGERY

Physiological changes during laparoscopic surgery result from the increased intra-abdominal pressure (IAP) caused by the creation of pneumoperitoneum, patient's positioning (head-up or head-down tilt) during surgery and systemic absorption of CO_2 insufflated.

PHYSIOLOGICAL RESPONSE TO RAISED INTRA-ABDOMINAL PRESSURE (IAP)

The level of IAP determines the cardiorespiratory changes during laparoscopy. Increased IAP induces a mechanical cephalad displacement of the diaphragm that reduces the pulmonary compliance, total lung volume, vital capacity and functional residual capacity (FRC). These alterations increase the ventilation-perfusion mismatch, which may be further increased when the patient is in the Trendelenburg position. This may cause intrapulmonary shunting and hypoxaemia, especially in neonates and infants because they have a low FRC, high closing capacity and high oxygen consumption. Bannister and colleagues[2] found that the magnitude of changes in the pulmonary mechanics correlates directly with the intra-abdominal pressure. It has been recommended that IAP should be limited to 5-10 mmHg in neonates and infants and to about 10-12 mmHg in older children.[3]

The cardiovascular response to an increase in intra-abdominal pressure involves changes in venous return, systemic vascular resistance and myocardial contractility.[4] A decrease in cardiac output (CO) may occur as a result of decreased venous return and an increase in systemic vascular resistance (SVR). The reduction in venous return is dependent on the degree of increase in abdominal pressure.[4] In infants and neonates, pneumoperitoneum also has a major impact on cardiac volumes and function. It has been shown that with a moderate increase in IAP (<10 mmHg), there is an increase in venous return and cardiac output resulting from the displacement of blood from the splanchnic venous field. However as IAP increases, venous return is impeded and cardiac output may fall. These are exaggerated if the patient is hypovolaemic.

Diffusion of CO_2 from the peritoneal cavity into the subcutaneous tissue, or along the fascial planes into the mediastinum can occur, occasionally leading to subcutaneous emphysema, pneumothorax or pneumomediastinum.[5]

PHYSIOLOGICAL ALTERATIONS CAUSED BY CARBON DIOXIDE ABSORPTION

A significant amount of CO_2 can be absorbed across the peritoneal surface resulting in hypercarbia. This frequently requires an increase in the minute ventilation. Hypercarbia can lead to further increase in systemic vascular resistance and myocardial depression. It also causes a sympathetic stimulation resulting in an increase in heart rate and blood pressure and sensitizes the myocardium to the arrhythmogenic effects of catecholamines, especially in the presence of volatile anaesthetic agents.

PHYSIOLOGICAL ALTERATIONS CAUSED BY PATIENT POSITIONING

Patient positioning can compromise cardiovascular as well as respiratory function. The Trendelenburg position along with the raised IAP decreases lung compliance. FRC is reduced by the Trendelenburg position while the reverse Trendelenburg position may improve respiratory compliance.[6] On the cardiovascular system, Trendelenburg position increases the venous return whereas reverse Trendelenburg position decreases it.

ANAESTHETIC MANAGEMENT

Pre-operative evaluation

Neonates and infants presenting for laparoscopy should be managed in the same way as for open laparotomy. The scenarios can vary from an elective procedure in a healthy infant to an emergency laparoscopy for an acute abdomen in a premature neonate. A thorough pre-operative history should be taken and a complete physical examination should be performed to identify any underlying medical condition and, specifically, heart murmurs. Routine pre-operative laboratory evaluation will depend on the clinical status, age and prematurity. Major bleeding can occur as a complication of the laparoscopic technique and conversion to laparotomy may become necessary. Thus, major laparoscopic surgery should only be performed when cross-matched blood is readily available.

Pre-medication

Pre-medication must be individualized for each patient, based on the post-gestational age, weight, physiological condition and willingness to co-operate in older infants. Anticholinergic pre-medication can prevent the vasovagal reflexes that are occasionally seen when the peritoneum is penetrated or when the abdominal cavity is insufflated.

Induction of Anaesthesia

Patients can be induced either intravenously or using inhalational agents. Sevoflurane is the inhalational agent of choice. Intravenous access is generally secured in the upper extremity if possible because the increased IAP may decrease the onset time of drugs administered into a vein in the lower extremity.

In the event of gastric distension after induction, a nasogastric tube should be inserted to decompress the stomach.

Airway management

Controlled ventilation is recommended. This enables the minute ventilation to be increased to deal with the CO^2 load and to maintain normocarbia.

Controlled ventilation with endotracheal tube has been the standard for laparoscopic surgery. With the introduction of newer supraglottic airway devices, more options are now available. The ProSeal laryngeal mask airway (PLMA) has been safely used in adult laparoscopies.[7] There are recent reports on the use of this device in children undergoing laparoscopic surgeries. Nandini[8] evaluated the use of PLMA in 30 children undergoing laparoscopic surgery of less than 60 minutes duration. They concluded that PLMA is a safe and effective option for maintaining the airway in children undergoing short duration laparoscopy. Sinha[9] compared the ventilatory efficacy of PLMA with that of tracheal tube in children undergoing elective laparoscopic procedures expected to last less than 1 h. They found that the paediatric PLMA and tracheal tube have comparable ventilatory efficacy for elective short laparoscopic procedures. There was one study that evaluated the suitability of the laryngeal mask airway (LMA) in 15 paediatric patients. They found that in selected patients and for very brief procedures (3-9 min), there were no significant changes in arterial oxygen saturation.[10] However, it would be unsafe to routinely use the LMA during paediatric laparoscopy and certainly even more so in neonates, in patients whose cardiorespiratory status is compromised, in extreme Trendelenburg positioning with high IAP, in long procedures and in patients with acute abdomen or those at risk of regurgitation and aspiration.

Maintenance of Anaesthesia and Monitoring

Maintenance of anaesthesia consists of a combination of an inhalational agent supplemented with intravenous opioids (fentanyl). It is recommended that the use of nitrous oxide be avoided since this agent may distend the intestinal loops during long-duration procedures and can cause post-operative nausea and vomiting.

Because of the alterations in compliance and resistance of the respiratory system as a result of pneumoperitoneum, changes in ventilatory parameters may be needed to prevent hypercarbia (by increasing respiratory rate, increasing peak

inspiratory pressure) or hypoxaemia (by increasing FiO_2, application of PEEP, lengthening of the inspiratory time, or use of an inspiratory pause). Regardless of the duration of the procedure, minute ventilation may need to be increased by 25 to 30% to maintain normocarbia.

Routine monitoring should include continuous electrocardiogram, automated non- invasive blood pressure measurement, pulse oximetry, inspired oxygen concentration, temperature and $ETCO_2$ measurements. Invasive haemodynamic monitoring of arterial blood pressure and central venous pressure is not routinely used unless indicated by the clinical status of the patient. Ideally, a venous catheter is inserted above the diaphragm (upper extremity) to avoid the consequences of the elevated IAP, which compresses the inferior vena cava and can block the access of drugs and fluids to the systemic circulation from access sites in the legs.

Sensible and insensible losses tend to be lower during laparoscopic surgery than during open procedures. Maintenance volumes of fluids are usually required, though it may be less than expected.

Continuous insufflation of large volumes of cold, non-humidified CO_2 into the abdominal cavity for long periods of time may lead to hypothermia. Measures should be taken to prevent perioperative hypothermia.

At the completion of surgery, all of the remaining intra-abdominal CO_2 should be evacuated and the neuromuscular blockade reversed. Residual CO_2 causes peritoneal irritation, giving rise to abdominal discomfort, shoulder pain and nausea and vomiting in the postoperative period.

Pain Relief

It is generally accepted that pain following laparoscopic surgery is less than that following open procedures. However, peritoneal irritation due to residual CO_2 may result in vague abdominal and shoulder discomfort. Infiltration of the port sites with a local anaesthetic provides postoperative analgesia. This can be supplemented with paracetamol or non-steroidal anti-inflammatory drugs (NSAID) (in absence of contraindications). After major laparoscopic surgery, a combination of paracetamol, NSAID and intravenous opioid may be needed for 24-48 hr.

PONV

Postoperative nausea and vomiting are common complications reported after laparoscopy and their incidence is reduced by prophylactic administration of antiemetic agents. Complete aspiration of the pneumoperitoneum at the conclusion of the surgery may prevent the occurrence of PONV. The various combinations of antiemetic drugs after induction of anaesthesia (Ondansetron 100 mcg/kg up to 4 mg, dexamethasone 150 mcg/kg, and droperidol 25 mcg/kg up to 0.625 mg) may help to prevent PONV.

COMPLICATIONS OF LAPAROSCOPIC SURGERY

The overall complication rate has been reported as 5.8%. Most complications are surgical and technique related. Complication rates are inversely correlated with laparoscopic experience. Major complications include injuries to major vessels, intestines or viscera by instruments or diathermy. Other rare complications include hypercarbia, gas embolism, pneumothorax and pneumomediastinum. In neonates, there is a risk of re-opening of right-to-left shunt via the foramen ovale when the IAP is excessively high, resulting in hypoxaemia.

CONCLUSION

Laparoscopic surgery in neonates and infants presents a challenge to both surgeon and anaesthesiologist. Anaesthesiologists must have a thorough understanding of the effects of insufflation of CO_2 on cardiovascular and respiratory systems and the effects of positioning during the procedure. They must also be aware of the potential complications and be able to manage them promptly.

Table I: Laparoscopic Procedures in Neonates and Infants, UKM Medical Centre 2008-2012

Diagnostic Purposes	Therapeutic Purposes
Impalpable testis	Fundoplication for gastro-esophageal reflux
Ambiguous Genitalia	Inguinal hernia repair
Abdominal mass biopsy	Repair of Congenital diaphragmatic hernia
Evaluation of ovarian pathology	Ovarian mass, oophorectomy
Biliary Atresia (on-table-cholangiogram)	Bowel Surgery: duodenal atesia, malrotation
Tumour biopsy	Duhamel for Hirschsprung's disease
	Splenectomy
	Nephrectomy, ureterectomy
	pyeloroplasty
	pyloromyotomy
	orchidopexy
	PSARP for anorectal anomaly
	Partial Pancreatectomy
	Excision of choledochal cyst
	Gastrostomy
	Appendicectomy
	Adrenalectomy

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Is Anaesthesia Harmful to the Paediatric Brain?

Wong Wai Hong, Tan It
Consultant Anaesthesiologists, Sunway Medical Centre

INTRODUCTION

Anaesthetists have always believed that as a general anesthetic wears off, the brain would return to the same state as before the anesthetic. Accumulating evidence is forcing anaesthetists to reconsider this.

Anaesthetic-induced developmental neurotoxicity including neuronal cell death (apoptosis) has been clearly established in laboratory neonatal animal models. Although the applicability of animal data to clinical anaesthesia practice remains uncertain, there is rising concern about the potential side effects of anaesthesia exposure in the very young when the brain is still developing. Some human clinical studies have found evidence for an association between major surgery and changes in neurobehavioral outcome, although the evidence is less clear for minor surgery. These associations are certainly at least partly because of factors apart from anaesthesia, such as coexisting pathology or the effect of surgery itself. The possibility of neurotoxicity during uneventful anaesthetic procedures in human neonates or infants has led to serious questions about the safety of paediatric anaesthesia.[1] As such, we may have to reconsider what we tell parents when we take informed consent for anaesthesia for surgery in the very young.

During the entire pregnancy women and healthcare professionals are wary of taking or prescribing medication because of the effects that the drugs may have on development. While concern is greatest during organogenesis in early pregnancy, development does not simply cease at birth. Therefore, concern perhaps should not go away the day the child is born.

