MALAYSIAN SOCIETY OF ANAESTHESIOLOGISTS

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CONTENTS

2 **Foreword From The President Of The Malaysian Society Of Anaesthesiologists**

3 **Preface From The Editors**

4 **Acknowledgements - Reviewers**

5 **Nitric Oxide In Anaesthesia**
Mohamed Hassan Bin Haji Mohamed Ariff

14 **Point Of Care Coagulation Testing In The Management Of Obstetric Haemorrhage**
Chan See Yun

21 **Airway Ultrasound: The New Airway Management Tool**
Adi Osman, Kok Meng Sum

31 **Real Time Clinical Debriefing: The Whys And Hows**
Rafidah Binti Atan

36 **High Flow Nasal Oxygen Therapy In Adults: A Positive Alternative**
Raha Abdul Rahman

42 **Anaesthesia And The Developing Brain**
Yoga Bhavani A/P M Shanmuganathan

50 **Managing Acute Post Operative Pain In Opioid Tolerant Patients**
Mazlila Meor Ahmad Shah

57 **The Role Of Peripheral Nerve Blocks In High Risk Adult Patients For Non-Cardiac Surgeries**
Beh Zhi Yuen, Shereen Tang Suet Ping, Shahridan Fathil

Foreword

It gives me immense pleasure as the President of the Malaysian Society of Anaesthesiologists to pen the foreword for this edition of the MSA Year Book entitled "Past, Present and Future".

The Year Book has grown from its humble origins of its first edition till date, as a showcase of peer reviewed articles of anaesthesia interest. The array of articles is diverse in nature and its contribution by our national anaesthesiologists is testament to the strength in current research within our fraternity.

I trust you will find this edition 'Past, Present and Future' with its compilation of comprehensive articles insightful, current and abreast. I take this opportunity to thank the authors for their contribution and personal time in producing this Year Book. The fraternity and I express our profound gratitude for your undertaking in dissemination of knowledge through your articles of interest.

Invited peer reviewers add astute to the every edition through their careful and due diligence for quality control. This group of esteemed reviewers are tasked to closely examine and navigate the research articles to accepted international standard. I wish to express my profound gratitude to all peer reviewers of this edition.

This Year Book is made a reality through the hard work and determination prowess of its editors, Dr Norliza Binti Mohd Nor and Dr Ahmad Suhaimi Bin Amir. Your invaluable contribution to the Year Book will be a catalyst for future editors to follow your foot steps. I thank you for a job of par excellence.

I trust you will find this Year Book enlightening and its contents of benefit to your daily practices.

Dato' Dr Hjh Jahizah Hj Hassan
President
Malaysian Society of Anaesthesiologists 2018/2019

Preface

First and foremost, we would like to express our heartfelt appreciation to all authors and reviewers of the 9th edition of MSA Year Book on behalf of the editorial board and the Malaysian Society of Anaesthesiologist. It was with the mere cooperation, enthusiasm and spirit of the authors and reviewers that we could make this MSA Year Book a success.

The theme for this edition, "Past, Present and Future", was chosen as the articles compiled for this year's production are from various anaesthetic subspecialties, written by some of the experts within the fields. The overwhelming responses from authors have been a real motivation and support in taking forward the production of this Year Book from its first inception in 2006/2007. For the success of any journal, authors have been a real motivation and the inputs from reviewers are essential and therefore merit sincere appreciation.

Pleasant reading.

Dr Norliza Binti Mohd Nor
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Nitric Oxide In Anaesthesia

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INTRODUCTION

This year, 2018, marks 20 years since the Nobel Prize for physiology and medicine was awarded jointly to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad "for their discoveries concerning nitric oxide as a signaling molecule in the cardiovascular system".[1]

HISTORICAL PERSPECTIVES

The composition of the air we breathe in consists mainly of oxygen and nitrogen; both stable and do not react with each other under normal circumstances. Nitric oxide (NOx) was first discovered by Joseph Priestly in 1772 and named nitrous air. It was known as a pollutant and is also a toxic by-product of nitrous oxide production in the early days of this anaesthetic gas production. Its presence in the atmosphere is insignificant, about 10 to 100 parts per billion (ppm), but can increase in heavy traffic conditions to about 1 ppm. At the end of a glowing cigarette it can rise to about 400 to 1,000 ppm. Initial research into NOx was from discoveries of the cell regulator labeled as endothelium derived relaxing factor (EDRF).[2,3] The physiologic impact of NOx was unleashed upon the scientific community when it was determined that EDRF and NOx were one and the same. Since this seminal paper the number of scientific papers published on NOx suddenly exploded in an exponential fashion. This phenomenon was so dramatic that the 18th December 1992 publication of Science Magazine dedicated its cover to NOx and named it "Molecule of the Year".[4] The anaeshtetic community even suggested that it could be named molecule of the decade.[5]

My interest in NOx was stimulated by these events and soon after starting work at the National Heart Institute (Institut Jantung Negara) in 1992. I wrote to the medical gas suppliers in Malaysia (Malayan Oxygen - MOX) as to how I could get my hands on NOx for use in paediatric cardiac patients with congenital heart disease and accompanying pulmonary hypertension (HPT) (personal letter to MOX in December 1994).*

NOx made such an impact to the medical scientific world that in 1998 the three American scientists mentioned earlier were jointly awarded the Nobel Prize in Physiology or Medicine. Dr Ferid Murad of Texas, visited the IJN in 2006 and gave a lecture on the history of NOx research and how it can be of use in many medical situations at present and future possibilities.#

PHYSIOLOGY OF NITRIC OXIDE

Synthesis of NOx

Briefly, NOx is a generated in vivo from the amino acid L-arginine in the presence of the enzyme nitric oxide synthase (NOS). NOx exerts its effects as a vasorelaxant via activation of guanylate cyclase (sGC), which enhances cyclic guanosine monophosphate (cGMP), ultimately resulting in smooth muscle relaxation. However, its role in biologic systems extends way beyond vasomotor control. In fact, NOx plays a dual role both as a pro- and anti-inflammatory mediator. It down regulates leukocyte responses, decreases platelet aggregation, facilitates neurotransmission, augments bronchodilation and attenuates inflammatory response.[6]

Because the half-life of NOx is only a matter of seconds, the gas acts only on cells in close proximity to where it is produced.[7] Some entities, such as pulmonary hypertension, asthma, atherosclerosis and diabetes, exhibit abnormalities in endothelial NOx production. In severe sepsis, NOS produces large amounts of NOx for protracted periods of time, and is largely responsible for the profound systemic vasodilation characteristic of the systemic inflammatory response syndrome (SIRS).

---

* Personal communications: After many enquiries, I wrote to MOX in early 1993 and only received a reply from British Oxygen on 20th January 1994, the letter which is still in my possession.

Pictures of him giving a lecture in IJN on inhaled NOx are available in the IJN archives.

Three distinct isoforms of NOS have been described.[8]

i) Neuronal NOS (nNOS or NOS I), found predominantly in nerve tissues where it modulates peripheral neurotransmission. It induces cerebral vasodilatation and plays an important role in information storage, memory, pain and behavior. This has caused much research concerning NOx role in pain modulation and also introducing new forms of analgesics.

ii) Inducible NOS (nNOS or NOS II) is induced by inflammatory reponse. Unlike the other types of NOS (I and III), NOS II is generally not considered constitutive and is independent of calcium regulation. While NOS II is expressed by immune cells such as neutrophils and macrophages, it is also present in other cell lines including hepatocytes.

iii) Endothelial NOS (eNOS or NOS III) is constitutively expressed by endothelial cells and is critical for the regulation of vascular function, more specifically vasorelaxation. Its activity is increased by calcium releasing modulators (e.g. acetylcholine, bradykinin) and vascular shear stress. It is an important modulator of systemic and pulmonary vascular resistance and in the myocardium it opposes catecholamine-induced inotropic effects.

Commercial preparation of NOx is produced by the chemical reactions of sulphur dioxide and nitric acid or via the oxidation of ammonia over platinum at 5000Centigrade. For medical grade NOx, the final product is further purified to reduce the content of the noxious byproduct like nitrogen dioxide. It is stored in aluminum alloy tanks and has a shelf life of two years.

Actions of NOx

An important consideration in the use of inhaled NOx is to understand that it has a rather narrow therapeutic range. Pulmonary hypertension and hypoxemia may be considered states of endogenous NOx deficiency, which are corrected by the administration of I - 40ppm inhaled NOx. On the other hand, levels above 80ppm provide an increasing risk of toxicity from NOx itself, or from NOx reactive products e.g. nitrogen dioxide (NO2) which must be kept at a low concentration (not more than 2ppm). Furthermore nitrogen dioxide is more readily formed when high doses of NOx are used in conjunction with high inspired oxygen content. High levels (>2ppm) can cause alveolar capillary leak and airway hyperactivity. Higher levels of nitrogen dioxide (>10ppm) induce alveolar damage and can lead to ARDS.[9]

Most actions of NOx are mediated through its activation of soluble enzyme guanylate cyclase, which catalyzes the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cyclic GMP). Cyclic GMP has two major actions: relaxation of vascular smooth muscle and suppression of the inflammatory response. Cyclic GMP is converted to GMP by phosphodiesterase I and V. Thus, the local action of NOx can be enhanced by the administration of a selective phosphodiesterase V inhibitor, such as sildenafil. NOx itself is rapidly inactivated by binding to intracellular heme and haeme proteins (oxyhaemoglobin, oxymyoglobin, guanylate cyclase, cyclooxygenase, cytochrome P450). This accounts for the selective effect of inhaled NOx on the pulmonary circulation; it is inactivated in the blood and therefore does not enter the systemic circulation.[10]

Methylene blue blocks soluble guanylate cyclase and blunts vasodilation without inhibiting NOx production, and in low doses have shown some favorable effects on regional perfusion. A recent article on the use of methylene blue to counteract vasoplegia that is unresponsive to traditional vasoconstrictors looks promising.[11]

In addition to vascular smooth muscle relaxation, NOx plays other important roles in inflammation. It reduces platelet aggregation and adhesion, inhibits several features of mast cell induced inflammation, and serves as a regulator of leukocyte recruitment. NOx also acts in the host's response to infection. The

production of NOx is increased during host defense, and genetic inactivation of iNOS enhances microbial replication in animal models.

Inhaled NOx provides selective pulmonary arterial and venous vasodilation. The effect is dose dependent in the range of 5-40ppm and is proportionately greater with increasing degrees of pulmonary vasoconstriction.[12] Elevated pulmonary vascular resistance and mean pulmonary artery pressure (MPAP) are consistently decreased. The decrease in right ventricular afterload in turn may enhance right ventricular performance, with improvement in ejection fraction and end-diastolic volume.

Inhaled nitric oxide improves oxygenation in hypoxemia due to acute ventilation-perfusion (V/Q) mismatch. Intrapulmonary shunt is improved because inhaled NOx is carried to the alveoli with best ventilation, where it increases pulmonary blood flow by local vasodilation, and is then rapidly inactivated by binding to hemoglobin. The improvement in oxygenation is often maximal with low doses of inhaled NOx i.e. 0.5-10ppm. The response is variable, unpredictable and may be transient. Inhaled NOx has been demonstrated to have some bronchodilator effects, but these appear to be mild and variable.[13]

Nitric Oxide Toxicity

1. Methaemoglobinemia

The affinity of NOx for hemoglobin is 1500 times greater than carbon monoxide. NOx oxidizes the ferrous ion (Fe^{2+}) in hemoglobin to ferric ion (Fe^{3+}), to create methaemoglobin (MetHb), which is incapable of binding oxygen. MetHb shifts the hemoglobin dissociation curve to the left thus decreasing tissue oxygen delivery. Normally MetHb levels are kept below 2% by red cell MetHb reductase. Excess production of MetHb appears to be directly related to the dose of inhaled NOx and is extremely uncommon when the dose is kept less than 20ppm. NOx use in neonates (as in congenital hearts with pulmonary hypertension) has to be monitored regularly for MetHb since the persistent presence of fetal haemoglobin which also shifts the oxygen dissociation curve to the left will further be additive and potentiate the effects of MetHb on oxygen delivery to the neonates. Furthermore neonates and small children have a smaller pool of hemoglobin to compensate for this effect. MetHb can be treated by infusion of methylene blue (which increases levels of MetHb reductase) or ascorbic acid.[14]

At IJN, our protocol is to measure MetHb levels before starting inhalational NOx therapy and then to continue on a 12 hourly MetHb monitoring as long as the patient is on NOx therapy. The accepted high level is 3% and if it exceeds 5%, the NOx should be reduced in concentration or discontinued but other pharmacological means (milrinone or glyceryl trinitrate infusion) are instituted to reduce pulmonary hypertension. We once had a child who was on inhalational NOx therapy over a short period of time and the MetHb level was 39%; immediate reduction of NOx was instituted and methylene blue given intravenously at a dose of 1mg/kg over 10 minutes. The MetHb level reduced dramatically to 7.6% over 30 minutes. However in the next hour the nurses were frantically calling me because the patient's urine had turned blue (due to the methylene blue - a never seen before phenomenon in our ICU).

2. NOx Reactive Byproducts - Nitrogen Dioxide NO2

NOx reacts very rapidly with oxygen to form NO2. This is toxic to tissues especially the lungs. NO2 formation is accelerated by utilizing high NOx concentrations together with high inspired oxygen (which is usually the casein lung diseases). In the lung it causes alveolar-capillary leak and airway hyperactivity. It is recommended to keep NO2 levels low, preferably at less then 1ppm (most delivery devices will alarm when the level of NO2 is 2ppm).

3. Rebound PHT and Hypoxaemia with NOx discontinuation

Sudden discontinuation of NOx in the presence of reactive pulmonary hypertension can precipitate acute pulmonary hypertensive crisis with resultant right ventricular failure and cardiovascular

collapse.[15] This may be explained by several mechanisms:

i. NOx synthase downregulation due to extrinsic NOx administration

   OR

ii. inactivation of NOx synthase by free peroxynitrite formation

It should also be noted there is also a ceiling effect of NOx to improve hypoxaemia and further increase in NOx delivery will not be beneficial to improve ventilation perfusion mismatch. Thus it is usually not necessary to administer NOx at values of more than 40ppm for long periods of time. To this end, we always make it a point to have a second spare tank connected in series with the delivery system. This is to avoid sudden drops in NOx delivery at odd hours of the day precipitating an acute pulmonary hypertension crisis.

Weaning of NOx is also taken in stages of reducing NOx concentration by 2-4ppm at every stage. This is usually supplemented with the addition or increasing cardiac support with milrinone or glyceryl trinitrate in combination with other inotropes. Sometimes the pulmonary hypertension can be resistant to inhaled NOx administration, even after a few days. We have included the phosphodiesterase inhibitor, sildanefil to supplement the effect of NOx on pulmonary pressures. In children, we administer sildanefil in syrup form starting at 0.25mg/kg per day and increasing it to 1mg/kg/day in divided doses.[16]

Method of NOx Delivery

When I first enquired about acquiring NOx, the major question posed at that time was how to deliver NOx in minute but accurate amounts to patients in the ICU and operating theatre. An ideal delivery system for NOx should have certain requirements namely:

i. Must be simple, safe and reliable because it is mainly used in critically ill patients.

ii. Must be accurate and not vary with the ventilatory mode and during different phases of the ventilation.

iii. Must be able to monitor and measure concentration of oxygen, NOx and also nitrogen dioxide.

iv. The availability of a second backup NOx tank.

v. Ability to be used during transport.

Anaesthesia ventilators that are incorporated with the anaesthesia machine pose a particular challenge in NOx delivery because of recirculation of expired gases, which could cause NOx to build up to undesirable concentrations. Stand alone or critical care ventilators in the operating theatre could be employed during anaesthesia in the operating theatres.

In the intensive care unit, the NOx delivery can be achieved either by in circuit delivery or a commercial system that is incorporated with the ventilator. However, even if the fresh gas flow is kept at or above the minute ventilation, the NOx flow readings may be rendered inaccurate by anaesthetic gases and recirculation of NOx.

Our initial efforts to obtain the NOx gas were futile as the companies selling it (British Oxygen and its local subsidiary Malaysia Oxygen) has classed it as an experimental gas making its purchase a red tape headache. While at a conference in Montreal, Canada, I managed to contact a Canadian company to supply NOx and also its delivery system. Our first purchase of a NOx delivery system was a Pulmonox II model in 1995. The NOx tank has 800ppm NOx in carbogen. This system delivers NOx into the ventilator end of the inspiratory limb circuit and monitors the oxygen, NOx and nitrogen dioxide levels at the patient end of the inspiratory limb. Due to its NOx delivery being in circuit rather than in ventilator delivery, at a fixed NOx flow into the circuit, the concentration of NOx tend to vary according to minute ventilation and phase of respiration.

Our subsequent purchase of NOx delivery system by Ohmeda (I-NOvent), which uses an injector module

that can inject proportionally to the measured ventilator flow to provide the desired dose. The system can also be adapted to a manual bag system for transport, providing NO at 20ppm. Currently, the Ohmeda Company in Malaysia has stopped selling and servicing the I-NOvent systems. We are using the NOxBOx system by Lifecare Medical Systems which has a distributor in Malaysia and Singapore. It also has a portable module, useful when transporting patients dependent on NOx between the ICU and operating theatre. This system is similar to the Ohmeda in circuit delivery system. A newer model recently introduced by the NOxBOX incorporates the injector module to keep the NOx concentration relatively constant when the ventilator mode and flow rates are being manipulated and changed. This is similar to the I-NOvent system.

CLINICAL APPLICATIONS

Inhaled NOx has its main effects on the lungs and the heart. Inhaled NOx provides selective pulmonary arterial and venous vasodilation. The effect is dose dependent in the range of 5-40ppm, and is proportionately greater with increasing degrees of pulmonary vasoconstriction. This effect causes the right heart afterload to decrease with resultant improvement of right heart function seen in an increase in right ventricular output and lowered right ventricular end-diastolic pressure. Coronary perfusion pressure is maintained which is of particular benefit in the presence of right ventricular ischaemia. Inhaled NOx is immediately inactivated by binding to haemoglobin in the lungs. As such the effect of inhaled NOx on vasodilation is only seen in the pulmonary circulation and not in the systemic circulation. This is in contrast when systemic vasodilators are used; they not only reduce pulmonary pressures but they also will have systemic hypotension which can compromise an ischaemic heart.[17]

Inhaled NOx improves oxygenation by reducing ventilation-perfusion mismatch. This is due to the fact that inhaled gases tend to go to areas where it is ventilated and NOx being a vasodilator will increase blood flow to areas of the lung where there is ventilation. In areas of the lung where there is little or no ventilation, the body's reflex mechanism of hypoxic pulmonary vasoconstriction will divert blood away from unventilated lungs. This improvement in oxygenation is seen at low doses of inhaled NOx and has a plateau effect once higher doses are used (>20ppm). Inhaled NOx also has some mild and variable bronchodilator effects.

Inhaled NOx in Cardiovascular Medicine

Inhaled NOx has had a major impact predominantly in cardiology, cardiac surgery and intensive care medicine. Use of inhaled NOx in pulmonary hypertension in the neonate period (PPHN) represents the most convincing evidence thus far of a positive impact on outcome, and is the basis for its current approval by the FDA. A number of multicenter studies has indicated that inhaled NOx improves oxygenation and decreases the need for ECMO from 55-70% to about 40% of patients.[18] However, this has not translated into improved survival rates compared with conventional therapy.

Inhaled NOx has its major impact in surgery for congenital cardiac lesions with pulmonary hypertension. Furthermore inhaled NOx and in combination with high frequency ventilation may decrease the requirement for ECMO especially in PPHN. A good review of NOx application in the neonatal intensive care unit by Porta et. al. is worth reading.[19]

The most widely used indication in cardiac surgery has been the effect of iNO in reducing pulmonary vascular resistance and pulmonary pressures, especially in the setting of pulmonary hypertension (PHT), which is the most critical determinant of right ventricular afterload, during impending right ventricular failure. In theory, this particular effect could be achieved by any broad intravenous vasodilator including the NOx donor, nitroglycerin or sodium nitroprusside or phospodiesterase inhibitors or calcium antagonists. However, these agents would also produce systemic vasodilation potentially reducing RV perfusion pressure. This could be disastrous in the setting of distending

RV, where elevated intraventricular pressure is already compromising myocardial perfusion leading to myocardial ischemia, further reduction in contractility and diastolic function, triggering a downward spiral that can only lead to hemodynamic collapse.[20] Moreover, all these intravenous vasodilators would dilate all perfused microvessels in the lung even in non-ventilated regions and thus may cause ventilation-perfusion mismatch in the lung increasing pulmonary shunt circulation with resultant effects of arterial hypoxemia. These unique effects of inhaled NOx can be utilized for hemodynamic purposes in conditions of PH with impending RV failure or for oxygenation purposes in the setting of hypoxia.

Inhaled NOx would have a number of potential benefits in the intra and postoperative management of patients undergoing single and double lung transplantation. In a landmark study in lung transplanted patients, Meade and coworkers tested the hypothesis that universal usage of inhaled NOx would lead to a 50% reduction in the length of ventilation and improve ischaemia-reperfusion injury.[21] However, they did not detect a significant effect of inhaled NOx administered 10 minutes after reperfusion on physiologic variables or outcomes in lung transplant patients.

Many patients with end-stage heart disease have longstanding severe pulmonary hypertension that persists and can worsen after cardiopulmonary bypass. The transplanted heart easily develops acute right-sided failure because the compliant new right ventricle is unused to high pulmonary vascular resistance of the recepient. Inhaled NOx can decrease elevated MPAP and thereby protect the right ventricle, while maintaining left ventricular filling by increasing pulmonary arterial blood flow. At IJN we have used inhaled NOx in our armementarium when managing heart and lung transplantation.

Apart from heart and lung transplantation, inhaled NOx is also useful when implanting ventricular assist devices (right and left ventricular devices - RVAD and LVAD). LVAD filling and stroke volume is very dependent on the sufficiency of pulmonary venous return to the left atrium and ventricle. Elevated pulmonary vascular resistance impedes pulmonary blood flow and restricts LVAD filling. Almost all patients requiring LVAD insertion have some degree of pulmonary hypertension, and since the right ventricle is usually involved in global cardiomyopathy, it may quickly fail once there is good cardiac output from the assisted left ventricle. In this setting, the perioperative use of inhaled NOx is very effective at decreasing high pulmonary vascular resistance and protecting the fight ventricle, while enhancing LVAD filling and flow.[22]

Inhaled NOx in ARDS

The utilization of inhaled NOx to treat patients suffering from ARDS dates back to the early 1990s.[23] In patients with ARDS who have acute pulmonary hypertension, inhaled NOx predictably decreases elevated pulmonary vascular resistance without causing systemic hypotension. Mean pulmonary artery pressure and right ventricular afterload are decreased as a consequence, and right ventricular function (as assessed by ejection fraction) may improve.

Permissive hypercapnia is a strategy used in the management of ARDS to attempt to decrease ventilator induced lung injury caused by barotrauma or volutrauma.[24] However, hypercapnia exacerbates pulmonary vasoconstriction. Inhaled NOx attenuates this increase and thus facilitates the use of permissive hypercapnia. At low doses (5-10ppm) it also attenuates neutrophil sequestration and oxidant activity, i.e. it appears to have an anti-inflammatory effect. Prospective studies have not been able to demonstrate a significant improvement in mortality.[25] This could be due to the fact that in many cases, ARDS mortality is related to sepsis and multisystem failure rather than oxygen toxicity or ventilator-induced lung injury.

Other Uses of Inhaled NOx

In primary pulmonary hypertension, inhaled NOx is used to test pulmonary vascular reactivity. A positive response (i.e. decreased MPAP) suggests a favorable

response to long term vasodilator therapy with prostacyclin or calcium channel blockers. The bronchodilator action of inhaled NOx appears to be rather weak in patients with bronchospastic COPD. There has been some controversy in its role in the treatment of COPD-induced hypoxemia, which is related to ventilation-perfusion mismatch rather than intrapulmonary shunting. Some studies found that inhaled NOx worsened oxygenation in these patients, presumably by overcoming hypoxic pulmonary vasoconstriction (HPV).[26] In others, where inhaled NOx was added to supplemental oxygen, a beneficial effect has been observed on both hypoxemia and pulmonary hypertension. A ceiling effect on oxygenation improvement was noted at 5ppm inhaled NOx, whereas a progressive decrease in MPAP was achieved through the dose range of 5-20ppm.

Other areas where NOx may be helpful is in managing sickle cell crisis. Sickle cell disease results from the genetically induced replacement of the amino acid glutamine by valine in the hemoglobin ß-chain, resulting in the formation of HbS. The oxygen dissociation curve of HbS is shifted to the right and releases oxygen readily. Unfortunately deoxygenated HbS tend to aggregate into large polymers that deform red blood cells causing sickling and precipitate causing occlusion of vessels. Inhaled NOx at high concentrations (80ppm) can shift the HbS oxygen dissociation curve back towards normal, hence can be protective in such patients.[27]

Future Applications of NOx

NOx plays a central role in cell regulatory pathways and is essential in the mediation of leukocytic cytotoxicity via superoxide. Several studies have highlighted the roles of NOx in the regulation of tumor-targeting immunological processes.[28] The role of NOx in cytotoxic pathways has broadened research into potential applications of NOx-donors in the treatment of cancer. A common idea emerging in recent literature related to NOx and cancer is that the capacity of NOx to enhance or inhibit tumor proliferation is dependent upon the concentration of NOx. Higher levels of NOx are correlated with induction of tumor cell apoptosis while lower levels have been correlated with enhanced tumor survival.[29]

A number of NOx-donors have been investigated as potential cancer therapeutics, as recently reviewed by Huerta et a.[30] Examples of these include organic nitrites glyceryl trinitrite (GTN) and metal-nitrosyl complexes with sodium nitroprusside (SNP) are some of the proposed new drugs in experiment. However these are in the early stages of research and we will await future data.