NORMAL HUMAN BRAIN DEVELOPMENT[2]

The nervous system is derived from the ectoderm, the outermost tissue layer, of the embryo. In the third week of development the neuroectoderm appears and forms the neural plate along the dorsal side of the embryo. This neural plate is the source of the majority of all neurons and glial cells in the mature human. A groove forms in the neural plate and, by week four of development, the neural plate wraps in on itself to make a hollow neural tube.

Because this neural tube later gives rise to the brain and spinal cord any mutations at this stage in development can lead to lethal deformities like anencephaly or lifelong disabilities like spina bifida. The most anterior part of the neural tube is called the telencephalon, which expands rapidly due to cell proliferation, and eventually gives rise to the brain. Gradually some of the cells stop dividing and differentiate into neurons and glial cells, which are the main cellular components of the brain. The newly generated neurons migrate to different parts of the developing brain to self-organize into different brain structures.

Once the neurons have reached their regional positions, they extend axons and dendrites, which allow them to communicate with other neurons via synapses. Synaptic communication between neurons leads to the establishment of functional neural circuits that mediate sensory and motor processing, and underlie behavior. The human brain does most of its development within the first 20 years of life.[2,3]

In the 1950s, animal research showed development in the sensory regions after birth. During sensitive periods, the environment plays a major role in normal development. This research indicated that from early postnatal time through the next several months or years, the brain went through synaptogenesis followed by synaptic pruning which represent the creation and elimination of synapses during growth.

In the 1960-70s, studies were done on human brains to reveal development past the early childhood years, especially in the prefrontal cortex. This was identified by the process of myelination where the developed regions axons were myelinated first while the association areas were still able to develop through adolescence.

Synaptic reorganization takes place most predominantly during childhood and adolescence. During these periods the brain becomes sensitive to change which allows it to develop in unique ways dependent upon the individual's age, gender, and environment along with many other variables.[4]

Differences in environment can affect how the brain develops and at what pace. The environment can include factors like location and surroundings as well as circumstances in the environment. Environment can also be identified as an individual's emotions or response to certain stimuli. In this case, the concept of "self-organization" which postulates that the brain organizes itself based on each individual, must be explored further.[5]

Apoptosis

The developing brain has several significant differences from the adult brain that makes it more vulnerable to anaesthetics. Early in development the number of neurones formed is significantly greater than in adult mammals. At the same time, there is an exuberant burst of synapse formation (synaptogenesis) before synapses are eventually pruned to establish behaviourally relevant connections between neurones. Programmed cell death, or apoptosis, is responsible for the elimination of 50-70% of developing neurones under normal circumstances.[6-9]

Apoptosis is a highly regulated mechanism of controlled cell involution and death that has both physiological and pathological roles. This apoptotic pruning of brain cells establishes normal cortical architecture and function. Apoptosis also serves to remove neurones after pathological insults, such as ischaemia or hypoxia, after withdrawal of neurotrophic factors, and after exposure to anaesthesia in early development.[8]

However, it is difficult to determine the extent to which apoptosis after anaesthesia involves cells that were already destined to die, or whether anaesthesia induces excessive apoptosis in viable cells that might negatively impact maturation of the nervous system.[9]

THE EFFECTS OF ANAESTHESIA ON THE DEVELOPING BRAIN - ANIMAL STUDIES

Studies that show harm

It is now accepted that anaesthesia causes neurodegeneration in a variety of animal species, including primates.[10-12] In animals, exposure of developing brain to most general anaesthetics causes some degree of neuronal apoptosis[13-17] as well as changes in dendritic morphology.[18-20]

All volatile anaesthetics, propofol, and midazolam have been shown to be neurotoxic in studies on infant mammals.[13,14,21-25] Ketamine has also been shown to result in changes in the spinal cord.[26]

Brambrink et al.[27] demonstrated increased neuronal apoptosis after 5 h of 0.7-1.5% inhaled isoflurane in 6-day-old rhesus monkeys. This is close to 1 MAC for a monkey, and also close to 1 MAC for humans (1 MAC in human neonates and infants is about 1.6-1.8%). There is also some evidence, that animals exposed to anaesthesia in their infancy have subsequent deficits in learning and other behavioural changes. [13-14]

The most robust neurotoxicity data available in primates were obtained by exposure of rhesus monkey foetuses and newborns to 24 h of ketamine anaesthesia. This produced neurodegeneration assessed using biomarkers for apoptosis both at day 122 of gestation and at post-natal day 5 (P5), but not at P35, while a smaller exposure of 3 h on P5 demonstrated no neurodegeneration.[10]

A follow-up study documented long-lasting cognitive deficits in rhesus monkeys after exposure to 24 h of ketamine anaesthesia at P5-6.[28] The animals were longitudinally assessed with the Operant Test Battery from the National Center for Toxicological Research, a test battery for which monkey and human child performance is similar.[29]

Beginning at 10 months of age, control animals outperformed ketamine-exposed animals in accuracy and response speed for a learning task and a colour and position discrimination task; this effect

persisted for at least 10 months. A primate model has now demonstrated that a single prolonged exposure to an anaesthetic during a critical neurodevelopmental period can have profound and long-lasting effects on cognitive performance.

Demonstration of anaesthetic toxicity in animal models requires substantial exposure in dosage and duration. Some estimate of the minimum required exposure for a significant effect on neurodevelopment comes from studies that have demonstrated significant apoptotic and necrotic cell death in neonatal monkeys exposed to ketamine for 9 h or isoflurane for 5 h.[11,27]

Can short exposures cause harm?
Ketamine exposure for 3 h was not sufficient to induce massive cell death, so it is possible that there is an exposure threshold, or minimum dose and exposure time for neurodegeneration.[25]

Anaesthetic exposure must occur during the critical period of neurogenesis and synaptogenesis to have significant apoptotic sequelae. It is difficult to compare data from rodents which have a late postnatal brain growth spurt, to primates which have exuberant *in utero* brain growth spurts.

Studies that show no adverse effects
However, conflicting reports also exist showing no adverse effects after exposure to midazolam, ketamine, thiopental, propofol, nitrous oxide, isoflurane, sevoflurane, and xenon. Indeed, under some circumstances, xenon appears to rescue neurones from isoflurane-induce apoptosis.[30]

Can anaesthetics be beneficial?
There are also some interesting data demonstrating some agents mitigate the effects of anaesthesia induced apoptosis. Lithium, xenon and dexmedetomidine have all been shown to reduce the toxicity.[31-33]

In the animal model it is well recognized that anaesthetic agents can have a neuroprotective role. In some studies, low doses of ketamine (too low to cause apoptosis per se) were indeed found to reduce the injury and loss of function caused by inflammation.[34,35]

THE EFFECTS OF ANAESTHESIA ON THE DEVELOPING BRAIN - HUMAN STUDIES

It is difficult to extrapolate the laboratory findings in animals to clinical practice. Areas of uncertainty in translation to humans are: the exact period of vulnerability, the dose required to cause injury (animals require high doses of intravenous anaesthetics and most studies have exposed animals to long periods of anaesthesia), the clinical outcome likely to be seen, and the role of anaesthesia among the other factors which contribute to injury. There are many examples of laboratory findings which are difficult to translate to clinical practice, for example, neuroprotection of general anaesthetics.

Prior to the animal data being published, several human cohort studies had demonstrated an association between major surgery in the neonatal period and poor neurodevelopmental outcome.[36-39]

Premature infants who underwent laparotomy had poorer neurodevelopmental outcome compared with matched controls and children who are born with oesophageal atresia have increased long-term learning emotional and behavioral problems compared with the general population.[40,41] Many of the babies in these studies had other malformations, had major surgery or were very premature; all significant confounding factors when looking at anaesthesia exposure and outcome.

Wilder et al.[42] used a large established birth cohort maintained at the Mayo Clinic. Looking at children who had surgery or not before the age of 4, they found the risk of learning disability increased with the number of anaesthetics a child had received. There was no evidence for an increased risk of association after just one exposure. Two exposures to anaesthetics increased the likelihood of future learning disabilities in reading, writing, and math by 50% and three or more exposures created an even greater risk for learning problems. However, exposure for less than two hours did not appear to be linked to learning difficulties. The association between disability and multiple exposures to anaesthetics persisted when adjustment was made for chronic illness.

Di Maggio et al.[43] performed a cohort study using the New York State medicaid records comparing children who had hernia repair before the age of 3 matched with those who had no surgery. After adjusting for several potential confounding factors, they found children who had hernia repair had twice the risk of diagnosis of behavioral or developmental disorder.

Flick et al[44] performed a matched cohort study in which children (N = 8548) born between January 1, 1976, and December 31, 1982, in Rochester, Minnesota, were the source of cases and controls. Those exposed to anaesthesia (n = 350) before the age of 2 were matched to unexposed controls (n = 700) on the basis of known risk factors for learning disabilities. Exposure to multiple, but not single, anaesthetic/surgery significantly increased the risk of developing learning disabilities (hazard ratio: 2.12 [95% confidence interval: 1.26-3.54]), even when accounting for health status.

Sprung et al[45] studied all children born between January 1, 1976, and December 31, 1982, in Rochester, MN, who remained in Rochester after age 5. Cases of attention-deficit hyperactivity disorder (ADHD) diagnosed before age 19 years were identified by applying stringent research criteria. Among the 5357 children analyzed, 341 ADHD cases were identified (estimated cumulative incidence, 7.6%; 95% confidence interval [CI], 6.8%-8.4%). After adjusting for gestational age, sex, birth weight, and comorbid health conditions, exposure to multiple (hazard ratio, 1.95; 95% CI, 1.03-3.71), but not single (hazard ratio, 1.18; 95% CI, 0.79-1.77), procedures requiring general anaesthesia was associated with an increased risk for ADHD.

In another recent study, children exposed to anaesthesia for surgery and diagnostic testing before 3 years of age had a 1.7-1.8 times increased incidence for deficits in language and abstract reasoning at 10 years old. Differences were found even in children who only had a single exposure.[46]

In a Dutch twin study, Bartels et al.[47] studied the association between anaesthesia exposure and school performance in 1143 monozygotic twin pairs. In discordant twin pairs (where one twin was exposed to anaesthesia and the other was not), there was no difference between twins in school performance.

Discussion of the human studies

Children do not have anaesthesia for no reason. It is usually administered for surgery or a diagnostic procedure. Infants having surgery or diagnostic procedures are very likely to have pathology or chromosomal abnormalities which may also influence neurobehavioral outcome. Children who require multiple procedures will be even more likely to have other abnormalities which may affect neurodevelopment. The surgery may result in cardiorespiratory, metabolic, inflammatory or a stress response that may also influence outcome. Large cohort studies may adjust for some of these confounding factors but such adjustment of known confounders is never perfect. Most importantly it is almost impossible to ever adjust for the surgery itself as children do not have surgery with no anesthesia.[1]

Using a twin study design minimizes the effect of environment and genetics on the association. However, even twin studies are not without possible bias. If there is a genetic predisposition to the condition that required surgery then those not having surgery, and hence not exposed may in fact be at greater risk of subsequent poor outcome as the child may suffer from the condition without the benefit of surgery; thus masking any toxic effect of the anaesthesia.[48]

On the other hand, it is well described that infants undergoing major surgery who have inadequate anaesthesia or analgesia have a poorer outcome. It is presumed that surgery and pain result in harmful metabolic, immunologic and humoral responses that could at least partly be reduced by anaesthesia and analgesia.[49]

In summary, so far currently published clinical studies cannot confirm or rule out the possibility that anaesthesia-related neuronal apoptosis and dendritic changes may result in clinically relevant neurobehavioral changes.