NOx is an important neurotransmitter involved in the nociceptive process. In the dorsal horn of the spinal cord it contributes to the development of central sensitization. Experimental data have also demonstrated that NOx inhibits nociception in the peripheral and also in the central nervous system. The production of NOx by nNOS in the central nervous system requires the influx of calcium. This influx occurs through, and is dependent on activation of N-methyl-D-aspartate (NMDA) receptors.[31] The involvement of NO in nociceptive processes is supported by experiments in which inhibitors of NOS were used in order to reduce NOx production.

Several lines of evidence have indicated that NOx induces analgesia and also that it mediates the peripheral and central antinociceptive effect of analgesic compounds, such as opioids and non-steroidal anti-inflammatory drugs.[32] Thus the clinical use of NOx should be considered as an important strategy for pain therapy. In fact, modification of pre-existing analgesic and anti-inflammatory drugs by addition of NOx-releasing moieties has been shown to improve the analgesic efficacy of these drugs and also to reduce the expression of their side effects.

The cyclooxygenase inhibitor nitric oxide donors (CINODs) are an example of a new class of anti-inflammatory/analgesic drugs generated by addition of a NOx generating moiety to the parent non-steroidal anti-inflammatory drugs.[33] This

strategy reduces the gastro-intestinal toxicity of NSAID and confers a potent anti-inflammatory activity. NCX-701 or nitroparacetamol is a new drug resulting from the combination of paracetamol and a nitroxybutyroyl moiety which releases nitric oxide at a low but steady level. It has been shown to be effective in acute nociception and in neuropathic pain, with a better outcome when compared to paracetamol alone, since the combination of these molecules also results in an enhancement of the analgesic activity of paracetamol. In addition, whereas paracetamol lacks antiinflammatory activity, NCX-701 might reduce inflammation.[34]

The most exciting new frontier in NOx application is in reducing inflammatory response especially reperfusion injury while on cardiopulmonary bypass. Gaseous nitric oxide has been demonstrated to have a myocardial protective effect following ischemia-reperfusion. The delivery of gaseous nitric oxide to the cardiopulmonary bypass circuit for children undergoing cardiac surgery, results in myocardial protection, improved fluid balance, and an improved postoperative intensive care unit course.[35] This recent article is something we hope to try out soon.

CONCLUSION

Nitric oxide is a unique molecule, historically relegated as an unwanted pollutant in the atmosphere and later being named as a molecule of the year by the scientific community. It has achieved considerable acceptance for perioperative administration in lung and heart transplantation and LVAD insertion. Our main use of NOx at present has been limited to pulmonary hypertension and ARDS.

There is still much to learn about its regulatory function in the body and to this end newer areas of research as in tumour therapy, pain management, lung diseaseand inflammatory response modulation especially sepsis. In India, the area of NOx research is surging forward with the formation of a scientific society, the 'Society for Nitric Oxide and Allied Radicals (SNOAR)' in 2013 in Delhi.[36] Hopefully more research and uses on NOx will be seen.

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Point Of Care Coagulation Testing In The Management Of Obstetric Haemorrhage

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INTRODUCTION

Obstetric haemorrhage is a major risk factor for maternal morbidity and mortality worldwide. The causes are multi-factorial which makes its occurrence and severity unpredictable. The underlying haemostatic imbalances such as consumptive and dilutional coagulopathies may develop during haemorrhage. Monitoring of the coagulation status in these patients may be crucial for effective haemostatic management, goal-directed therapy, and improved outcomes. In UK, postpartum haemorrhage has been reported to be responsible for 73% of all severe morbidity during pregnancy and is the most common obstetric cause of intensive care admission.[1]

Guided perioperative management of coagulopathy with the use of point of care testing (POCT) has been shown to significantly reduce transfusion requirements. Conventional tests of coagulation have a long response time and can, in certain circumstances, be misleading.[2] Haemostasis requires the presence of ample coagulation factors and platelets for sufficient thrombin generation and adequate fibrinogen levels (the substrate for fibrin production) to produce a stable clot. Viscoelastic testing (VET), including thromboelastography (TEG) and rotational thromboelastometry (ROTEM) measure changes in clot tensile strength over time, providing information on the dynamics of clot formation. VET give a rapid description of the cell-based model of coagulation together with both cellular and humoral contributions to coagulation. The administration of fresh frozen plasma, platelets, cryoprecipitate, factor concentrates and antifibrinolytic drugs can be guided by specific patterns of VET measurements.[3]

POCT is an integral part of the second pillar of patient blood management (PBM). With POC testing, the causes of intra- and post-operative bleeding can be detected adequately and timely, treated in a targeted way and prevent massive bleeding and haemorrhagic shock. Transfusion management can be optimised and transfusion related adverse events and complications can be avoided. Several studies have shown that POCT results in a reduction of transfusion requirements, a shortening of intensive care and hospital stay as well as an improvement in patient outcome and a reduction of hospital costs.

TEG and ROTEM are increasingly used at the POC for clinical coagulation assessment. Compared with laboratory coagulation assessment, TEG and ROTEM-based tests have increased sensitivity for identifying some abnormalities in the coagulation process.[6] Laboratory tests are typically performed on plasma and end with formation of the first fibrin strands, whereas TEG/ROTEM-based monitoring is performed in whole blood, and assess the process from coagulation initiation through to clot lysis, including clot strength and stability. TEG/ROTEM-based assessment can therefore provide a sensitive assessment of how changes in haemostatic balance impact upon coagulation. This allows a more complete diagnosis of coagulopathy, and rapid evaluation of the effects of haemostatic intervention on coagulation.

BASIC INFORMATION REGARDING TEG AND ROTEM

TEG/ROTEM-based monitoring can be performed at the POC. Viscoelastic properties of the sample are recorded to produce a profile of coagulation dynamics (Figure 1),[7] which is used to generate values indicating the speed and quality of clot formation (Table I). Importantly, several of these values can be obtained within minutes (e.g. CT, A5, A10) and are therefore potentially useful for guiding rapid haemostatic intervention.[8,9]

Table I: Parameters recordable using TEG and ROTEM[4]

Parameter Recorded	TEG® Value	ROTEM® Value	Description
Coagulation initiation	*r* (reaction time)	CT (clotting time)	Time taken to reach an amplitude of 2mm
Clot formation	*k*	CFT (clot formation time)	Time taken for amplitude to increase from 2 to 20mm
	α^{o} (alpha angle)	α^{o} (alpha angle)	Tangent of the slope between amplitude at 2mm and at 20mm
Clot strength/quality		A5, A10, A15, etc	Clot amplitude reached 5, 10, 15min after Ct has passed
	MA (maximum amplitude)	MCF (maximum clot firmness)	Maximum amplitude reached
	G (clot rigidity)	MCE (maximum clot elasticity)	Calculable from MA and MCF valuse*
Clot lysis	LY30 (lysis)	LI30 (lysis index)	% of MA/MF remaining 30min after MA/MF has been reached
		MI (maximum lysis)	Greatest % decrease in MCF observed during assay period

Parameters recordable using TEG® and ROTEM® -based tests. * G=(5000xMA)/(100-MA); MCE=(100xMA)/(100-MA)

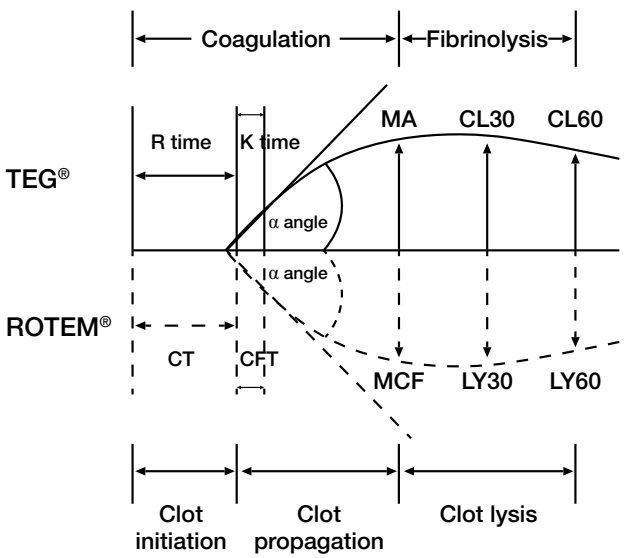

Figure 1: Comparative tracing of a normal TEG® and ROTEM®.[5]

The bold line represents TEG® and corresponding ROTEM® tracing is represented by dotted line. R, reaction time; α angle, slope between R and K for TEG® and slope of the tangent at 2mm amplitude for ROTEM®; MA, maximum amplitude; CL 30, clot lysis at 30min; CL 60, clot lysis at 60min; CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness; LY30, lysis at 30min; LY 60, lysis at 60min

Figure 2 below showed the schematic representation of a healthy and coagulopathic coagulation profiles of parturients using ROTEM and TEG-based coagulation profiles in the peripartum period. Generally, the shapes of the graphs are similar, the differences being the value names.

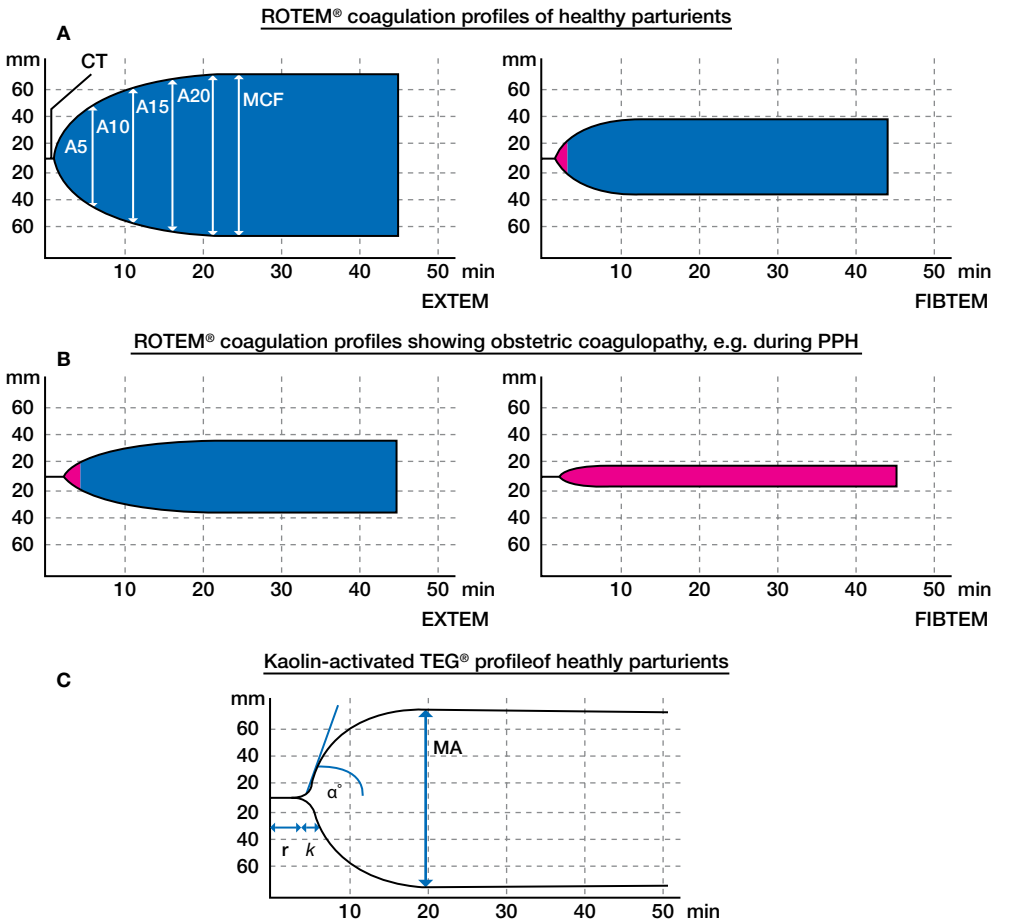

Figure 2: ROTEM- and TEG-based coagulation profiles in the peripartum period.[10]

Schematic representation of healthy (A) and coagulopathic (B) obstetric coagulation profiles for EXTEM and FIBTEM tests. Coagulation parameters which are typically reported for these tests are indicated in the top-left panel. The profiles reflect EXTEM and FIBTEM test results reported for healthy patients around the time of delivery,[11,15] and for patients with PPH associated with poor fibrin-clot quality.[8] Clot lysis parameters are not indicated; if (hyper) fibrinolysis is suspected, an APTEM test can be performed. APTEM profiles mirror EXTEM profiles under healthy conditions, and show enhanced coagulation vs EXTEM during fibrinolysis.[16] (C) is a healthy, obstetric coagulation profile for kaolin-activated thrombelastography, with typically reported parameters indicated for this test. The profile reflects kaolin-TEG values observed for healthy patients in the third trimester,[17] and before elective Caesarean delivery.[18] Owing to the lack of available evidence for typical test results, profiles are not presented for kaolin-TEG during PPH, or for other TEG-based tests in obstetric patients. α°, alpha angle; A5-A20, clot amplitude at 5-20min after CT; CT, clotting time; MA, maximum amplitude; MCF, maximum clot firmness; PPH, postpartum haemorrhage; r, reaction time.

LIMITATIONS OF STANDARD LABORATORY COAGULATION TESTS

Utility of standard laboratory coagulation testing in obstetric haemorrhage management is hampered by long assay turnaround times (typically 30-60min).[11,12] Slow turnaround is incompatible with efficient management of bleeding in obstetric haemorrhage, particularly as the result will not reflect the current haemostasis and delayed treatment is a strong predictor of poor outcome, including maternal death.[13]

Traditionally, haemostatic intervention is guided either by formulaic replacement or by clinical judgment alone. Such practice may result in unnecessary and/or inappropriate transfusions.[14] A retrospective analysis reported that 72% of fresh frozen plasma (FFP) transfusions would not have been given if transfusion guidelines had been adhered to, but it is not possible to define whether inappropriate transfusion triggers were used, or if delays in obtaining test results led to inappropriate treatment. Moreover, depleted fibrinogen levels in many patients suggested that alternative replacement therapy may have been more effective than FFP.[10]

DISCUSSION

This is based on my experience in using ROTEM guided resuscitation in obstetric haemorrhage in King Edward Memorial Hospital (KEMH) in Perth, Australia. KEMH is a tertiary referral centre for Obstetric and Gynaecology in Western Australia. ROTEM has been utilized as part of goal directed resuscitation since 2010 and usually needs about 6 to 9 months for its familiarization. It is based in laboratory with computer centralization and it is a 24-hour service.

The most common finding in ROTEM is usually a normal result. The elevated fibrinogen level is due to the physiological changes in pregnancy. Normal level in third trimester 4-6g/L. women are designed to have some degree of bleeding thus utilising the fibrinogen. Normal results are still useful to avoid unused thawed blood products.

I would like to highlight a case of a parturient who developed delayed postpartum haemorrhage secondary to uterine atony, whose resuscitation was guided by a serial ROTEM. Furthermore, this case emphasized how the administration of specific blood products and hemostatic agents guided by the TEG/ROTEM can optimize patient outcome compared to traditional 1:1:1 ratios of packed red blood cells (PRBCs)/fresh frozen plasma (FFP)/ platelets in severely hemorrhaging patients.

A CASE OF ROTEM GUIDED RESUSCITATION

27 year-old G1P0 at 37 weeks period of gestation was diagnosed with MELAS syndrome (Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) at 7 weeks gestation when she presented with a classical temporal stroke syndrome. Radiological imaging showed that she had normal cerebral blood vessels and on further investigations, she was confirmed to have mitochondrial disorder which was the cause of her cerebral infarct. Due to the diagnosis, she was also investigated further and was found to have Wolff-Parkinson-White syndrome and an ECHO showed that she had mild concentric hypertrophy and possible hypertrophic cardiac disease. She underwent Caesarean delivery under combined spinal epidural. Her indication for Caesarean delivery was cephalopelvic disproportion and also prevention of straining which may cause a rise in the intracranial pressure. Her baseline serum lactate was 2.2mmol/l. She was stable throughout the operation and post operatively she was transferred to the high dependency unit (HDU). After 2 hours in HDU, she became haemodynamically unstable with her pad fully soaked. She was promptly transferred to the operation theatre for Examination Under Anaesthesia (EUA) and Bakri Balloon insertion under General Anaesthesia.

Her initial fibtem was 3mm, slightly prolonged clotting time (Extem CT 118s) which was the result of low fibrinogen. Her platelet level was 65000. She was transfused with cryoprecipitate, FFP and platelets.

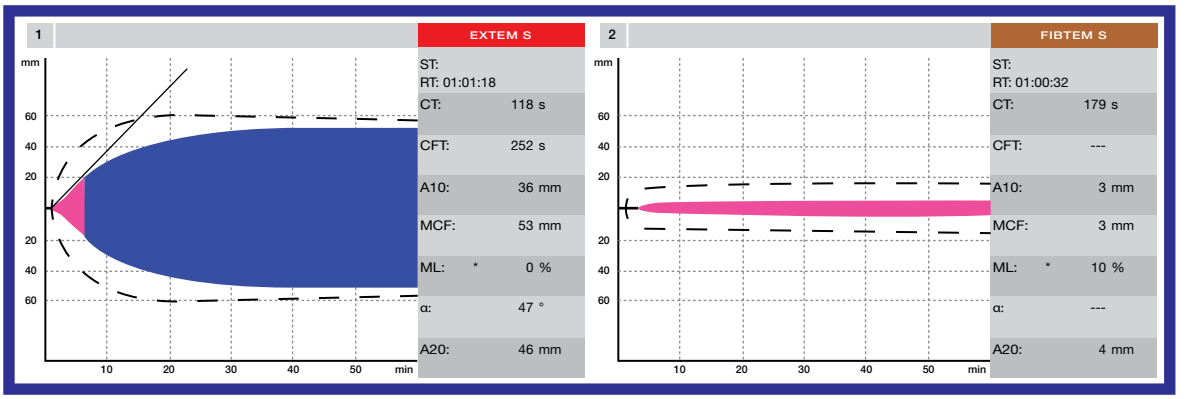

Figure 3: Her initial ROTEM results were as shown

In this case, tranexamic acid (TXA) treatment was initially withheld, given the absence of fibrinolysis on the early ROTEM results. However, subsequent ROTEM showed that she developed severe hyperfibrinolysis, her clot firmness was 5mm and this was reversed with tranexamic acid.

The patient's coagulopathy improved within 4 hours following ROTEM goal-directed resuscitation. She remained stable but with transient respiratory insufficiency that required mechanical ventilation and acute kidney injury with lactic acidosis which required a one-time haemodialysis. She eventually made a full recovery.

This case emphasizes how the administration of specific blood products and hemostatic agents guided by the ROTEM can optimize patient outcomes compared to traditional 1:1:1 ratios of packed red blood cells (PRBCs)/fresh frozen plasma (FFP)/platelets in severely hemorrhaging patients.

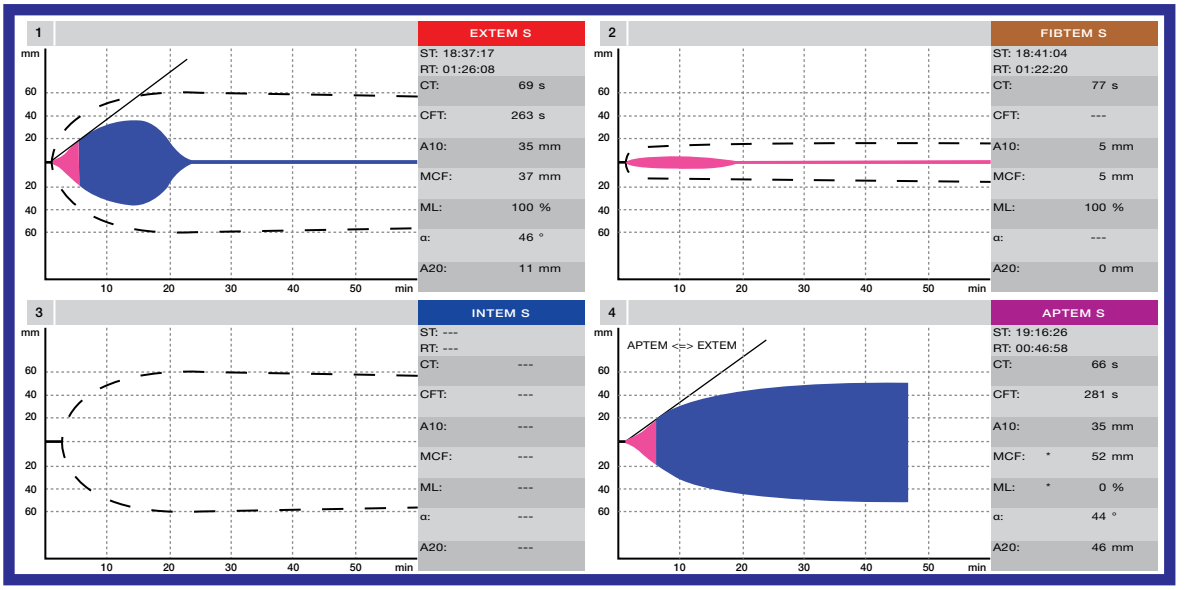

Figure 4: Her subsequent ROTEM results were as shown

CHANGE OF PRACTICE

Recombinant Factor VIIa

In KEMH, the usage of ROTEM showed the evolution of managing blood products. The usage was reduced markedly and wastage was avoided as well as a reduction in transfusion related complications. They have managed to avoid using recombinant Factor VIIa (rFVIIa) in managing obstetric haemorrhage since the availability of ROTEM guided resuscitation. It is recommended to restrict the use of rFVIIa to its licensed indications, as outside these indications, the effectiveness of rFVIIa in reducing transfusion requirements and mortality remains unproven. Furthermore, the risk of arterial thrombo embolic events, as well as the costs, are high with the usage of rFVIIa.[6]

COLLOIDS

The application of ROTEM in clinical practice has reduced the usage of colloids as starches interfere with coagulation. Starches interfere with fibrinogen polymerization and clot strength which can be seen in ROTEM or TEG.

Doubts also exist about the precision of Clauss fibrinogen measurement after volume replacement with hydroxyethyl starch (HES). Haemodilution using HES can lead to the over-estimation of Clauss plasma fibrinogen levels by 120%.[19] The amount of HES used appeared more influential than molecular size; 50% haemodilution resulted in greater fibrinogen over-estimation than 30% dilution. Compared with haemodilution using isotonic saline or albumin, HES also decreases fibrin-based clot firmness measured using thromboelastometry.[20] Thus, HES provides a twin hazard by compromising clot quality while over-representing plasma fibrinogen.

OTHER USAGES

1. Bleeding disorder and thrombocytopenia, when is it safe to do an epidural?
   ROTEM is able to provide information regarding platelet function and aggregation despite low count. Clot firmness measurement using ROTEM is quite accurate.
2. Preoperative ROTEM assays that include fibrin clot and platelet interaction may detect patients at increased risk for postoperative thromboembolic complications after major non-cardiac surgery.[21]

SUMMARY OF ADVANTAGES AND DISADVANTAGES OF VET[22]

Advantages

- Fast turnaround versus lab-based testing
- Whole blood used allow interaction between plasma clotting factors, platelets and red cells
- Real time visual display of clot evolution at point of care
- Reduction in non-evidence based transfusion, reduction in transfusion related complications

Disadvantages

- Measure coagulation under artificial conditions in a cuvette rather than flow within an endothelialized blood vessel
- Training and competency are needed
- Rigorous quality assurance standards more difficult to institute outside laboratory
- More expensive than standard coagulation testing

CONCLUSION

Worldwide, obstetric haemorrhage remains a major cause of maternal morbidity and mortality but, unfortunately, it is difficult to predict due to various factors. Rapid diagnosis and correction of coagulopathy is vital. Current approaches to management of obstetric haemorrhage are hampered by limitations of laboratory coagulation testing, unfamiliarity with TEG/ROTEM based monitoring and limited understanding of the complex pathophysiology that underlie obstetric haemorrhage.

The opportunity of using ROTEM in managing obstetric haemorrhage during my stint in Perth is invaluable. I sincerely hope that the knowledge gained can be applied in our local settings to improve our healthcare services. Australia is known to have a very low maternal mortality rate of 6 per 100000 live births compared to Malaysia of 40 in 2015.[23]

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Airway Ultrasound: The New Airway Management Tool

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INTRODUCTION

The role of ultrasound in the medical field has expanded beyond the radiology department. Bedside Point-Of-Care Ultrasound (POCUS) gained the upper hand for being simple, non-invasive and portable. Traditional beliefs that ultrasound is futile in the imaging of air-filled structures has been refuted. Studies in recent years have integrated the use of upper airway ultrasound into POCUS examination, a paradigm shift in upper airway assessment.[1] This article highlights the role of upper airway ultrasound in airway assessment and management.

APPLIED SONOANATOMY OF THE UPPER AIRWAY

Ultrasound is operator-dependent. Basic comprehension of ultrasound physics and airway anatomy, transducer selection, patient positioning, and probe orientation contribute to accuracy of interpretation.