ANAESTHESIA FOR DELIVERY

Exposure to ethanol during pregnancy is one well-known risk factor which may influence neurobehavioral changes in children, but increasingly many other drugs and environmental exposures have been investigated. For example magnesium is one agent which has been shown to cause neuronal apoptosis when given in high doses in the animal model.[50]

Apart from exposures to drugs and environmental toxins, there is also interest in the effect of illness, anaesthesia, surgery and other major medical interventions in the newborn period. With so many potential determinants, it will inevitably be very difficult to isolate any role that anaesthesia may indeed have.

Using the Mayo birth cohort, Sprung et al.[51] compared children who were born by caesarean section under general anaesthesia, those born by caesarean delivery under regional anaesthesia and those born by vaginal delivery. They found that children born by caesarean delivery under regional anaesthesia had less risk of a learning difficulty than those born by vaginal delivery and no difference between those born by Caesarean section under general anesthesia and vaginal delivery. The reason for this result is unclear. To explore the possibility that the regional blockade was protective, the same group went on to compare those born without general anesthesia by vaginal, with and without regional analgesia, and found no difference in risk of learning disability.[52] Could it be that vaginal delivery may affect the brain - does the pressure from passage of the head through the pelvic opening cause harm?

Concern about anaesthesia exposure at delivery is mitigated by epidemiologic studies of mothers exposed to regional and general anaesthesia during vaginal and caesarean delivery whose children did not show an increased incidence of learning disabilities compared with those unexposed.[51-53]

OUTSIDE THE OPERATING THEATRE

The operating room is not the only area where anesthetic neurotoxicity may be relevant. Ketamine and midazolam, both implicated in potential toxicity, are also frequently given in the NICU and PICU.[54]

In these settings, they may be given for much longer periods of time. However, determining the clinical relevance of any toxicity in these settings is perhaps even harder than for the operating room as these children often have multiple comorbidities which may also influence outcome. So far there is mixed evidence. A Cochrane review found some evidence for a worse short-term outcome in neonates who had prolonged midazolam infusion.[55]

By contrast, the Epipage cohort study found no evidence for an association between sedation exposure and outcome; however, in this study many children received opioids for sedation rather than midazolam.[56]

WHERE DO WE GO FROM HERE?

More studies are clearly required to clarify these issues of long-term cognitive effects of early anaesthetic exposure in humans. It will be extremely challenging to resolve the interactions between genetic factors, environment, anaesthesia, surgery, etc. on long-term neurocognitive outcome, which is already a difficult endpoint to assess. Resolving the effects of surgery, anaesthesia and co-morbid conditions alone are a particular challenge as it is ethically impossible to perform surgery without anaesthesia and anaesthesia is rarely given alone without a surgical procedure.

An ongoing study that will attempt to separate the effects of general anaesthesia from the surgical procedure is the GAS study (A Multi-site Randomized Controlled Trial Comparing Regional and General Anaesthesia for Effects on Neurodevelopmental Outcome and Apnoea in Infants) of infants requiring inguinalherniorrhaphy.[57]

Infants will be randomized to receive either general anaesthesia with sevoflurane or spinal anaesthesia without sedation followed by neuro-cognitive testing at ages 2 and 5 yr (clinicaltrials.gov/ct2/show/NCT00756600). There are other trials that are underway or recently completed.[58-60]

Research should not just focus on the neurotoxicity of anaesthesia. Other factors which may contribute to poor outcome (such as pain, inflammation, stress and cardiorespiratory stability during surgery) should also be investigated. The question still remains how can we provide the best anaesthesia and preoperative management for these children to reduce any neurobehavioral risk? Answering this question will be challenging and involve far more than just determining if anaesthesia is toxic to developing brain.[1]

CONCLUSION

So what are the implications of the animal and clinical studies for clinical paediatric anaesthesia? In short, there is still insufficient data to make firm and specific recommendations.

The U.S. Food and Drug Administration and the International Anesthesia Research Society have posted a summary of the issues on their web site (http://www.smarttots.org).[61]

They acknowledge that *'Research using juvenile animal models show that exposure to some anesthetics and sedatives is associated with memory and learning deficits and other neurodegenerative changes in the central nervous system. Insufficient human data exists to either support or refute the possibility that similar effects could occur in children'* and that *'The early research in animals has raised concerns about some anesthetic drugs that need to be investigated further to determine if there is a risk to infants and children younger than four years of age. However, this research is very limited and is not yet conclusive. Dangers to infants and children from anesthesia are unproven at this point. There is no direct evidence that anesthetics are unsafe for children'.*

They conclude that *'Children do not undergo surgical procedures that require anesthesia unless the surgery is essential to their health. Therefore, postponing a necessary procedure may itself cause problems and would not be an option for the majority of children. For example, children with chronic ear infections may have delays in the development of speech related to problems with hearing. Surgery to treat this problem may improve learning whereas a delay may result in long-term difficulties in the normal development of speech.'*

'Although research in animals is often very helpful, it may sometimes cause undue concern and prompt changes in medical practice that have unintended consequences that are not in the best interest of children. Much more research is needed to provide parents with additional information about the safe use of anesthetic and/or sedative drugs in children. Until more information is available it is important that children continue to receive any necessary surgery and anesthesia.'

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Neurophysiological Monitoring for the Occasional Neuroanaesthetist

Hari Krshnan S K Puvaneswaran
Consultant Anaesthesiologist, Sime Darby Medical Centre Ara Damansara

Neurophysiological intraoperative monitoring (NIOM) represents a diagnostic tool to monitor the integrity of the neurological structure during neurosurgery by electrophysiological methods. It is a useful tool to increase safety and prevent neurological deterioration during surgery. Based on meta-analysis data, multimodal NIOM is better than single parameter monitoring, especially in spine surgery. However, no randomized controlled trial has been done to prove the efficacy of NIOM and most evidence supporting the use of NIOM is based on non-controlled prospective or retrospective case series.

Spine surgeons are of the opinion that NIOM should be recommended for all spine surgeries which are deemed risky (i.e. deformity surgery or surgery requiring implants). However, there is a need to develop evidence based protocols on intervention needed when NIOM is impaired during surgery.[1,2]

Neurosurgeons have a different opinion on NIOM.[3,4] A survey conducted on 109 neurosurgeons from 16 different countries concluded that 76% of surgeons found NIOM important, especially in risky surgical manoeuvres. However, neurosurgeons with long standing experience of NIOM found that its influence on the course of surgery was less compared with those who were new to NIOM. But the overall consensus is that NIOM is gaining popularity and will play an important role in the field of neurosurgery.

When NIOM is used, it will pose a challenge for the anaesthetist involved. Our type of anaesthetic will be dictated by the parameters which are being monitored. Many techniques are available but the aim is to keep the anaesthetic constant so that it does not interfere with neurophysiological parameter being derived.

TYPES OF NIOM COMMONLY EMPLOYED[5,6]:

1. Somatosensory Evoked Potential (SSEP):
SSEP monitors the integrity of sensory pathways including peripheral nerves, the spinal cord, the brainstem, subcortical structures and the sensory cortex. A mixed motor/sensory nerve is stimulated and this initiates a motor response which is recorded as a muscle twitch and the sensory response will be an averaged electroencephalogram (EEG) recording, which is detected by electrodes placed over the sensory cortex (refer Figure 1).

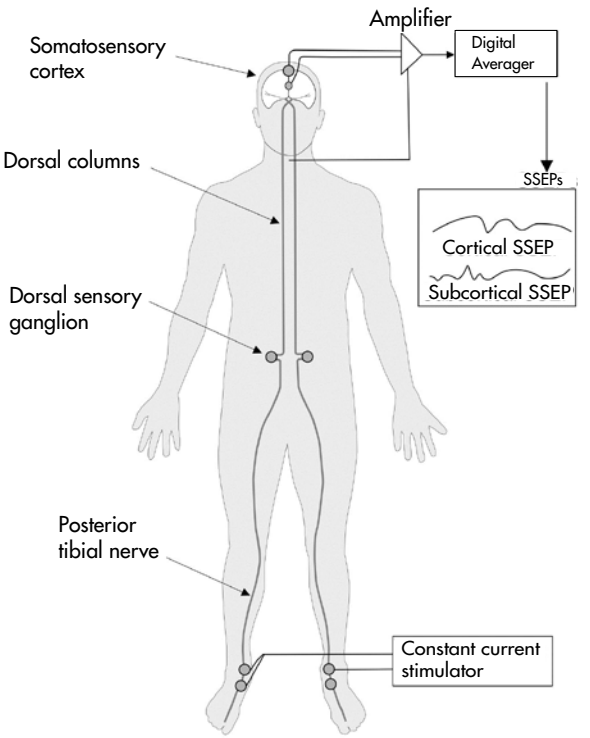
Common mixed motor/sensory nerves used include the ulnar (C8-T1), median (C6-T1), common peroneal (L4-S1) and posterior tibial (L4-S2) nerves.

Stimulation of the nerves → impulses ascend ipsilateral dorsal column → synapse near nucleus cuneatus → decussate at cervico-medullary junction → ascend contralateral medial leminiscus → synapse at thalamus → contralateral parietal sensory cortex.

SSEP on its own is not able to predict neural injury involving the motor component of the spinal cord as the impulses are transmitted via the sensory tract in the posterior column, which is supplied by the posterior spinal arteries. The motor tract on the other hand is supplied by the anterior spinal artery. Hence, it is possible to have motor injury post-operatively in spite of normal SSEP readings. Therefore, it is usually advocated to use multimodal (i.e. SSEP + MEP) during spinal surgery.

Intraoperative use of SSEP is mainly for procedures where spinal cord injury is a possibility, especially during spinal distraction when spinal perfusion can be impaired. It has been advocated by the Scoliosis Research Society and European Spinal Deformities Society and is said to reduce neurological injury to 0.55% versus the standard of 0.7 to 4% and this has made SSEP during scoliosis surgery the standard of care.

Figure 1: SSEP Monitoring



Loss or decrease in SSEP may be due to disruption of any component of the sensory pathway. The common definition of impaired SSEP reading is a 10% increase in latency and a 50% decrease in amplitude or both. Common causes of false positive changes (i.e. with no neurological damage) include:

1. Anaesthetics
2. Hypothermia
3. Acute changes in $PaCO_2$
4. Hypotension
5. Hypovolaemia
6. Anaemia

Lesions in which SSEP is employed:

1. Spinal Deformities / Tumours / Vascular Lesions
2. Posterior Fossa Lesions
3. Thalamus Lesions
4. Parietal Cortex Lesions

2. Motor Evoked Potential (MEP):
Although SSEP has been successful in detecting neurological injury, there have been incidences of motor injury in spite of normal SSEP readings during surgery. Hence, there is a need to monitor the motor component of the spinal cord during surgery. As discussed earlier, the anterior 2/3 of the spinal cord, where the motor pathways are located, is only supplied by a single anterior spinal artery with radicular branches from the aorta. Hence, it is more susceptible to hypo-perfusion especially in the watershed areas in the thoracic region.

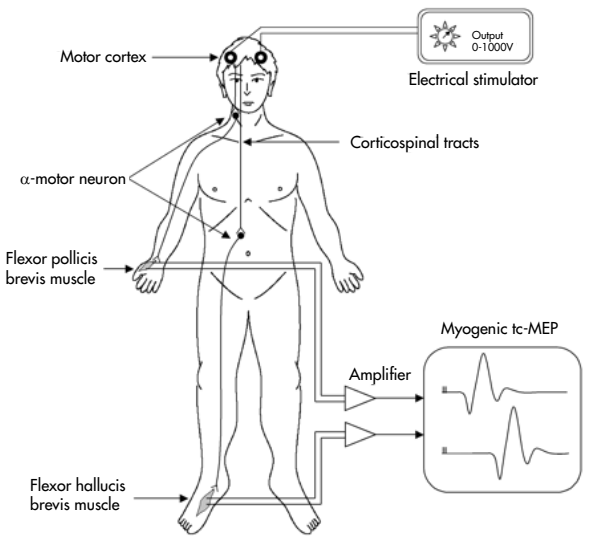
Comparatively, the posterior 1/3 of the spinal cord is supplied by 2 posterior spinal arteries. MEP can also detect hypoperfusion especially in the middle cerebral artery distribution via the lenticulostriate vessels to the internal capsule.