Structures to be identified

- Tracheal Cartilage
- Cricoid Cartilage
- Thyroid Cartilage
- Hyoid bone
- Cricothyroid membrane
- True Vocal Cords
- False Vocal Cords
- Esophagus

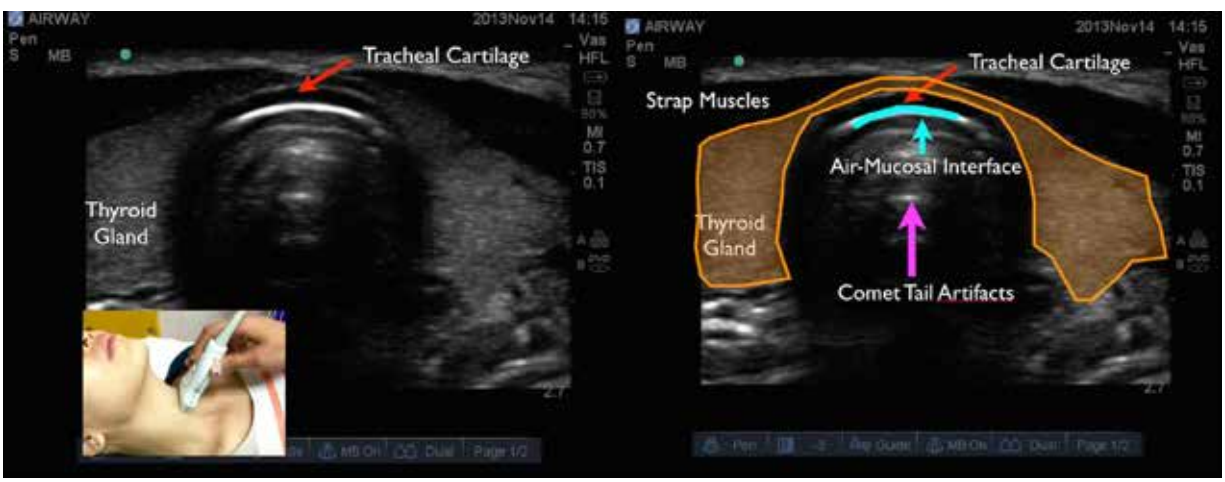

Figure 1: Tracheal cartilage is seen as an inverted 'U' in transverse plane. The Air-Mucosal Interface is formed by reverberation artifacts

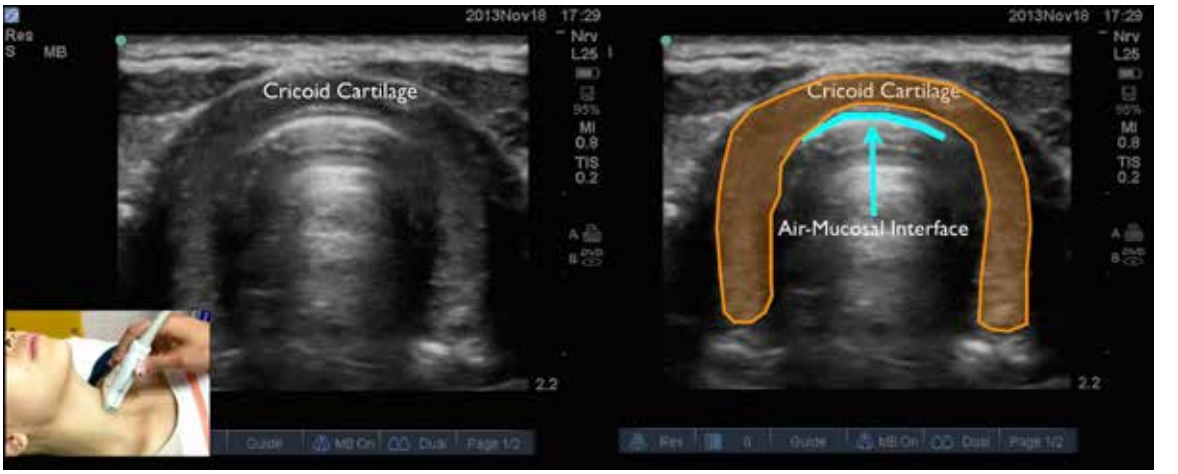

Figure 2: Cricoid cartilage is seen as an oval hypoechoic structure in transverse plane

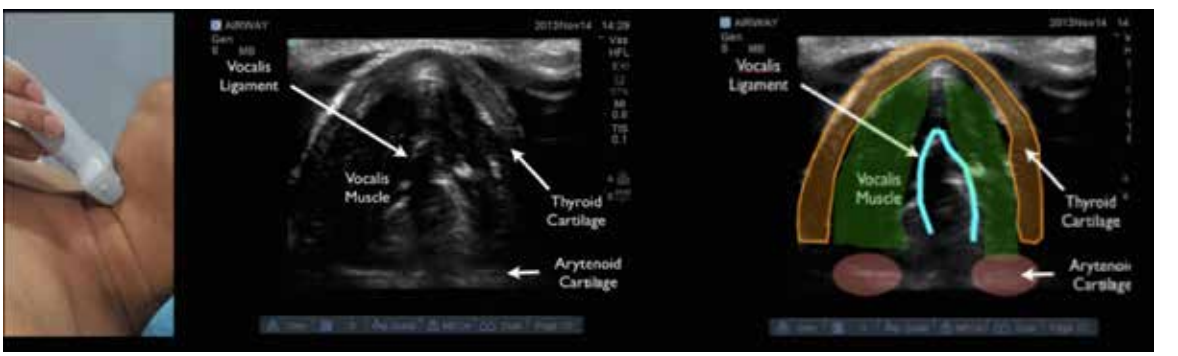

Figure 3: View of the vocal cords at the level of the thyroid cartilage. The hyperechoic appearance of the vocal ligaments delineate the vocal cord

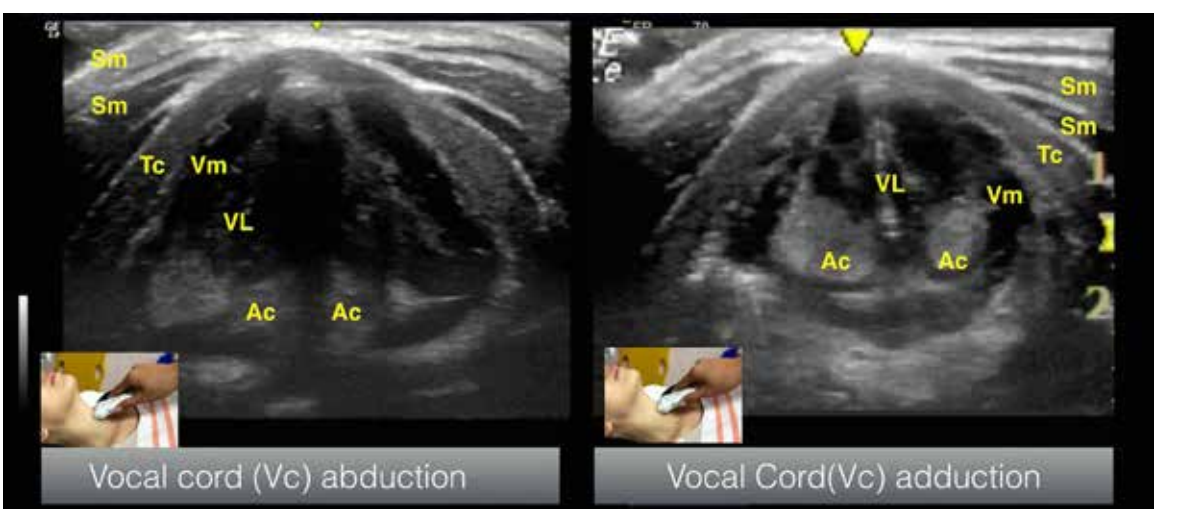

Figure 4: Vocal cord seen in transverse view during abduction and adduction. Sm: Sternocleidomastoid muscle, Tc: Thyroid Cartilage, VM: Vocalis Muscle, VL: Vocalis Ligament, AC: Arytenoid Cartilage

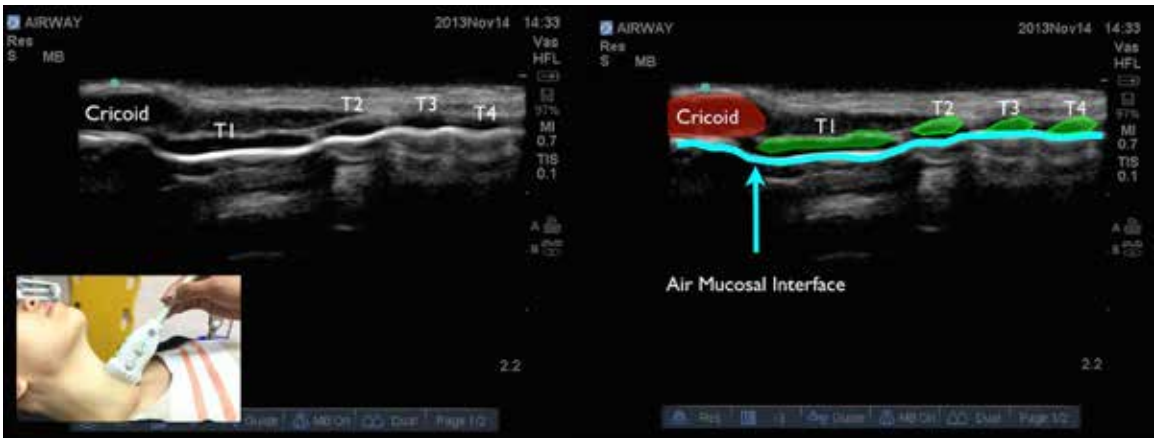

Figure 5: In the longitudinal plane, the cricoid cartilage is seen as a hypoechoiec structure with a 'bump' or 'hump' appearance. Tracheal cartilage in longitudinal plane appears as a "string of beads". T1-T4: 1st - 4th tracheal cartilage

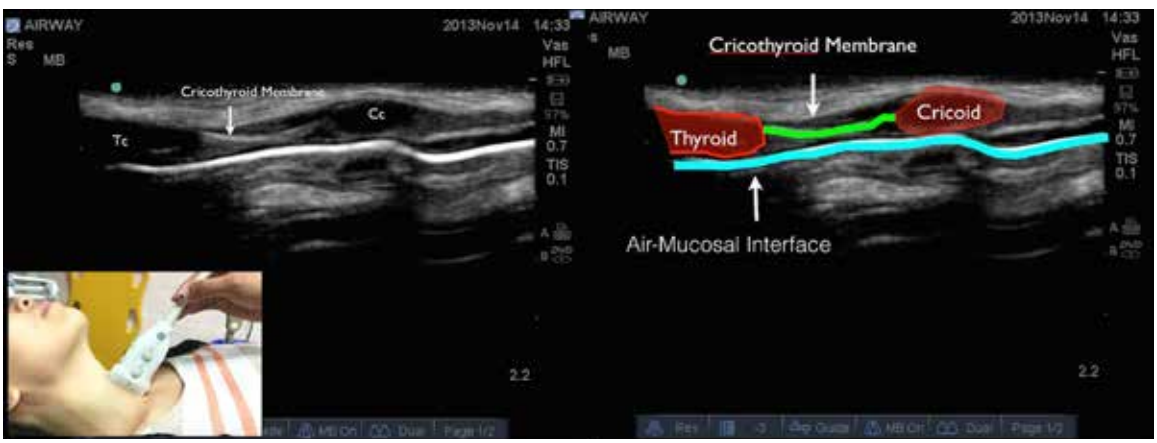

Figure 6: Cricoid cartilage, Thyroid cartilage, and Cricothyroid membrane in the longitudinal plane. Cc: Cricoid Cartilage, Tc: Thyroid Cartilage

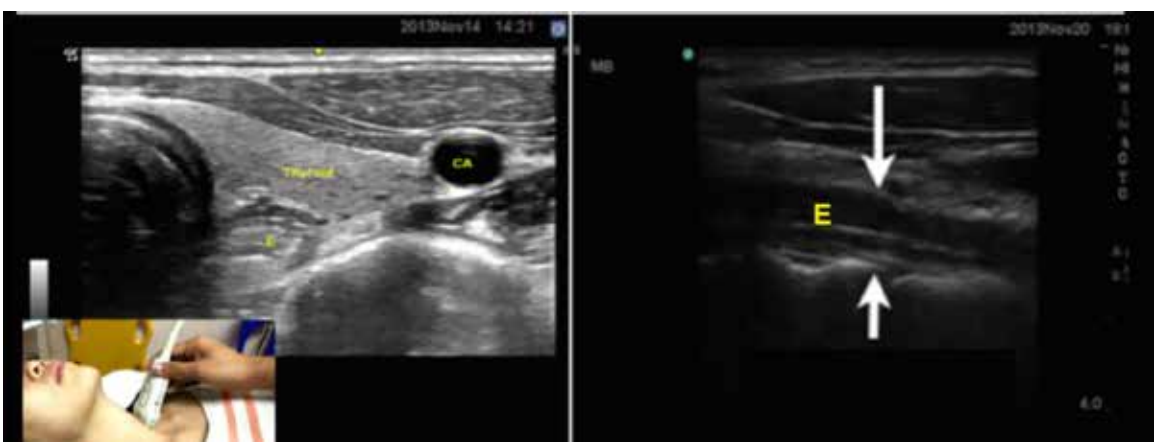

Figure 7: View of esophagus at the level of the first and second tracheal cartilage posterior to the left thyroid. Visible peristaltic movement can be seen inside the esophageal lumen during swallowing activity (Longitudinal view)
E: Esophagus, CA: Carotid Artery

CLINICAL APPLICATIONS OF UPPER AIRWAY ULTRASOUND IN POCUS EXAMINATION

Upper airway ultrasound can be used for the evaluation of:

- Airway Size and Prediction of Endotracheal Tube (ETT) Size
- Prediction of Difficult Laryngoscopy
- Airway device placement and depth:
  - Endotracheal Tube (ETT) Confirmation
  - Endotracheal Tube (ETT) depth
  - Laryngeal Mask Airway (LMA) confirmation
- Procedures: Percutaneous Cricothyroidotomy and Percutaneous Dilational Tracheostomy (PDT) Predicting the size of a left double-lumen bronchial tube Pathological airway structures:
  - Epiglottis
  - Vocal Cord Assessment
  - Trachea location and surrounding structures
- Predicting post extubation stridor
- Superior Laryngeal Nerve Blocks for awake fibreoptic intubation

AIRWAY SIZE AND PREDICTION OF ENDOTRACHEAL TUBE (ETT) SIZE

The accuracy of ultrasound evaluation of airway size is validated against magnetic resonance imaging[2] and computed tomography scan.[3] A correctly sized endotracheal tube can potentially avoid the hazards of subglottic stenosis and inadequate ventilation especially in the paediatric population where the narrowest airway lies in the subglottic region.