MEP requires direct stimulation of the motor cortex transcranially. This produces electrical responses carried via the motor pathways in the spinal cord, which can be monitored by epidural electrodes (Spinal MEP). These impulses summate at the anterior horn cells and are carried by the peripheral nerves (Neurogenic MEP) to the supplied muscles resulting in contraction and a compound muscle action potential (CAMP), the Myogenic MEP (Figure 2).

The CAMP is recorded in the upper extremity (e.g. abductor pollicis brevis) and lower extremity (e.g. tibialis anterior and lateral gastrocnemius) muscle with a surface or needle electrode. If neuromuscular blockade is used, spinal MEP via epidural electrodes or Neurogenic MEP is a possibility. However, epidural electrodes are technically difficult and Myogenic MEP is more sensitive than epidural responses.

Normally, Myogenic MEP is the preferred monitoring technique as it monitors the entire motor system from motor cortex, motor columns down to the muscle, including the ischaemia-sensitive ventral grey matter. A decrease in amplitude and prolonged latency of the MEP response suggests neurological injury as does an increase in the threshold voltage required to produce a response. The change in duration and morphology of the myogenic response may predict motor damage. However, there is still a debate about what constitutes a significant change to denote possible motor injury.

Figure 2: MEP monitorin



Factors that can affect MEP recordings:

1. Anaesthesia, mainly muscle relaxants and inhalational agents
2. Hypothermia
3. Hypovolaemia
4. Hypotension
5. Hypoxia
6. Hypo- or Hypercapnia
7. Patients with pre-existing muscle weakness
8. Children (require stronger stimuli due to incomplete myelination of motor nerves)

Lesions in which MEP is employed:

1. Spinal Deformities / Intramedullary tumours
2. Cerebral tumours near motor cortex
3. Cerebrovascular structures near motor cortex

3. Brainstem Auditory Evoked Potential (BAEP):
BAEP records the integrity of the auditory pathway from the tympanic membrane till its termination in the brain. It is produced by stimulating the cochlea with clicks and recording the brainstem response with electrodes placed over the scalp (Figure 3). It is mainly used to assess cranial nerve VIII function during resection of acoustic neuroma, cerebellopontine tumour resection, microvascular decompression of VII and V nerve and vertebral and basilar aneurysm clipping.

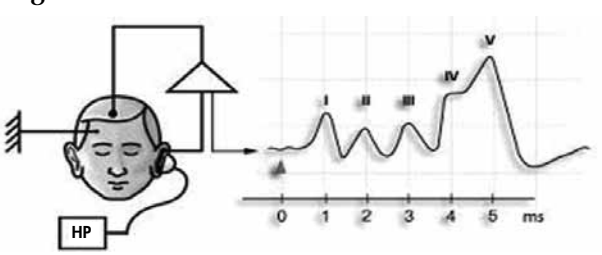
Prior to eliciting a BAEP, the patient should have adequate hearing function. With middle ear and cochlear deficits, no wave will be generated. 5 distinct BAEP waves are described and waves I, III and V are usually used for monitoring. There are small case series in which BAEP can be used to detect brainstem hypoperfusion during aneurysm clipping or brainstem retraction although some say that abnormal BAEP may only occur with global brainstem ischaemia.

Another almost similar modality, visual evoked potential (VEP) is also available, which is usually used for monitoring the visual pathway. It is useful for surgery near the optic nerve and optic chiasm (e.g. pituitary resection) and also lesions near the occipital lobe. However, because VEP readings are technically difficult to obtain, its use is not very common in neurosurgery.

Lesions in which BAEP is employed:

1. Acoustic Neuroma
2. Microvascular decompression of V and VII nerve
3. Posterior Fossa Lesions
4. Temporal and Parietal Lobe Lesions

Figure 3: BAEP



4. Electromyography (EMG):
EMG is obtained by placing 2 electrodes in or near a muscle and displaying the electrical activity generated from the muscle contraction. The monitoring can either be a free running EMG or stimulated EMG where a stimulus is applied and response recorded. EMG only records 1-2% of muscle fibres in a given muscle.

Abnormal EMG is described as burst or neurotonic activity. Burst refers to asynchronous polyphasic

waves caused by nerve trauma, tugging, stretch or fluid irrigation. Modifying the surgical stimulus usually resolves the abnormality with little evidence of permanent injury. Neurotonic activity is prolonged repetitive synchronous discharges that can last minutes to hours. It is associated with significant compression and stretch by retractors or surgical positioning. This requires immediate response as it can lead to motor dysfunction or chronic pain syndromes.

EMG has been beneficial especially in identifying nerves enclosed in tumours (e.g. acoustic neuroma) or scar (i.e. repeat spine surgery). Commonly monitored nerves are cervical (C2-7), lumbosacral (L2-S2), facial (posterior fossa), and recurrent laryngeal (vocal cords).

Lesions in which EMG is employed:

1. Acoustic Neuroma
2. Posterior Fossa lesions
3. Lumbar / Cervical Spine Defects.

ANAESTHETIC IMPLICATIONS FOR PATIENTS WITH NIOM:

As described earlier, the wide spread use of NIOM especially in spine surgery, is expected to increase in future. The onus will be on the anaesthetist to ensure the anaesthetic employed will have minimal effect on the NIOM. The type of anaesthetic to use depends on which modality is being monitored, and whether multimodal NIOM is used. The anaesthetist should also be aware of the physiological factors (e.g. hypotension) that can affect NIOM.

There is no guideline per se available at the time of writing this chapter in terms of what is the best anaesthetic to use during NIOM. However, the American Clinical Neurophysiology Society[7,8] has come up with a few guidelines in terms of recommended standards when NIOM is used intra-operatively. Most of these guidelines quote Jameson and Sloan et al regarding the type of anaesthetic recommended during NIOM. Table 1 describes the effect of anaesthesia on the different modalities of NIOM.

SSEP- The amplitude is decreased and latency is increased in a dose dependent manner by inhalational agents and to a lesser degree by intravenous (i.v.) agents. However, most readings can be obtained when using a MAC of 0.5 supplemented with either i.v. narcotics or i.v. hypnotics.

I.v. agents such as etomidate and ketamine have been shown to increase the amplitude rather than depress it. However, the adverse effects of these drugs must be taken into account. Muscle relaxants have no effect on SSEP as it monitors the sensory component; however, if MEP or EMG is used, NMBA's should be avoided. Total i.v. anaesthesia (propofol/narcotic infusion) maintains or minimally decreases cortical response and hence may provide the solution for effective monitoring.

MEP- Myogenic MEP are very susceptible to the depressive effects of anaesthetics, be it inhalational or i.v. Muscle relaxants weaken the muscle contraction in myogenic MEP and hence should be avoided especially during critical periods of the surgery where MEP is really required. Neurogenic MEP or epidural recordings are not really affected even by muscle relaxants. Again ketamine and etomidate appear to be favorable when combined with opioids but unfavourable side effects may limit their use during MEP. Dexmedetomidine has been successfully used during MEP recording but there are case reports of it interfering with the recordings. Blood levels >0.6 ng/ml can depress MEP.[9]

Multistimulus techniques have greatly improved the success of MEP monitoring especially under the depressive effects of anaesthetics. Higher pulse stimulus (3-6 pulses) can improve monitoring. However, the anaesthetic of choice is the least depressive anaesthetic (i.e. propofol/opioid infusion) which is able to maintain a stable and constant depth of anaesthesia. Computer controlled infusion systems (target-controlled infusion) may be beneficial compared to giving boluses of amnesics or opioids as it causes less depression of the MEP. Opioid infusion is also beneficial as it can help avoid the use of muscle relaxants by making the endotracheal tube more tolerable for the patient.

BAEP This is usually very robust and resistant to most anaesthetics. Inhalational agents may depress the response but the effect is minimal and good readings can still be obtained. Muscle relaxants have no effect on BAEP. However, it is very rare that BAEP is used as a single monitoring modality and it is usually used in combination with EMG and MEP. So the same principles apply as for MEP or EMG monitoring.

EMG Usually inhalational anaesthetics can be employed during EMG monitoring with minimal interference to EMG recordings. However, muscle relaxants should be avoided as it can interfere with muscle contraction and hence the EMG response. However, as with BAEP, it is usually combined with MEP and hence the same anaesthetic principles as for MEP applies.

What about NIOM in Paediatric Patients?[10]
In children less than 2 years old, there may be difficulty in obtaining SSEP & MEP as this age group may have immature nervous systems. Due to the partially myelinated tracts, the signal obtained can have a blunted peak or prolonged latency. However, by adjusting stimulating parameters, this can be overcome.[11] There are case reports of cortical signals obtained in infants as young as 5 days old.

Common Paediatric Operations in which NIOM may be indicated:

1. Posterior Spinal Fusion.
2. Dorsal Rhizotomy.
3. Tethered Cord Release.
4. Craniotomy for Posterior Fossa Tumour Resection.

Anaesthetic Management for loss of NIOM Signal Intraoperatively:

1. Ensure normal physiological parameters are maintained, i.e. oxygenation, normocarbia, temperature & blood pressure.
2. Keep the mean arterial pressure > 90 mmHg to maintain spinal cord perfusion pressure by:
   - the use of vasopressors or inotropes,
   - reducing dose of anaesthetic agents if appropirate, & / or
   - increasing intravascular volume with colloids or blood.
3. Reversing surgical correction e.g. screw removal or reduction of retraction, if the above steps do not improve SSEP/MEP in 15 minutes.
4. Wake up test to correlate with MEP/SSEP findings (this is mainly for spinal instrumentation and may be difficult in paediatric patients).
5. Steroids, i.e. methylprednisolone for further protection (after discussion with the surgeon).

Conclusion:
NIOM has increasingly become an important monitoring modality for the spine surgeon and neurosurgeon. It assists the surgeon in intra-operative decision making and may help in reducing the mortality and morbidity of the selected procedures for which it is employed. Although no randomized trials have been done in terms of the actual surgical outcome whether NIOM is used or not, the role of the anaesthetist is important in helping provide the ideal conditions so that NIOM can be successful.

There are no proper guidelines as to what type of anaesthetic is preferred when NIOM is used but the aim is to keep the anaesthetic depth constant during monitoring. Inhalational anaesthetics can be used as long as MAC is <0.5 but there is a preference for TIVA with propofol and opioids. Whatever anaesthetic is used, there is a need for cooperation between the anaesthetist, surgeon and neurophysiologist so that there will be a beneficial outcome for the patient.

Table 1: Summary of the effect of anaesthetic drugs on NIOM

AGENT	SSEP		MEP	EMG	BAEP
	Latency	Amplitude	Amplitude		
VOLATILES	↑↑↑	↓↓↓	↓↓↓	↓/0	0
N_2O	↑	↓↓	↓	0	0
PROPOFOL	↑↑	↓↓	↓↓	0	0
BARBITURATES	↑↑	↓↓↓	↓↓	0	0
BENZODIAZEPINES	↑	↓	↓↓	0	0
OPIOIDS	+/-	+/-	+/-	0	0
KETAMINE	↑	↑↑	+/-	0	0
ETOMIDATE	↑	↑↑	↑	0	0
MUSCLE RELAXANT	0	0	↓↓↓	↓↓	0

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Point-of-Care Ultrasound in the 21st Century - The Present and The Future

Amit Varma*, Farina Salleh, Shahridan Fathil***
*Anaesthesia Department ,Alexandra Hospital, Singapore, **Emergency Department, Hospital Sungai Buloh

INTRODUCTION

Traditionally, ultrasound has been used as an anatomic imaging test, confined to the radiology or imaging department in specialized hands. It was then introduced in Emergency Departments as an adjunct for quick assessment of the trauma patient for detection of pericardial or intra-abdominal fluid and has now become an essential diagnostic and therapeutic tool across various disciplines. Ultrasound is now being used in the diagnosis of various conditions, as a guidance tool for numerous procedures and in a range of locations.

DEFINITION

Point-of-Care (POC) Ultrasonography is defined as ultrasonography brought to the patient and performed by a provider in real time. Point-of-care ultrasound images can be obtained immediately in real time and can be correlated with patient's presenting signs and symptoms to arrive at an accurate diagnosis.[1]

THE PRESENT

POC Ultrasound has become an essential component of patient care across multiple medical disciplines.

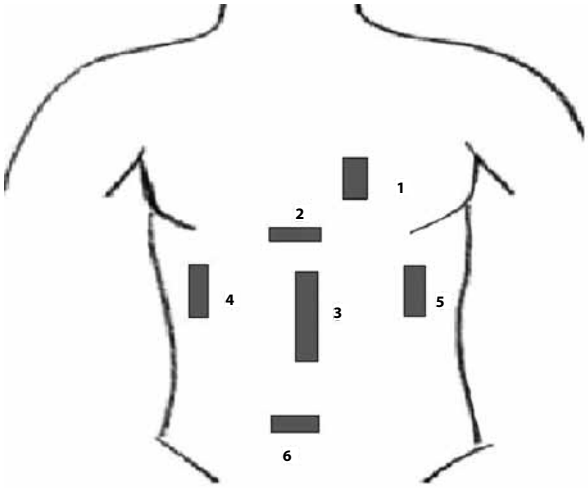
Its early use as a POC tool has been well documented in resuscitation in trauma where it has now become an accepted standard of care. Being non-invasive and portable, it bridges the gap between physical examination and diagnostic imaging. Focused Assessment with Sonography in Trauma (FAST) has become the initial choice of imaging test for trauma care as part of the Advanced Trauma Life Support (ATLS) protocol developed by the American College of Surgeons.[2]

The usage of POC ultrasound has also been extended outside the healthcare facility. It is used in the pre-hospital Franco-German model of Emergency Medical Service (EMS).[3]

There is also emerging evidence for use of point of care ultrasound in resource-limited settings. From the use of FAST scan in trauma to emergency obstetric patients, it has been demonstrated that use of POC ultrasound can reduce morbidity and mortality in developing nations where there is low availability of proper imaging modalities.[4]

SHOCK AND HYPOTENSION

POC ultrasound can be useful when managing patients in shock. Abdominal and Cardiac Evaluation with Sonography in Shock (ACES) and Rapid Ultrasound in Shock in evaluation of the critically ill (RUSH) are two ultrasound protocols for undifferentiated shock conditions.[5,6]

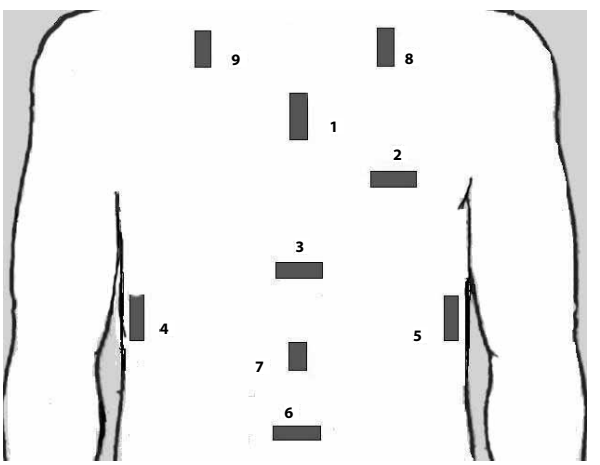


ACES ultrasound windows include:

1. Heart - to evaluate for myocardial contractility and evidence of tamponade.

2. Inferior vena cava (IVC) - to assess IVC diameter and collapse index indicating hypovolaemia.
3. Abdominal aorta - to look for aneurysms.
4. Right upper quadrant - to look for peritoneal or pleural fluid.
5. Left upper quadrant - to look for peritoneal or pleural fluid.
6. Pelvis - to look for peritoneal fluid.

The RUSH exam employs a similar protocol but divides the assessment into a 3-part physiological assessment of the "pump" i.e. cardiac function; "tank" i.e. volume status and possible sequestration of blood/fluid loss; and "pipes" i.e. aortic pathology and deep vein thrombosis.[6]



1. Parasternal Long cardiac view
2. Apical four chamber view
3. Inferior Vena Cava view
4. Morrison's pouch with hemothroax view
5. Splenorenal angle with hemothorax view
6. Bladder view
7. Aortic Slide View

8,9. Pneumothorax View

CRITICAL CARE

The use of ultrasound has become increasingly popular in critical care. A "head to toe" ABCDE ultrasound enhanced critical management has been proposed as a logical approach in critical care medicine.[7] It is a comprehensive ultrasound examination encompassing **airway**: airway patency and obstructive causes, **breathing**: respiratory performance and dyspnea/hypoxemia causes, **circulation**: haemodynamics and shock/hypotension causes, **disability**: neurological status and coma/focal signs causes and **exposure**: exclude missed findings.

OPERATING THEATRE

The perioperative scope of POC ultrasound for the anaesthetist has expanded from the mainstream modalities of transoesophageal echocardiography, ultrasound-guided vascular access and regional anaesthesia to include lung ultrasound.[8]

Delineation of tumour margins with intraoperative ultrasound by surgeons has been shown to improve surgical planning and successful resection rates.[9, 10]

DISASTERS and MASS CASUALTIES / COMBAT

Use of POC ultrasound has been documented in disaster and mass casualty incidents. It has made diagnosis and intervention fast and efficient in these resource-poor environments without compromising on patient safety or care.[11,12] The American military has adopted the usage of ultrasound in the diagnosis of bone fracture in the field.[13]

RESUSCITATION

Ultrasound can be used in resuscitation to detect potentially reversible causes of cardiac arrest like pulmonary embolism, cardiac tamponade, myocardial infarction, tension pneumothorax and aortic dissection. Cardiac akinesia during resuscitation is also a good predictor of failure to obtain return of spontaneous circulation.[14]

Integration of ultrasound in Advance Life Support has the potential to conform to the minimization of interruptions in cardiac compression.[15,16] However it requires considerable training for it to become the standard care.

SPORTS INJURIES

Musculoskeletal ultrasound is an essential tool in the diagnosis and treatment for sports related injuries, and is now an established component of postgraduate training in sports medicine.[17]

THE FUTURE

It is evident that ultrasound can be the initial imaging modality across various disciplines and over a spectrum of disease conditions.

TECHNOLOGY

The traditional ultrasound machines are gradually being replaced by smaller, more portable devices resulting in ultraportablity and increased accessibility.[18]

Smart phones can now be transformed with the appropriate hardware and software applications into ultraportable ultrasound gadgets.[19]

PROVIDERS

With proper training, ultrasound can become a powerful tool across all levels of healthcare personnel. It is thus imperative not to limit the use to only physicians but to equip other members of the healthcare community like nurses and paramedics with essential ultrasound skills as well.[18]

EDUCATION

Training in POC Ultrasound has always been at the postgraduate level in the form of competency based teaching and certification.

There is growing evidence that inexperienced undergraduate students can perform POC ultrasound at professional standards after focused training.[20]

PROTOCOL

Due to its multi-disciplinary and broad-spectrum use, uniform consensus and evidence-based protocols must be formulated to prevent variability in diagnosis and treatment, especially in trauma and critical care settings.[21]

ACCESIBLITY

The Millennium Development Goals (MDG) is an initiative by the United Nations aimed at universally eradicating disease and poverty.[22] Reduce Child Mortality and Improve Maternal Health are 2 out of 8 MDG on which POC ultrasound and Information and Communication Technology (ICT) may have an impact.[23]

The appropriate ICT will enable basic healthcare providers in remote and resource poor environments to acquire ultrasound images under supervision and transmit the images to faraway experts for interpretation and advice.[24]

CONCLUSION

POC Ultrasound is used across various specialties and clinical conditions. With the appropriate technology, training and improved accessibility, it can indeed become the stethoscope of the 21st century.

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Clinical Research and Research Ethics

Maria Lee Hooi Sean
Unit Head, Hospital Clinical Research Centre, Sultanah Aminah Hospital, Johor Bahru

INTRODUCTION

In tandem with current developments in the world, the Ministry of Health has launched the Malaysian Good Clinical Practice (GCP) Guidelines in 1999. These guidelines are internationally accepted ethical principles and quality standards that Malaysian researchers need to uphold.

The Clinical Research Center (CRC) was set up in 2000 and was given the mandate to streamline clinical research activities in Malaysia and develop research capacity among clinicians. One of the activities of CRC is to disseminate the international ethical principles and standards through GCP workshops, working hand in hand with the National Committee for Clinical Research, which is the board that oversees the GCP syllabus and certification. In 2004, multiple choice questions were introduced to test on understanding and the minimum score to qualify for GCP certification is set at 80%.

This paper is aimed to introduce the international ethical principles that have been adopted in Malaysian GCP and the background stories that have driven the international move for GCP. Various forms of ethical deviations will be highlighted with examples. There will be a brief discussion of where Malaysian clinician researchers are and where we are heading.

ETHICS & RESEARCH

Ethics is defined as the moral principles that govern a person's behaviour or the conducting of an activity.[1] Medical professionals are governed by the professional ethics that embody three main components[2]:

a) standards of professional competence;
b) standards of professional integrity;
c) accepted professional procedures.

Research is the systematic investigation into and study of materials and sources in order to establish facts and reach new conclusions.[3] So ethics of clinical research is about norms, values, right and wrong, good and bad, and what ought and ought not to be done in the context of clinical research.

What makes clinical research an acceptable activity in search of new knowledge while preserving professional code of conduct and be morally right?
Emanuel *et al* published an article in year 2000 that delineated 7 requirements that provide a systematic and coherent framework for evaluating clinical studies.[4] This framework was proposed after synthesizing traditional codes, declarations, and relevant literature on the ethics of research with human subjects such as the Nuremberg Code, Declaration of Helsinki, Belmont Report and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.[5-8] These 7 requirements have incorporated all relevant ethical considerations. In Malaysia, these requirements have been adopted as part of the checklists for the reviewers of Clinical Research Center, National Institutes of Health Malaysia when they assess the clinical research protocols submitted to National Medical Research Register for institutional as well as medical ethics approval.