Ultrasound measurement of the subglottic diameter is superior to age-based[4-6] and height-based formula[4] in estimating ETT size. Age and height-based formula can only predict accurately 35% of cuffed ETT size and 60% of uncuffed ETT size compared to ultrasonography (98 and 96%, respectively).[4] Kim et. al. even suggested a formula to choose the appropriate ETT size in children.[7]

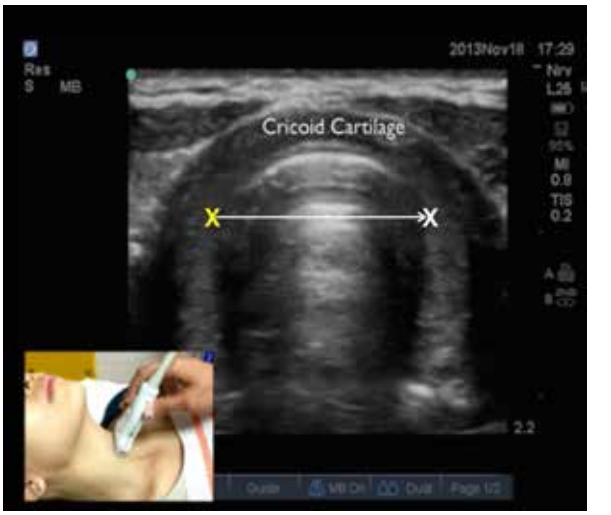

Figure 8: Airway size measurement using subglottic transverse diameter

PREDICTION OF DIFFICULT LARYNGOSCOPY

The ability to predict a difficult airway can potentially save lives and remained an area of great research interests. Preliminary findings are promising, although most were pilot studies with small study samples. There were four studied methods to date:

1. Visualisation of hyoid bone - The inability to visualise the hyoid bone on ultrasound using the sublingual approach predicts difficult intubation. This method has high sensitivity, specificity and high positive likelihood ratio with moderate negative likelihood ratio.[8]

2. Hyomental distance ratio - A shorter hyomental distance ratio of 1-1.05 in the morbidly obese patients can predict difficult laryngoscopy. This is the distance between hyoid bone and mandibular mentum in the neutral to the hyperextended neck position.[9]

3. Anterior neck thickness - Anterior neck thickness at different anatomical levels has been found to be predictors for difficult intubation.[10-13] These are studied at the level of the vocal cords, hyoid bone and thyrohyoid membrane but none are reproducible in different population.

4. Tongue thickness and tongue thickness to thyromental distance ratio - Tongue thickness of more than 6.1cm measured using the sublingual approach; and higher tongue thickness to thyromental distance ratio of more than 0.87 are capable of predicting difficult tracheal intubation.[14]

ENDOTRACHEAL TUBE (ETT) CONFIRMATION

Capnography has traditionally been regarded as the gold standard to identify correct placement of ETT. Adi et. al. demonstrated that upper airway ultrasound is as good as waveform capnography for the same purpose, with a kappa value of 0.85 with no delay in confirmation.[15]

Tracheal Rapid Ultrasound Exam (T.R.U.E.) method can diagnose esophageal intubation with high sensitivity and specificity using static transtracheal approach.[16]

Ultrasound confirmation of ETT placement is especially advantageous during situations where capnography is unreliable or not readily available in events involving cardiovascular arrest.[17] Low flow states, bronchoconstrictions or faulty capnography devices[15,18,19] and in emergency situations.[20]

ENDOTRACHEAL TUBE (ETT) DEPTH

Clinical assessment by auscultation and observing chest rise may fail to identify up to 55% of endobronchial intubations.[21]

Tracheal Rapid Ultrasound Saline Test (TRUST) technique utilised saline-filled ETT cuff to confirm correct ETT placement to prevent endobronchial intubation in children.[22] Even novice sonographers could accurately identify a saline-inflated ETT cuff at the level of the suprasternal notch in a cadaver study.[23]

LARYNGEAL MASK AIRWAY (LMA) CONFIRMATION

Ultrasound can be used to detect LMA malrotation in children with high sensitivity and specificity and an accuracy of 87%.[24] This is based on graded sonographic arytenoid cartilage elevation on transverse plane. LMA cuffs can be seen sonographically in the airway when cuffs are inflated with saline and contrast agents.[25]

PERCUTANEOUS CRICOTHYROIDOTOMY

Cricothyroidotomy is a life-saving procedure in the "cannot intubate cannot ventilate" situation. Upper airway ultrasound improves procedural safety by providing accurate anatomical landmark especially in those difficult to be distinguished by traditional landmark techniques[26-28] and airway injuries were three times lower.[29] Locating the cricothyroid membrane is fast with short learning curve[30] and cricothyroidotomy can be performed successfully in a quick manner,[31] an important feature in the emergency situation. Ultrasound can be used both pre-procedure by surface marking of

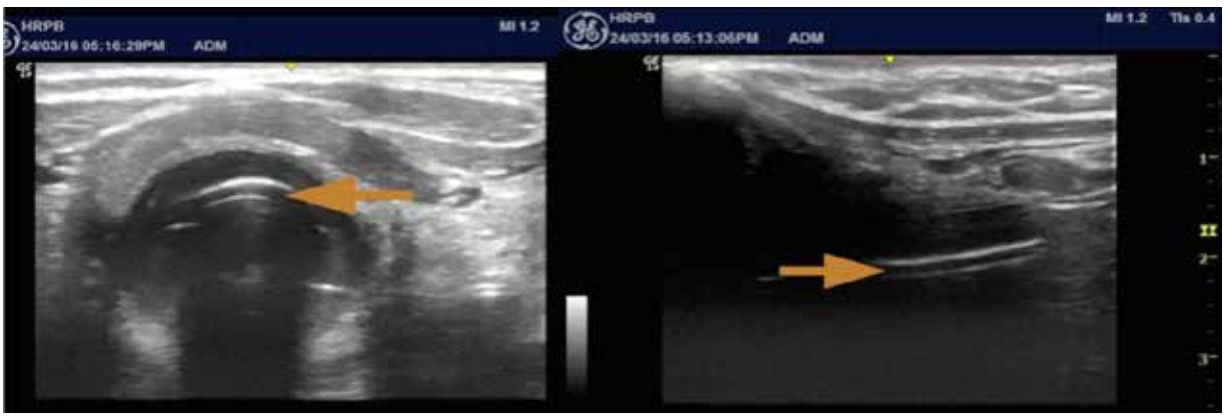

Figure 9: Tranverse and longitudinal image of ETT in trachea. ETT position in trachea is seen as two hyperechoic lines, which is described as "double tract" sign (arrow).[15]

the cricothyroid membrane prior to an anticipated difficult intubation, or as a real-time procedural guidance.

PERCUTANEOUS DILATIONAL TRACHEOSTOMY (PDT)

Upper airway ultrasound improves safety of PDT.[32-34] It enables precise location of procedure site,[35] allows selection of tracheostomy tube size and length[36] and avoid trauma to the airway,[37] vessels and anterior neck structures.[32,33] 25% of patients underwent re-siting of puncture site after ultrasound assessment.[33] Both pre-procedural ultrasound and real-time guidance is beneficial especially in patients with distorted anatomy. In the critically ill patients, the success and complication rates of ultrasound guided PDT in the TRACHUS randomised controlled trial is similar to bronchoscopic-guided PDT.[38] Ultrasound guided PDT is superior to the conventional landmark method with higher success rate in shorter time[39] and less attempts with high accuracy.[40,41]

PREDICTING THE SIZE OF A LEFT DOUBLE-LUMEN BRONCHIAL TUBE

Selection of a left-sided double lumen tube can be based on ultrasound measurement of the outer tracheal width at the level just above the sternoclavicular junction. This measurement has been shown to correlate with the internal tracheal width and left mainstem bronchus size on the computed tomography scan.[3]

EVALUATION OF PATHOLOGICAL AIRWAY STRUCTURES

Epiglottis

Patients diagnosed clinically with epiglottitis gave the appearance of a thickened epiglottis on the ultrasound.[42] There is however no standard cut-off limit for epiglottic thickness to date. The "alphabet P sign" was described in these patients, showing a hyperechoic thickened epiglottis in relation to the acoustic shadow of the hyoid bone at the level of the thyrohyoid membrane longitudinally.[43]

Vocal Cord Assessment

Assessment of vocal cords during adduction and abduction enable us to determine vocal cord palsy non-invasively.

LARYNGEAL INJURY

Upper airway injury due to blunt neck trauma can lead to life-threatening upper airway obstruction. Point of care ultrasound (POCUS) enables us to identify important normal sonoanatomy of the upper airway, and offering us an opportunity to rule classified based on Schaefer classification and expedites the subsequent management.[44]

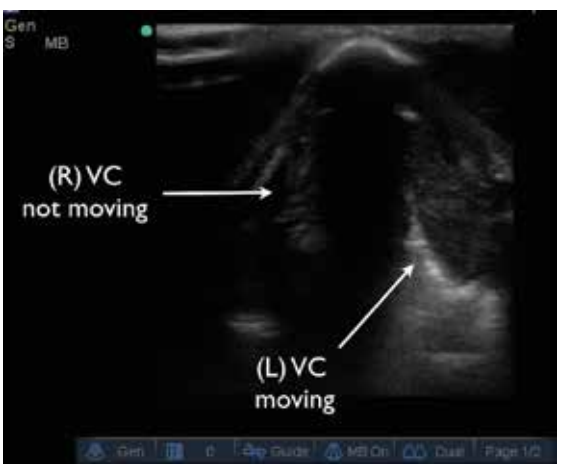

Figure 10: Right vocal cord palsy confirmed by direct sonographic visualization of vocal cords

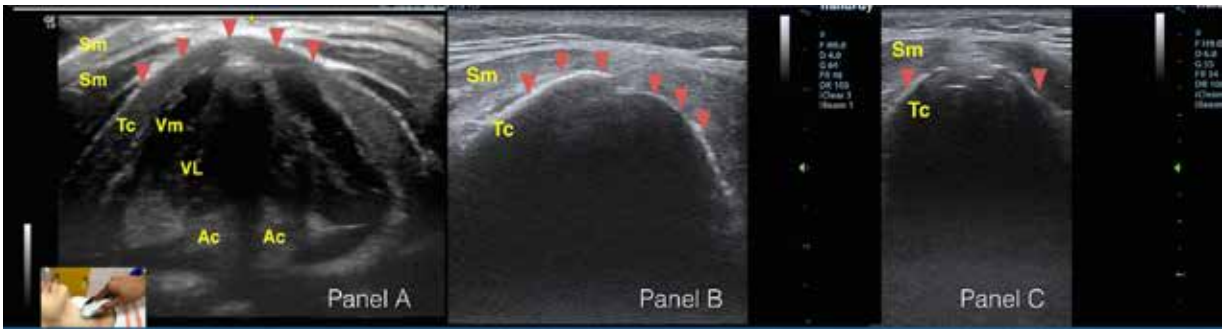

Figure 11: POCUS airway using 15MHz linear transducer shown a normal sonoanatomy of thyroid cartilage (Panel A) and discontinuity of anterior cortex of thyroid cartilage with surrounding tissue oedema (arrow head in Panel B and C)

PREDICTING POST EXTUBATION STRIDOR AND AIRWAY OEDEMA

Ultrasound measurement of air column width difference at the level of the vocal cords before and after ETT cuff deflation has the potential to predict postextubation stridor. This difference represents the amount of air passing through the vocal cords. A smaller difference is an indirect indication of airway, which presents clinically as postextubation stridor.[45,46]

ULTRASOUND-GUIDED TRANSLARYNGEAL BLOCKS

Real time Sonographically guided superior laryngeal nerve blocks is useful to facilitate awake fibreoptic intubation under direct visualisation of the nerve.[47]

UPPER AIRWAY ULTRASOUND EDUCATIONAL LEARNING CURVE

Upper airway ultrasound is operator-dependent and requires adequate training to become proficient. Interpretation of sonogram is equally important as are the ultrasound techniques. Studies showed that both aspects has shallow learning curves and can be learnt easily by novice with little initial ultrasound knowledge.[23,48,49]

CONCLUSIONS

Upper airway ultrasound is a useful, cost-effective and reproducible tool in the management of the critically ill patients. The integration of upper airway ultrasound to complement repertoire of pre-intubation airway screening may be the way forward in the future standard of care. It is a potential first-line airway assessment and management tool.