The seven requirements for ethical clinical research have been tabulated and taught in the Malaysian Good Clinical Practice Guidelines Workshops.[4]

Why is there a need for research ethics governance?
The purpose of clinical research is to develop generalisable knowledge that should bring about improved health and therefore is valuable to society. Research subjects in clinical research setting will invariably be the patients that come to seek medical care from the clinicians. These research subjects (who are also our patients), are the means researchers (who are also the treating clinicians) use to securing such knowledge. Whenever clinical research is carried out, medical professionals have

#	Requirements	Explanation
1	Societal / Scientific value	Research that will improve health and well being or increase knowledge
2	Scientific validity	Use of acceptable scientific principles & methods and competent investigators, to produce reliable and valid data
3	Fair subject selection	Selection of subjects so that vulnerable individuals are not targeted for risky research, and the rich and socially powerful not favored for potentially beneficial research
4	Favorable risk-benefit ratio	Minimize risks, enhance potential benefits, risks are proportionate to the benefits to the subject or society
5	Respect for subjects	Subjects should have their privacy protected, the opportunity to withdraw, their well-being monitored & maintained, be informed of new information concerning research, compensated for injury
6	Informed consent	Provide adequate information to subject so that he or she can make voluntary decision
7	Independent review	Review of the above by individuals unaffiliated with the research

to assume a dual role; wearing the 2 hats, one hat as a doctor that should have the patients' well-being protected, and the other as a researcher in search for scientific truth. Christine Grady in the book "*Principles and Practice of Clinical Research*" has aptly described our dilemma: "*The primary ethical struggle in clinical research is that a few individuals are asked to accept burden or risk as research subjects in order to benefit others and society ….. ethical concerns arise because of the potential for exploitation and / or abuse of these human research subjects.*"[9]

Measures to safeguard the research subjects with respect to their safety, dignity and autonomy are necessary. History has shown that when observing research ethics and protecting human subjects were left to investigators' discretion, exploitation and abuse of research subjects were not uncommon. Interests of science frequently supersede concerns for patient safety. Many research misconduct have been reported, discussed, and condemned. Three events were salient and influential of subsequent development in research ethics:

1. Nazi experiments on POW & Nuremberg Trial (1946)

The Nazi Medical Experiments were described in United States Holocaust Memorial Museum website.[10] Prisoners of wars were subjected to merciless experiments to study ways to improve warfare technique and survival. In the study to show 'the effects of explosive decompression', live dissections were done on human subjects. A mobile decompression chamber was used and subjects were made to descend from altitudes of 40,000 to 60,000 feet without oxygen. It was found that severe symptoms of cerebral dysfunction occurred - at first convulsions, then unconsciousness in which the body was hanging limp and later, after wakening, developed temporary blindness, paralysis or severe confusional twilight states. Dr Rascher, who wanted to find out whether these symptoms were due to anoxic changes or to other causes, did what appeared to him the most simple thing: he placed the subjects of the experiment under water and dissected them while the heart was still beating, demonstrating air embolism in the blood vessels of the heart, liver, chest wall and brain.[11]

In the infamous Dachau hypothermia experiments, 300 prisoners in the concentration camp were submerged in the cold tank to answer a warfare observation that military personnel generally did not survive immersion in the North Sea for more than sixty to a hundred minutes. Its purpose was to establish the most effective treatment for victims of immersion hypothermia, particularly crew members of the German air force who had been shot down into the cold waters of the North Sea. The participant was usually forced, but occasionally it was "voluntary" in response to promises, rarely fulfilled, of release from the camp or commutation

of the death sentence. Some were anaesthetized, others conscious; many were naked, but others were dressed. Several different methods of rewarming the subjects were also tested. It was reported that the subjects shrieked in pain when their extremities froze white, 80-90 were killed in the process.[11]

By 1984, more than 45 publications had made reference to Dachau immersion-hypothermic experiments. There were much criticisms and debates on whether we should use evidence from unethical experiments like these and the implications of the use of ethically tainted data. In 1990, Berger presented a critical analysis of the experimental protocol and the results reported as well as an examination of the credentials and reliability of the investigators. He found that the Dachau hypothermia study has all the ingredients of a scientific fraud, and cannot advance science or save human lives. Future citations are inappropriate on scientific grounds.[12]

2. Beecher's paper on "Ethics & Clinical Research" in Medical Journals (1966)

Dr Henry Beecher is a renowned Harvard Medical School professor in Anesthesiology. In 1966, he published 22 examples of abuses in NEJM 1966.[13] His paper received attention and was accepted for publication after he presented his review of 18 examples of clinical research that he deemed unethical to a group of journalists convened at a conference by corporate sponsors. His report prompted the public and health professions to recognize that questionable research practices could be carried out, and even rewarded, in advanced, democratic states, and that careful attention to ethics should be part of every scientist's approach to research.[14] Beecher's paper highlighted that fully informed consent is not just a signature on the consent form but is all about how the process of getting that signature is obtained. He pointed out that 'in any precise sense statements regarding consent are meaningless unless one knows how fully the patients was informed of all risks, and if these are not known, that fact should also be made clear…'.[13] Informed consent of such quality can only be achieved in the presence of a conscientious, compassionate, and responsible investigator.

A variety of ethical errors were described, some of the examples shown below[13]:-

1) known effective treatment withheld
   a. Withholding penicillin for streptococcal respiratory infection from 109 patients to see complications like rheumatic fever and effect of sulfonamides in preventing non-suppurative complications.
   b. Withholding chloramphenicol for typhoid fever to determine relapse rate.

2) study of harm in institutionalized / vulnerable subjects:
   a. Purposely infecting institutionalized mentally defective children with hepatitis to determine the period of infectivity of infectious hepatitis.
   b. Injecting live cancer cells into hospitalized patients (who were merely told they would be receiving "some cells" - the word cancer as entirely omitted) to study immunity to cancer.

3) physiologic studies
   a. 11 children who underwent surgery for congenital heart disease also had total thymectomy done and full-thickness skin graft from an unrelated donor was sutured to the chest wall in each case to study of effect of thymectomy on the survival of skin homograft. 7 children served as control.
   b. 31 patients were subjected to cyclopropane anaesthesia and given toxic levels of carbon dioxide in the breathing system to study the cardiac arrhythmias associated with cyclopropane.

4) study to improve the understanding of disease
   a. to study the syndrome of hepatic coma, 9 patients with chronic alcoholism and advanced cirrhosis were given certain nitrogenous substances like ammonium chloride, di-ammonium citrate, urea or dietary protein and observed for signs.
   b. melanoma was transplanted from a daughter (described as terminal at that time) to her volunteering and informed mother, "in the hope of gaining a little better understanding of cancer immunity and in the hope that the production of tumor antibodies might be helpful in the treatment of the cancer patient"

3. Tuskegee Syphilis study (1932-1972)
Begun in 1932 by the US Public Health Service (PHS) as a short study to determine the natural history of untreated late latent syphilis in hundreds of African American men who already had the disease, the research went on and on for another four decades, through the era of treatment with arsenicals and heavy metals into the penicillin years. The study subjects were deprived of proven effective treatment with penicillin, which became available during the course of the study. Deception was deemed necessary by the researchers to make the men believe they were being helped: the diagnostic lumbar punctures were called "special treatment" and the aspirins and iron tonics were purported cures for their "bad blood". Although many published medical journal articles described the study, it only ended in 1972 when a young investigator, unable to get the government to stop it, told the story to the media. It took another 25 years, and much political effort, before the US Government issued a formal apology in a White House ceremony.[15]

ORIGIN AND DEVELOPMENT OF TODAY'S ICG-GCP: FROM NUREMBERG CODE TO DECLARATION OF HELSINKI TO BELMONT'S REPORT

Human experimentations during World War II on prisoners of war were greatly criticized. After the war, in the Nuremberg trials of 1946, 23 Nazi physicians and scientists were put on trial for the murder of concentration camp inmates who were used as research subjects. The publicity and proceedings of these trials eventually led to the delineation of 10 fundamental ethical principles for human subject research in the Nuremberg Code in 1947.[5] The **Nuremberg Code** became the first codification of research guidelines to protect human subjects which called for the:

- need of voluntary consent;
- right to withdraw;
- scientific value;
- favourable risk-benefit ratio; and
- avoidance of suffering in research subjects.

Unethical human experimentation did not end with the demise of the Third Reich and the Nuremberg Code did not succeed in its mission of protecting human subjects from abuses and deceptions by the clinician researchers. Henry Beecher, a professor of research in anaesthesia from Harvard Medical School described to us in 1966, 20 years after the Nuremberg trials, 22 examples of research done in the democratic states of America, in which human rights were flagrantly disregarded.[13]

In response to the Nuremberg Code, after years of deliberation and committee discussions, the World Medical Association, an international body representing physicians and researchers from countries around the world, adopted the Declaration of Helsinki which established new rules for human experimentation. The guideline was adopted at the WMA 18th General Assembly in Helsinki in 1964. It has gone through 6 revisions since then, latest in October 2008 at Seoul. The **Declaration of Helsinki** is the most widely accepted guidance worldwide on medical research involving human subjects. It emphasized that:

- Research with humans should be based on the results from laboratory and animal experimentation;
- Research protocols should be reviewed by an independent committee prior to initiation;
- Informed consent from research participants is necessary;
- Research should be conducted by medically / scientifically qualified individuals;
- Risks to study subject should not exceed benefits; and
- Accuracy of results must be preserved.

However, like all other guidelines, they lack the force of law. In spite of ethics codes, research abuses continued while ethical conduct was left to the investigators' discretion.

Following the exposure of the unethical research in Tuskegee, the **National Research Act** (1974) was signed into law. The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research was created. One of the charges to the Commission was to identify the basic ethical principles that should underlie the conduct

of biomedical and behavioural research involving human subjects and to develop guidelines which should be followed to assure that such research is conducted in accordance with those principles. A national regulation with force of law behind it eventually entrusted the governance of ethics to the institutional review board, IRB.

As an outgrowth of an intensive four-day discussion that was held in February 1976 at the Smithsonian Institution's Belmont Conference Center, followed by 4 years of monthly deliberations of the Commission, **Belmont Report** (1979) was published in the Federal Register of USA.[7] The Belmont Report delineated 3 fundamental ethical principles

1. Respect for person;
2. Beneficence and non-maleficence; and
3. Justice.

The 3 fundamental ethical principles and the 7 requirements of ethical research

The first principles of 'Respect for Person' calls for 2 basic ethical convictions: that individuals must be treated as autonomous agents and persons with diminished autonomy are to be protected. The requirement of informed consent in research and respect for research subjects are in response to this principle.

Second is the *Hippocrates* principle of "As to diseases, make a habit of two things: to help, or at least to do no harm (*primum non nocere*)". In research, it is an obligation that the researcher must maximize possible benefits and minimize possible harms. Requirements of favourable risk-benefit ratio, social value and scientific validity are in response to this principle.

The third principle, justice, calls for fair treatment to all and in research, the concern is with regard to distributive justice, i.e. distribution of scarce benefits or burdens. Selection of subjects for research must be responsive to this principle so that the rich and powerful are not selected for beneficial trials and the poor are not selectively subjected to take all the risks.

These ethical principles and requirements are now formalized in various international guidelines and national regulations. The most accepted and adopted ones are the Declaration of Helsinki [http://www.wma.net/] and International Ethical Guidelines for Biomedical Research Involving Human Subjects [http://www.cioms.ch]. Both are referenced by International Conference on Harmonization– Good Clinical Practice (ICH-GCP) guidelines and WHO GCP. Malaysia adopted and adapted these guideline principles into Malaysian GCP in 1999, which has been revised in 2004 and 2011.

ETHICAL DEVIATIONS

With the global adoption of GCP guidelines and a constant fixture of institutional review boards (IRBs) in clinical research which are designed to ensure that researchers comply with human research subject protections, including conflict-of-interest controls, the human guinea pig type of clinical research described above is unlikely to take place. However, subtle or less explicit human right violations, especially in the consenting process, may fail to be detected if investigators avoid existing IRB processes or if IRB members do not take responsibility for addressing actual or potential conflicts of interest.[16] Other forms of ethical deviations have become more rampant especially in the environment of "publish or perish". Ethical deviations occur in various forms which can be classified into error or fraud.

Error:
1. Failing to comply with regulations protecting research participants.
2. Scientific mistakes.
3. Failure to publish full articles.

Fraud:
1. Falsifying or fabricating data or documents.
2. Gift authorship and plagiarism.

Once discovered, the researchers might have to face one or more of the following consequences:

1. public criticism and shame.
2. termination of academic or service appointment.
3. suspension of research grant.