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Real Time Clinical Debriefing: The Whys And Hows

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INTRODUCTION

Debriefing is simply defined as post experience analytic process.[1] A more detailed definition is a *"discussion of actions and thought processes after an event to promote reflective learning and improve performance"*. Debriefing attempts to fill the gap between experiencing an event and making sense of it.[2]

Among anaesthesia circles, this term is mostly understood in the context of post-simulation experience, where participants gather after a simulation scenario and a facilitator conducts the debriefing with the purpose of analysing team performance. Debriefing after real clinical events are not unheard of, but this usually occurs after a traumatizing event such as death on the operating table. Even this is often not offered, due to various perceived constraints or a general lack of awareness.

There are therefore two main types of debriefing; one for psychological support, as in after a death on the table, also known as critical incidence stress debriefing (CISD), and another for performance improvement, as occurs after a simulated learning experience. The context of this article will primarily focus on the latter form of debriefing; with the ideas and concepts discussed below largely obtained from the list of references, as outlined under bibliography, at the end of this article.

BACKGROUND HISTORY

The history of debriefing precedes the use of simulation as a training and learning tool, with strong roots in the military and aviation industry.[3] Military debriefings were conducted in the 1940s during World War II in the form of "interviews after combat", directly after a mission, with the purpose of reconstructing events to the smallest detail, and not to address psychological distress. The 'interviews' thereafter became more systematic with the aim of improving future strategies and is subsequently known as 'after action reviews'. One can clearly imagine the format this took at its original implementation - largely error-focused. What they quickly learnt was that error-focused subjective feedback only created resentment and did not result in improvements to team performance. The military subsequently improved their techniques and currently 'after action reviews' are conducted in a non-punitive atmosphere, based on objective performance indicators. These reviews are conducted following real missions, as well as simulated ones.

Another industry in which debriefing takes a firm root is aviation. The original platform for this was known as "cockpit resource management", subsequently renamed as "crew resource management" when the approach became multi-disciplinary. The aviation industries are therefore pioneers not only of modern simulation as a tool to improve performance, but also effective approaches to debriefing practices.

In the healthcare industry, the science of debriefing relating to team performance is mostly applied in the context of immersive simulation. In the 1980s, David Gaba pioneered human patient simulation in teaching crisis resource management following the aviation model. Post-simulation debriefing is an inherent part to these activities. In fact, most simulationists consider it unethical to not conduct a debriefing after a simulation experience.

Gaba described debriefing as "an integral part of the process of any experiential-learning technique" and various debriefing models have been created to guide the process. All have well-established rules in terms of creating a psychologically 'safe' environment. Most of the models contain similar elements and although some groups strongly promote particular styles of debriefing, none of the approaches has evidence to support its superiority over another. At the moment, the concept of debriefing in our

local setting is understood in relation to debriefing following these simulation activities.

THE WHYS AND HOWS

What should become immediately obvious, however, is that debriefing, which is critical after simulated events, also has tremendous value after real events. All highly performing teams engage in debriefing, not as an optional course of action, but as a foundational behaviour. What this means is that the act of debriefing is essential to the creation of high performing teams. If we wish to be identified as those among such circles, then this habit needs to be adopted. Reflection may occur naturally after an experience anyway but, debriefing, as a process, ensures that it occurs in a systematic, objective and fruitful manner.

Real time clinical debriefing (or real time debriefing) has been defined as "facilitated discussion of a clinical event focused on learning and performance improvement". Other terms used include post event debriefing and clinical event debriefing. As highlighted earlier, this form of debriefing is different from CISD which is debriefing after adverse events to deal with psychological distress.

Clinical event debriefing, however, need not only occur following a critical event. In fact there is great sense in debriefing after normal, essentially 'non-critical' events. The word 'event' need not suggest something untoward had happened; an 'event' could be a routine anaesthetic. Debriefing, however, *must* be conducted following critical events.

There are many advantages in debriefing following routine events. Facilitators gain debriefing experience and will hopefully perform better in debriefings following critical events, which is likely to be more challenging. Furthermore, if time is regularly expended to debrief after routine events, then a debriefing is more likely to happen after critical events. Debriefing after routine events also facilitates a cultural change that welcomes open conversations about team performance. The team gets to learn from near misses and errors, as well as successes.

For routine events, there are many high value topics that could guide the main points of discussion for a quick debrief. The team can debrief about how well they adhered to guidelines or whether they faced technical, equipment or procedural issues during routine care. Discussions about behavioural skills such as teamwork and communication may also emerge; although this may need to be deliberately raised, until the team gets into the habit of talking about these. For example, anaesthesia teams could opt to have a debrief after every case in the list, while the intensive care teams may opt to debrief following resuscitations (which is a routine event in the ICU), invasive procedures or interactions with family or other teams. All these events challenge the cognitive, technical and behavioural skills of participants.

Certain events, however, mandate a debriefing. Incidents for which debriefing should be made compulsory include adverse events, near-adverse events, emotionally upset team members, difficulties during clinical procedures, miscommunication or if there was a demonstration of poor teamwork.

A question was posed if we should standardize which clinical events to debrief? There are distinct advantages if this approach is adopted, including making team members anticipate a debriefing which in turn helps them to be mentally prepared. Standardising which clinical events to debrief may also help in increasing debriefing frequency, until this becomes a habit or culture. Standardizing events that require debriefing can also help to align departmental goals.

Literature on clinical event debriefing is scant compared to simulation literature, although multiple papers have described its technique and documented its value. Effective debriefings claim to improve individual and team performance by up to 25%, and a number of other papers have provided supportive evidence as well.

Among other benefits found from the literature include participants acknowledging its benefit in the following: clearing the air, providing feedback to learners and colleagues, identifying knowledge and process gaps, identifying system errors, promoting team unity and cohesiveness, and identifying potential medico-legal issues.[4]

While the above paper highlighted a detailed list of benefits, the simple reason for clinical debriefings is that we are exposed to opportunities for learning and improvement every day, and clinical event debriefings somewhat formalises that educational opportunity. If debriefings are conducted early enough, the process may assist with the team's ability to recall details of the event as it is still fresh. This is an excellent opportunity as no detail is too small if our aim is to improve patient care. What is apparent, however, is that despite the rational and evidence supporting this, most medical teams are not doing this or even making an attempt.

A meta-analysis of team-based debriefings after events found improved effectiveness in teams that were debriefed versus those that were not.[5] When debriefings occur following events which are fairly common such as CPR (cardiopulmonary resuscitation), authors have found improved rates of return of spontaneous circulation (ROSC), improved neurologic outcomes, shortened hands-off compression times and reduced delay to start of chest compression. In light of this, the American Heart Association (AHA) specifically recommends debriefing after CPR. Evidence therefore exist not only in regards to improved team performance, but also improvement in patient outcomes.

How do we conduct these debriefings? Multiple frameworks have been described, ranging from mental checklists to written ones. It is widely recognised among simulation enthusiasts that debriefing is one of the hardest skills to master and that good performances take time to develop. In general, debriefing should focus on the team's performance rather than the individual. Those familiar with simulation debriefings will likely find the process intuitive. Essentially the elements are the same: first allow team members to 'vent' i.e. allowing a free flow expression of feelings and impressions. This is often followed by team members recalling details of the event and then the main section of the debriefing ensues, which is an analysis of what went well first, before delving into what did not go so well and needs to be done differently next time. There are many simple models that can be adopted for this process and they essentially contain the same elements as described above: reaction, analysis and summary.

In terms of timing, debriefings can be hot, warm or cold. Hot debriefings are done immediately after the event, warm debriefings minutes to hours after and cold debriefings days to weeks after. Morbidity and mortality meetings conducted in our local context are essentially cold debriefings. In the author's perception, the term 'real time debriefing' seem to refer to hot and warm debriefings, as opposed to the more general term of 'clinical event debriefing' which would encompass all.

While any form of debriefing is probably better than none, there are distinct advantages and disadvantages for different timings for debriefing. Hot debriefing, which occur immediately after the event, has the advantage of having all or most of the team members readily available. As details of the events are still fresh, there may be a higher likelihood that seemingly smaller issues, e.g. where to put the emergency trolley, will be raised and can be potentially quickly addressed. The immediacy may also help to reduce recall bias. The downside of hot debriefings is the limited time available, as normal daily routines have to continue. The proposed duration of these debriefings however is only 10 minutes and any issues that need a longer discussion should be postponed to a later time (warm debriefing) or discussed much later i.e. during cold debriefings. The venue also needs to be considered; it can be held at the patient care area or the team can move to an adjacent non-patient care area. Issues like confidentiality needs to be considered when deciding where to hold the debriefing. Other

downsides of hot debriefings include team members not being mentally or emotionally prepared. In short, the events are still fresh in mind and emotions are high leading to a higher likelihood of problems being raised. The difficulty is the disruption to the normal workflow, finding a place to do this confidentially and members not having the time to reorganise their thoughts or make sense of their experiences.

The advantages of warm debriefing, held minutes to hours later, is that it is possible to find a better time to perform the debriefing and a better place that offers some privacy. The disadvantages include having more difficulties rallying all team members as some may have moved on to other tasks or areas. Apparently trivial difficulties (which may actually be important to patient care) may already have been forgotten. In the author's limited experience in attempting this in the ICU setting, warm debriefings seem like the most practical option; with debriefing taking about 10 to 15 minutes and conducted after morning rounds have concluded.

Cold debriefings, held days to weeks later, are probably very familiar to those working in Malaysian settings and mostly comes in the form of morbidity and mortality meetings. Cold debriefings should encompass more than just morbidity and mortalities, however, as this indicate that some harm had already come to a patient. Discussions on near-misses are important and are seldom done. The author has only experienced working in one department where near-misses were discussed and this was intuitively helpful. Cold debriefings may follow some hot debriefings when more complicated issues arise as it has the advantage of gathering key persons i.e. unit leaders who are not part of the original team members. Topics such as root cause analysis, system and process improvement can be discussed in greater detail. The disadvantage faced by cold debriefings is the difficulty of gathering all who were involved and the risk of recall and hindsight bias.

A good way to combine the various approaches is to have hot or warm debriefings as a daily routine and organise cold debriefings when deeper issues i.e. those requiring system changes are identified; to allow time for key persons, especially those outside of the team, to be identified and gathered. As highlighted previously, routine hot or warm debriefings offer many advantages; it comes to be expected and it instils a culture of safety and of speaking up. It also makes it more likely that a debriefing will occur after an adverse event which is not optional and should be considered a standard of care for staff.

CONCLUSION

To end this discussion the author would like to make a few proposals taking into context the anaesthetic practice. Teams should spend 5 to 10 minutes after each patient regardless of how it went. The following script for debriefing is simple enough to follow as a script/mental checklist:[6]

Review the clinical events

1. What was done well?
2. What needs to be done differently next time?
3. Follow up issues?
4. Conclusion

It is important to talk about what was done well first as it is frustrating for team members to have done many things well and not have that acknowledged, with the facilitator focusing only on what did not go well. Prolonged discussion of system issues without an immediate solution should also be avoided as this is counterproductive and leads to frustration. Such deeper issues should be acknowledged, recorded and scheduled for discussion at a later time during cold debriefing sessions with unit leadership.

Any member of the team can facilitate. In our local context this is likely to be initiated by the specialist or senior medical officer but there are essentially no rules. The disadvantage of senior colleagues initiating this is the potential of him/her to inhibit or bias on the discussion. Adding a co-debriefer, who is more junior, may help to counter this. The team involved in the discussion should be multidisciplinary, of special mention would be to include the nurses who are key members of any clinical team.