4. suspension or removal of practicing license.
5. civil suit.
6. retraction of their published paper.

However, these punishments did not deter clinicians from committing fraud. Fraud offers big rewards for relatively little risk and often is motivated by considerations beyond financial gain.

a. Scientific fraud: falsification or fabrication

The worst deviation from ethics is scientific fraud. We must accept that fraud exists, though with an unknown prevalence. Steen recently reviewed 742 English language research papers retracted from the PubMed database between 2000 and 2010 and found that the papers were retracted more commonly for error rather than fraud. However, the reported 26.6% (197) papers retracted for fraud will set the average prevalence of scientific fraud in the last decade at 18 fraud papers per annum or 1.5 fraud papers published per month. All will agree that these retracted papers are only the tip of the iceberg for fraud.[18] Furthermore, 31.8% of retracted papers were not noted as retracted in any way, and the fraudulent manipulated results will continue to be cited and lead to wrong conclusions.[18]

Steen demonstrated that fraudulent authors targeted journals with a high impact factor (IF), more than half of them were 'repeat offenders' (53% of fraudulent papers were written by a first author who had written other retracted papers), and diffuse responsibility across many co-authors. He concluded that papers retracted because of data fabrication or falsification represent a calculated, deliberate effort to deceive; a motivation fundamentally different from papers retracted for error.[19]

There have been many well publicized fraud cases over the past quarter century, happening across many disciplines and countries: Jon Sudbø, Norwegian researcher on oral cancer; Eric T. Poehlman, USA professor at the University of Vermont (UVM) on the metabolic changes and aging, particularly during menopause; Woo Suk Hwang, researcher of Seoul National University (SNU) on stem cell line produced from a cloned human embryo; John Anderton, physician from Edinburgh on sham drug trial; Dr Malcolm Pearce, a British gynaecologist who claimed work that had never taken place, just to name a few.[17,20-23]

Are anaesthetists spared? Of course not. We have the recent fraudulent cases of Dr Yoshitaka Fujii, Anaesthesiologist from Toho University fabricating his work on dexamethasone in postoperative nausea vomiting, Dr Don Poldermans from Erasmus Medical Center, Netherland in his work on perioperative beta-blockers and Joachim Boldt, a leading German anaesthesiologist in his work on starch colloid.[24,25]

1. Dr Poldermans and perioperative cardiac management

Dr Poldermans had been a professor of medicine and head of perioperative cardiac care at the Erasmus Medical Center. He spent years researching the risk of complications during cardio-vascular surgery and has some 500 publications to his name. One of Poldermans' most widely known areas of research involved the effects of beta-blockers on surgical patients, for which he conducted some of the foundational trials. A search of Medline revealed at least 75 publications on that subject alone.

His downfall began when the group planned to submit data for the DECREASE VI study to a conference. A junior researcher felt the data was not in order and contacted a friend who informed the board of directors. With the completion of the investigation in November 2011, Poldermans was fired for violations of academic integrity. He was found to have used patient data without written permission, used fictitious data, and submitted two reports to conferences which included knowingly unreliable data.[26]

So far, there was no indication about which, if any, of Poldermans' publications will be retracted. Sixteen of his papers have been cited at least 100 times, according to Thomson Scientific's Web of Knowledge, and one, in the *European Heart Journal*, has been cited more than 700 times.[27]

2. Joachim Boldt & Hydroxyethyl starch[28]

Boldt was a leading German anaesthesiologist with more than 200 papers to his name. He spent much of his career studying the safety and

efficacy of colloids. In 28 Oct 2010, the journal *Anesthesia & Analgesia* issued a retraction notice to retract the article published in December 2009 "Cardiopulmonary Bypass Priming Using a High Dose of a Balanced Hydroxyethyl Starch Versus an Albumin-Based Priming System".[29] The paper in question reported on a study of 50 patients undergoing cardiopulmonary bypass (CPB). Some were given hydroxyethyl starch and others received albumin. According to the authors, "high-volume priming of the CPB circuit with a modern balanced HES solution resulted in reduced inflammation, less endothelial damage, and fewer alterations in renal tubular integrity compared with an albumin-based priming. Coagulation including platelet function was better preserved with high-dose balanced HES CPB priming compared with albumin-based CPB priming."

Investigations started after the Journal received several letters from concerned readers that the variability in the cytokine assay was too low to be believed. However later, there was evidence to suggest that the study was fabricated based on following reported findings:

1. There are no original patient data or laboratory data to support the findings in the study.
2. According to the head of the perfusionist team, no albumin has been used as a priming solution since 1999.
3. According to the pharmacy, no albumin has been delivered to the cardiac operating rooms for many years.
4. All laboratory measurements, including IL-6, IL-10, intercellular adhesion molecule, neutrophil gelatinase-associated lipocalin, and alpha-glutathione-S-transferase, would have been performed in the clinical laboratory at the Klinikum Ludwigshafen. These assays have only been performed on patients receiving hydroxy-ethyl starch priming solutions. The laboratory could identify no assays from patients receiving albumin priming solutions.[30]

All of Boldt's work was scrutinized and it was found that most of his work had no IRB approval. In February 2011, the journal *Anesthesia & Analgesia* announced the list of 22 articles it was retracting from the web site.[31] The vast majority of these papers were cited in the double digits, according to Thomson Scientific's Web of Knowledge, with the paper "Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery" published in *Anesth Analg* 2001 being cited 99 times. The state medical board, Landesärztekammer Rheinland-Pfalz (LÄK-RLP), overseeing an investigation into Boldt's publications, published the full list of 88 papers retracted on 12 March 2011.[32] This makes Joachim Boldt the holder of the record for 'the most retractions by a single author'.

How has Boldt affected us?

Older colloidal solutions are known to interfere with coagulation and renal function and may contribute towards inflammation. Newer colloidal solutions appear to have addressed these limitations. However, some of that research was performed by Boldt. The safety and efficacy of modern solutions is potentially compromised by the finding of misrepresentations in his research. Boldt, who has published nearly 350 articles, was a top figure in the world of fluid management during surgery mainly looking at hydroxyethyl-starch, and formed the basis of clinical guidelines for use of the therapy.

Retractions have led to revision of the review article "Contemporary fluid management in cardiac anaesthesia" by Habicher *et al*, which now gives a different conclusion: no recommendations on the safe use of starch solutions regarding renal function in cardiac surgical patients, regardless of the generation of starches used, can be made.[33] Many of us would be wondering how much, if any, of Boldt's work we can trust. This has resulted in the withdrawal of hydroxyethyl-starch solutions in some countries.

b. Another form of scientific fraud: gift authorship and authorship misrepresentation

As observed by Larry, one challenge for most scientists is avoiding and resolving issues that centre around authorship when publishing scientific manuscripts. While trying to place the research in proper context, impart new knowledge, follow proper guidelines, and publish in the most

appropriate journal, the scientist must often deal with multi-collaborator issues like authorship allocation, trust and dependence, and resolution of publication conflicts.[34]

International Committee of Medical Journal Editors (ICMJE) demand that all persons designated as authors should meet the qualifications for authorship (otherwise commit ethical violation of gift authorship), and all those who qualify should be listed (otherwise commit ethical violation of ghost authorship). To be credited, authors must meet three criteria:

1. to have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;
2. to have drafted or revised the article critically for important intellectual content; and
3. to have approved the final version to be published.

Gift authorship is the practice of treating authorship as something that is conferred as a benefit rather than earned through taking responsibility. This is a common deviation from ethical practice, either conferred by the junior to the senior voluntarily or more frequently demanded by the superior from the subordinate. The rewards are obvious, especially in the environment where volume rather than quality of papers produced are used as the yardstick for tenure, promotion and fame. Furthermore, the risk of detection is low.

Authorship misrepresentation is common among residency and fellowship applicants for various medical specialties. Yang et al reported prevalence of misrepresented publications in radiation oncology residency applications at 22%.[35] A recent meta-analysis of 13 studies from various fields of medicine found in the literature from 1995 to 2008 reported the mean percentage of candidates with misrepresentation per applicant pool at 4.9%. The most common type of misrepresentation reported was listing non-existent articles, followed by errors in authorship order and non-authorship. Program directors should be aware that self-promotion in the authorship list is a common form of misrepresentation.[36]

c. A common sin of failure to reach full publication (stopping short at conference presentation)

People volunteering to participate in research, particularly those agreeing to be allocated to an intervention by chance (i.e. randomized), often with potential of substantial health risks, expect that the information gleaned from their involvement will have one of several possible outcomes. Most immediately, it might improve their health; and it might provide accumulating information about the benefits and harms of the intervention under consideration. This is public accountability!

While such expectations are a minimum, they can only be realized if the data is actually reported. Such minimally reasonable expectations, sadly, do not always happen. Many if not all of us are guilty of not making the results known to the stakeholders. Often, we are contented at making a poster or an oral free paper presentation in conferences. If one were to investigate the number of scientific abstracts received and presented in our MSA ASM which actually made it to the indexed or any other searchable databases, one will find similar or worst results than that reported in the literature.

Yentis *et al* in 1993 reviewed the publication rate of abstracts presented at meetings of four anaesthesia societies (American Society of Anesthesiologists, International Anesthesia Research Society, Anaesthesia Research Society and Canadian Anaesthetists' Society) in 1985. They found that the mean proportion of abstracts from all four societies that were published as manuscripts within three years of presentation was 44% and within five years 50%.[37] The publication rates in many other faculties were not too far off ranging between 25- 50%.[38-45]

Publication rate has been used to judge the quality of the content of the meetings and to determine the validity of the research presentation.[46] Failure to full publication on an indexed database will lead to research results being not searchable, contributing to publication bias. The most obvious implication of publication bias is that[47]

1. Important information, particularly concerning less effective treatments, and harms, are kept hidden from public view. Selective reporting, regardless of whether it is a full report or selective outcomes within a report, will provide bias estimates of an intervention's effectiveness.
2. Systematic reviewers, whose modus operandi is to synthesize all available data, will produce biased estimates should their review only include statistically positive results. And they are not the only ones who will run into problems because of publication bias.
3. Clinical practice guideline developers often use the results of a systematic review as a starting point to develop evidence-based practice guidelines. If the systematic review is biased it might invalidate the clinical practice guideline.
4. At the other end of the research spectrum, granting agencies are starting to ask clinical trialists for a systematic review as evidence for the rationale for a proposed trial. A biased systematic review – only including reports of trials with statistically positive results – might invalidate the rationale for conducting RCTs.

All researchers should transparently report all results, both statistically positive and negative; all research undertaken must be written up and made publicly available to interested groups. There are several steps to help achieve the goal of full reporting of all research results.[47]

1. All research training programs should be required to review the data on publication bias and its consequences.
2. Students should be exposed to the moral obligation of reporting all research results.
3. Response to global initiative to register Randomised Controlled Trials.

National Institutes of Health Malaysia has launched a web-based register for all medical research called National Medical Research Register (NMRR) since 2007 and it is the Ministry of Health Malaysia's platform to capture all research activities in Malaysia for various reasons of which public accountability is one of the keys. The NMRR is also the web based tool designed to support the implementation of the National Institute of Health NIH guideline on the conduct of research in the Ministry of Health Malaysia (MOH). Various efforts like road shows at CMEs, awareness talk in research workshops and making mandatory registration of research as requirements in policy statements have been used to promote the registration of research on this public searchable register at www.nmrr.gov.my.

CONCLUSION

The primary duty of health care professionals is to improve health and health care quality. Time and resources must not be wasted in doing research that purely generate new facts and statistics but do not translate into common good. One should use clinical research as a tool to answer only important clinical questions where patients become the research subjects through whom we obtain the answers. In the process, the patient-doctor relationship must be maintained, their safety protected and their autonomy respected. In our eagerness to become a developed nation and the paper chase of world ranking based on research publications, we need to beware of the dangers of the "publish or perish" culture. Professor of research in anaesthesia, Dr Henry Beecher had warned us of this in his paper in 1966. He attributed the increase in ethical error to:

a) Great influx of research funding.
b) Increasing emphasis that experimentation in man must precede general application of new procedures in therapy.
c) Heightened prerequisite of research publications for promotion to professorship in medical schools and university hospitals.

These demands for research superseded the supply of responsible investigators leading to unfortunate separation between the interest for science and the interest for patients.[13] The Boldt debacle demonstrates how fragile and delicate scientific publication remains. Much of the process still relies on confidence, integrity and authority of the researcher. Maintaining the integrity of the scientific literature requires[48]:

1) government institutions that have the authority to investigate and punish guilty scientists.

2) journal editors
   a) to uphold the policy of only publishing ethical research.
   b) to issue a retraction when they learn that their journal has published a tainted article.

3) research institutions to accept their responsibility
   a) to investigate alleged fraud.
   b) to investigate every article published by a scientist who has published even 1 fraudulent article.

4) All authors
   a) to self-regulate and conduct only ethical and genuine research.
   b) to take pains to avoid citing retracted articles.
   c) to issue a correction when they inadvertently cite a retracted article.

It is an obligation that the results of the research to be make publically searchable by full publication in the indexed journals or at least registered in the publically accessible research register and Malaysia has one such register, the National Medical Research Register (www.nmrr.gov.my).

No one should be spared of upholding the truth. Scientific literature is a record of the search for truth. Therefore, practising research ethics is not a choice but an obligation!

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Strong Opioids in the Management of Chronic Non-Cancer Pain

Choy Yin Choy
Consultant Anaesthesiologist, Universiti Kebangsaan Malaysia Medical Center

INTRODUCTION

Chronic non-cancer pain [CNCP] is often difficult to control with non-opioid analgesics and there has been a trend over the last decade to use potent opioids in these patients. This trend has resulted in an increase in opioid misuse and abuse particularly in some first world countries such as the US, Canada and Australia. Opioid pharmacology is complex and it is essential to have clear understanding to manage patients properly. Comprehensive evaluation and diagnostic assessment is crucial, specific techniques may be valuable in some cases. Review of literature shows that the strength of available evidence in the use of opioids for chronic non-cancer pain is weak. The use of opioids for the management of CNCP is not inherently wrong. Opioids can be very useful for the alleviation of suffering in some groups of patients. A general guide is therefore needed to help practitioners to prescribe opioids appropriately. They should also be able to assess and balance the ability of opioids to relieve pain and improve function with the potential risks of opioid abuse and addiction.

PRINCIPLES OF TREATMENT

Begin with careful patient screening and selection. Establish goals of treatment and institute a patient-physician agreement. Select appropriate regime and monitor by frequent review of the patient. Perform appropriate adjustments based on routine assessment of analgesia, activity, aberrant behavior and adverse effects. Keeping accurate and complete medical records, with great care to provide proper patient care and to avoid abuse, is essential. Elaborate discussion with patient the need for discontinuation of opioid therapy if treatment goals are not achieved within reasonable period.

TREATMENT PLAN

- The medical history and physical examination form the initial step;
- Diagnostic, therapeutic, and laboratory results;
- Discussion of risks, benefits, and limitations of treatments;
- Initiate treatment - medications, including date, type, dosage, and quantity prescribed and instructions to the patient;
- Maintain therapy and monitor by periodic review of outcomes, including documentation of functional status, preferably using validated tools;
- The physician should keep accurate and complete medical records, which include all aspects of interventional pain management and medical care. Records should remain current and be maintained in an accessible manner and readily available for review. Physicians should not prescribe scheduled drugs for themselves or immediate family except in emergency situations;
- Elaborate discussion with patient the need for discontinuation of opioid therapy if treatment fails. Review exit criteria agreed upon in patient care agreement. Clarify that exit is for patient's benefit and that exiting opioid therapy is not synonymous with abandoning pain management or giving up on the patient.

PATIENT SELECTION

Before making a decision about starting opioid therapy, take a full medical history and perform a detailed physical examination. All other management modalities that have been tried should be reviewed. This includes appropriate assessment to see if the

chronic pain is due to a neuropathic component with appropriate trial on anti-neuropathic pain drugs. Review trials of analgesic and adjuvant medications. All non-pharmacological methods should be optimized. The patients who have been selected should be stratified for the risk of drug-related behavior. Assessment of psychosocial factors and family history is important. Strong predictors of opioid abuse include: a personal or family history of alcohol or drug abuse, age, sexual abuse and psychiatric illness. Review relevant laboratory, radiological and interventional diagnostic investigations. Decision to initiate treatment with strong opioids should only be made after this point.

INITIATION OF OPIOID THERAPY

Initiation of opioid therapy should be a joint decision made by the physician and the patient after unsatisfactory treatment with all other drugs and modalities of treatment. Discussion regarding the expected goal, improvement in functional outcome, possible adverse effects and risks associated with long term opioid therapy to be carried out at the outset of opioid therapy. When a decision of opioid therapy is agreed upon, it is recommended to have a treatment agreement that outlines the responsibilities of both physician and patient, with the aim of achieving a good outcome and avoiding and minimizing the complications and risks.

A. Information, Explanation and Discussion about opioid therapy

The physician should have a detailed explanation and discussion with the patient regarding the justification for opioid therapy as well as the risks and benefits of opioid therapy. Initiation of opioid therapy is always considered a trial of therapy and that cessation of therapy ensues if it fails to achieve the planned and predetermined outcomes. Outcomes of opioid therapy that are important to consider include progress towards identified treatment goals, presence of medication-related side-effects, changes in the underlying source of the pain, and the identification of aberrant drug-related behaviors. One of the factors identified to be related to recent increase in opioid related death is the patient's non-adherence to the medication regime. It is therefore important to educate the patient and family members to decrease opioid related death.

a. Goal of therapy

The patient should have realistic goals and expectations. This can be discussed in terms of pain reduction (usually a 30% reduction in pain score is considered a desirable outcome), improvement in functional status as well as quality of life.

b. Patient Expectations

There must be a thorough discussion regarding the desired therapeutic effects, and expected effect as well as the patient's expectations. It is prudent to highlight to the patient with chronic non-cancer pain that the aim of opioid therapy is NOT for pain elimination, even though this may be achieved in some circumstances. The patient should also be made cognizant that opioid therapy is part of the multidisciplinary approach for the functional improvement as an outcome.

c. Duration of trial of opioid therapy

The patient will be monitored for improvement in the dimensions that were discussed at the point of commencement. Generally speaking, a trial period (initiation and dose adjustment) of 12 weeks will help the physician to decide whether to continue or discontinue with the opioid therapy. Discontinuation of the therapy is warranted when patients develop intolerable adverse effects, dangerous complications, exhibit drug aberrant behaviour or fail to meet the goal that had been laid out. On the other hand, opioid therapy is to be continued with close monitoring, if there is desirable outcome with minimal tolerable side effects.

d. Potential risks with opioid therapy

Discussing the potential side effects and adverse effects is also paramount to the success of opioid therapy. Patients should be counseled on the common opioid related adverse effects (e.g. constipation, nausea, sedation, drowsiness, itchiness) as well as other serious risks and complications (e.g. abuse, addiction, overdose). Potential risks associated

with long-term use or high-dose should also be discussed (hypogonadism, central apnoea, opioid induced hyperalgesia).

The management of the complications and adverse events must also be well conveyed to the patients. Concomitant administration of benzodiazepines and antidepressants, which is common among chronic pain patients, increases the risk of side effects, and patients are to be advised not to take them concurrently. Sleeping aids, especially benzodiazepines, should be tapered off if possible before starting opioid therapy.

B. Opioid treatment agreement

A written opioid management plan should be obtained when embarking on opioid therapy after a joint decision made by the patient and the physician. The treatment agreement or an opioid contract is a written document that outlines the role of the physician as well as the patient. It inscribes the goals of therapy, prescription and safe keeping of the medications, expectations for clinic follow-up and monitoring, expectations regarding concomitant therapy and conditions for discontinuation. It highlights the responsibility of the patient and the physician in an attempt to prevent serious side effects or complications.

C. Detailed documentation of the opioid therapy trial

It is recommended that there should be a detailed documentation of opioid therapy. History and findings of physical examination, psychological assessment, concomitant medical illness, psychiatric illness and patient's medications should be clearly documented. Investigations, if indicated, should also be done and included in the documentation. The indication, as well as suboptimal or unsatisfactory outcome with other therapies, alternative therapy that support the opioid therapy should be clearly documented. Any history of substance and / or alcohol abuse must be documented. It may be helpful to have a checklist before initiation of opioid therapy.

D. Choice and Dose of Opioids

Opioid selection, dosing and titration should be tailored towards the patient's health status, previous opioid experience, goals of treatment, and identified or predicted possible harms of opioid therapy. The commonly available strong opioids in our country are morphine, oxycodone and transdermal buprenorphine.

Morphine

Morphine is one of the commonest first choice strong opioid for moderate to severe pain. It is recommended that the sustained-release (SR) formulation, which has a longer duration of action, be used. Recommended starting dose for opioid–naïve patients is Morphine IR: 10 mg every 4 hours; or Morphine SR: 15 mg every 12 hours. Morphine should be avoided in patients who have impaired renal function as accumulation of the active metabolite of morphine (morphine-6–glucoronide) in the body may lead to overdose.

Oxycodone

Oxycodone is available as Oxycontin (sustained release), which is suitable for chronic pain. There are conflicting statements about its addictive tendency. Some allege that oxycodone has higher addiction tendency but this is denied by others. Recommended starting dose for opioid naïve patients: IR: 5 mg every 4-6 hours; SR: 10 mg every 12 hours.

Buprenorphine

Buprenorphine is a partial agonist at the mu receptor. It takes 2-3 days to reach steady state and lasts up to 7 days. In the opioid naïve patient, it is recommended to start at 5 mcg/hour for three days and to adjust the dose 72 hours after starting the medication. Buprenorphine carries the risk of prolonged QT interval hence it is to be avoided in patients with long QT syndrome or in patients who are taking Class IA or Class III antiarrhythmic medications.

Special precautions to be observed in patients with the following conditions (high risk):

1. Renal impairment.
2. Liver impairment.
3. Respiratory disease (COAD, Sleep disorder).

4. Patient who are taking concomitant benzodiazepines or other unauthorized medication.
5. Patient with history of substance abuse.
6. Elderly and frail patients.
7. Patient with cardiac disease (cardiac disease, chronic heart failure).

Caution:

1. Pethidine should not be used for chronic pain management.
2. Agonist-antagonist subclass of opioids e.g. nalbuphine should not be used.
3. Avoid transdermal fentanyl because of susceptibility to early development of tolerance and high cost.
4. Methadone is to be used by a pain specialist only; early referral to a pain management specialist is encouraged.

E. Exit Strategy

The following criteria can be used to determine whether a patient should discontinue from opioid therapy:

- intolerable side effects at the minimum dose required for effective analgesia;
- reasonable attempts at opioid rotation unsuccessful in producing acceptable analgesia;
- persistent non-compliance with patient care agreement;
- persistent dose escalation without adequate analgesia and deterioration in physical, emotional, or social functioning attributed to opioid abuse.

Elaborate discussion with patient around need for discontinuation of opioid therapy. Review exit criteria agreed upon in patient care agreement. Clarify that exit is for patient's benefit and that exiting opioid therapy is not synonymous with abandoning pain management or abandoning patient.

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