A good facilitator should not dominate the conversation, nor lecture on what was done right or wrong. Questions should be posed open-endedly. There is great benefit in the facilitator practicing self-restraint and limiting their opinions before hearing from others. This exercise is only of value when all members have the chance to speak. The facilitator should empower others to speak up, while still offering their honest observations, opinions and suggestions. The conduct of the debriefing must be non-punitive and the facilitator must work hard to create an atmosphere of psychological safety. Every member of the team must feel included and the approach must not be centred on shame and blame. Suboptimal performances are constantly framed in the context of team responsibility.

Other unwritten rules include keeping the conversation brief and to focus on a few critical performance issues. There must be self-awareness to avoid tangential conversations. In the author's opinion, the single most important factor in giving effective debriefings is our attitude and beliefs about why errors occur.

What does a successful debriefing look like? It is one in which team members feel safe to critically analyse their own performance and that all members understand that patient care is a team responsibility and not of any individual.

What is the way forward from here? Well, we should all take Nike's advice and "Just do it". There are many resources out there to aid development of expertise in this area. In fact the science of debriefing has progressed further to the point that there are standardized instruments to assess the quality of debriefings. In terms of implementation, individual departments can work towards making routine debriefings a reality by pre-assigning facilitators by policy. Other measures include identifying a highly keen individual as a debriefing champion whose job is to encourage teams to debrief on a routine basis. These champions or facilitators can then be targeted for specific training to improve their debriefing skills. More advance centres have resorted to adjuncts to aid the process of debriefing, such as data recording facilities to reduce reliance on memory and aid objectivity. Some advanced centres even use real time video capture to aid their debriefings. Finally, debriefings should extend not only across professional groups but also among various disciplines and departments.

Perhaps one day we will get to the level of these elite practices. But first we have to start.

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High Flow Nasal Oxygen Therapy In Adults: A Positive Alternative

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INTRODUCTION

There are various non-invasive methods to deliver oxygen therapy. Most of the mode of deliveries use low oxygen flow. However, high flow oxygen delivery via nasal cannula has often been used as a non-invasive oxygen therapy in neonates and infants. Recently, its use has been increasingly popular in adult patients. There are studies suggesting high flow nasal oxygen (HFNO) as an alternative mode of oxygen therapy in adult critically ill patients, be it in intensive care unit (ICU) or during perioperative management. It is also known as nasal high-flow ventilation, high-flow oxygen therapy and high-flow nasal cannula oxygen therapy.

The HFNO delivery system comprises an air/oxygen blender, an active heated humidifier, a single heated circuit and a nasal cannula (Figure 1). The interface of HFNO system is just slightly larger than the nasal prong commonly used for oxygen delivery. At the air/oxygen blender, the inspiratory fraction of oxygen (F_iO_2) can be regulated from 0.21 to 1.0 with a high flow rate up to 60L/min. The gas is generally heated and warmed to 37ºC, and humidified with an active humidifier. It will be delivered through a heated circuit. This conditioned gas will help to preserve the normal mucociliary functions. The system can be assembled separately. At present, there are HFNO delivery devices available in the market or else, many positive pressure ventilators have incorporated HFNO therapy mode.

PHYSIOLOGY

Although HFNO is delivered through an open system, the high oxygen flows will be able to create resistance to the patient's spontaneous expiratory flow thus increasing the airway pressure in the patient's pharyngeal area. Although the pressure generated is relatively low compared with any of the closed system delivery, it is considered adequate to increase the lung volume or to recruit collapsed alveoli to a certain extent. In vitro studies, the airway pressure was reported to increase as the flow rate of HFNO was increased.[1] It also has shown that the end-expiratory lung volume was greater with HFNO than with low-flow oxygen therapy.[2] The increase in the pharyngeal pressure may not be high enough compared to non-invasive positive ventilation (NIV) or invasive mechanical ventilation.[3,4] The pressure generated by HFNO varies. It changes with the amount of flow delivered, the type of patients' breathing (with a significantly lower pressure in mouth breathers), the moment of the respiratory cycle and the degree of respiratory failure.[5] Furthermore, with the current HFNO devices available in the market, the positive end expiratory pressure (PEEP) generated level is not measured or regulated.

In HFNO therapy, the main portion of gas flow during inspiration enters the trachea but a smaller portion does exit through the mouth. Similarly, during expiration, it is possible that gasses that exit from the trachea separate at the back wall of the nasopharynx, assisting expiration out the mouth. The patient may experience an entrainment effect of expiratory gas during expiration and this may potentially assist expiratory efforts.[6]

High flow nasal oxygen is also able to clear the expired air in the upper airway and reduces dead space by decreasing the rebreathing process, creating more efficient ventilation. The dead space clearance is flow and time dependent. The clearance of expired air in upper airways by nasal high flow can extend below the soft palate and causes further reduction of the dead space.[7]

It has been shown that the respiratory rate was lower with high flow than with low flow oxygen therapy.[8] As the respiratory rate is reduced, although the arterial partial pressure of carbon dioxide (PaCO2)

and tidal volume (VT) remain unchanged, the total minute ventilation will be reduced.[9] It is also reported that the thoraco-abdominal synchrony achieved is better with HFNO when compared to ventilation with face mask.[10]

Dry and unwarm gasses are associated with discomfort, nasal and oral dryness, eye irritation, nasal and eye trauma and gastric distension.[9] Adequate conditioned gas i.e. warmed and humidified will have less impact on the physiological response of the lungs. It minimizes airway constriction and reduces the work of breathing, improves mucociliary function and may facilitate clearance of secretions.[5,6,9] It is also associated with less atelectasis, resulting in a good ventilation/perfusion ratio and better oxygenation.[5,9] The heated humidifiers provide better humidification compared to bubble humidifiers.[5] It is difficult to achieve stable delivery of constant fraction of oxygen (F_iO_2) with low flow system. However, oxygen delivery through high flow device may deliver constant actual F_iO_2 close to the predicted F_iO_2.[9,11] In HFNO therapy, the differences between the patient's inspiratory flow and delivered flow are small and it remains relatively constant.[11] At the same time, the interface of HFNO allows patient to breathe with their mouth open. It has been shown in healthy volunteers that F_iO_2 was higher with mouth-open breathing. A study showed that the measured F_iO_2 was close to the delivered F_iO_2 when the oxygen flow was above 30L/min.[12]

CLINICAL APPLICATIONS

The HFNO therapy was shown to improve preoxygenation prior to intubation in critically ill patients and reduced prevalence of severe hypoxemia. Its use in treating mild to moderate hypoxaemia has been associated with significant reductions in breathing frequency, heart rate, dyspnea score, supraclavicular retraction and thoracoabdominal asynchrony, and significant improvement in oxygen saturation. Compared to the venturi mask, HFNO therapy results in better oxygenation after extubation in critically ill patients for a similar F_iO_2. It was also associated with better comfort, fewer desaturations and interface displacements and a lower reintubation rate.

ACUTE RESPIRATORY FAILURE

Sztrymf et. al. replaced oxygen flow of 15L/min via a face mask to HFNO of 49±9L/min in patients with acute respiratory failure.[13] Their study showed that HFNO was associated with significant reductions in breathing frequency, heart rate, dyspnea score, supraclavicular retraction and thoracoabdominal asynchrony, and significant improvement in oxygen saturation. It had also been applied in acute hypoxaemic respiratory failures in the emergency department setting and was found to alleviate dyspnea and improve oxygenation.[14] The FLORALI trial has shown that the intubation requirements in non-cardiogenic acute respiratory failure patients with $PaO2/F_iO_2$ ratio of <200mmHg can be reduced with HFNO therapy.[15] However, there was no difference in intubation rate when patients had higher $PaO2/F_iO_2$ ratio. They also noted a significant reduction in mortality rate among patients receiving HFNO during their intensive care unit admission and within 90 days.

As described earlier, the HFNO generates only slight increases in airway pressure at the end of expiration and may not be as effective as NIV. However, it is more comfortable and better tolerated for longer duration due to its smaller interface. It was shown to be successful for hypercapnic respiratory failure patients who were unable to tolerate conventional NIV.[5,9] Its use also improved exercise capacity and oxygenation in patients with chronic obstructive pulmonary disease.[9] Since it also reduced breathing frequency, minute ventilation and PaCO2, it may be an alternative to be considered for the treatment in these groups of patients.[5,9]

PRE-INTUBATION OXYGENATION

Delivery of oxygen into the lungs during apnoea can be maintained by oxygenation through diffusion (apnoeic oxygenation). This effect is well described and is likely one of a number of mechanisms by which jet ventilation oxygenates the lungs. This effect extends to the critical care population requiring intubation, where fewer and less severe episodes of arterial desaturation are seen when preoxygenated with HFNO, rather than high-flow oxygen using

a conventional facemask.[11] Preoxygenation with HFNO was shown to significantly improve preoxygenation and reduced prevalence of severe hypoxemia compared with oxygen via non-rebreathing face mask.[16]

However, no significant differences in the immediate outcome were reported when HFNO was compared to other high flow or non-invasive therapy during preoxygenation prior to intubation. A multicenter randomized controlled trial in six French ICUs evaluated the efficiency of HFNO for preoxygenation, comparing it to the high F_iO_2 delivered via facial mask. This study concluded that there was no significant difference in the lowest level of desaturation between both high flow oxygen deliveries.[17] Another study reported no significant difference in intubation rates when HFNO was compared to NIV and standard oxygen therapy in patients with non hypocapnic acute hypoxaemic respiratory failure.[15] The use of HFNO during preoxygenation of critically ill patients was compared to bag valve mask (BVM). The study reported there were no significant differences in the oxygen saturations before or after intubation, mean lowest oxygen saturation during intubation, PaO2/F_iO_2 ratio and PaCO2 between the two groups but there was a significant reduction of oxygen saturation during the 1 minute of apnoea after the induction only in the BVM group.[18] Although no conclusive evidence up to date, the preoxygenation via HFNO showed comparable effect as other non-invasive positive ventilation.

POST EXTUBATION

It has been demonstrated that HFNO therapy post extubation in critically ill patients showed better oxygenation for the same set of oxygen F_iO_2 when compared to low flow oxygen therapy. It was also associated with better comfort, fewer desaturations and interface displacements, and a lower reintubation rate.[19-21] It was found as not inferior to non-invasive ventilation for preventing reintubation and postextubation respiratory failure patients in ICU.[22]

However, a multicenter trial (OPERA) reported no significant improvement in pulmonary outcomes when used as post extubation oxygen therapy among patients undergoing major abdominal surgery. Early preventive application of HFNO after extubation did not result in improved oxygenation when compared with standard oxygen therapy.[23]

SLEEP APNOEA

Continuous positive airway pressure (CPAP) has been widely accepted as treatment for patients diagnosed with sleep apnoea. The HFNO delivery was able to alleviate the upper airway obstruction in patients with sleep apnoea.[24] The HFNC with 20L/min of flow can reduce the amount of inspiratory flow limitation and decreased arousals and the apnoea hypopnea index.[9]

It is common for stroke patients to have disordered breathing during sleep which may be associated with poor outcome. It has been reported that HFNO at 18L/min was well tolerated and able to reduce the apnoea-hypopnea index and the oxygen desaturation index.[25] The percentage of slow-wave sleep significantly increased, and quality of sleep was better.

PRE-ANAESTHESIA INDUCTION

The use of HFNO during induction of general anaesthesia may be under-reported. However, recently, there were discussions focusing on the use of HFNO in the management of difficult airway and its ability to increase the time to desaturation, and decrease the severity of the desaturation in anaesthetized patients.[11] Whether elective or an emergency induction, especially in difficult intubation scenario, oxygenation during apnoea is dependent on an optimum preoxygenation. Oxygenation is maintained with only the difference in the rates of excretion of carbon dioxide and absorption of oxygen as the driver of gaseous flow during apnoea is described as apnoeic oxygenation. Recently, Patel & Nouraei[26] suggested that the combination of the apnoeic oxygenation and the

continuous positive airway pressure together with the gaseous exchange through flow-dependent dead space flushing with HFNO resulted in extension of the apnoeic time. In their study, oxygen was delivered via OptiFlow™ nasal cannula described as Rapid-Insufflation Ventilatory Exchange (THRIVE) induction technique. They included patients with laryngotracheal stenosis, vocal fold pathology and obstructive sleep apnoea, and benign and malignant hypopharyngeal obstruction.

The use of HFNC therapy during invasive procedures such as fibreoptic intubation or bronchoscopy has also been reported.[27-29] Both, to prevent hypoxemia or worsening of hypoxemia. The high-flow nasal oxygen-delivery system improves oxygenation saturation, decreases the risk of desaturation during the procedure, and potentially, optimizes conditions for awake fibre-optic intubation.[27] The safety of the procedure may be increased, because any obstruction, hypoventilation, or periods of apnoea that may arise may be tolerated for longer, allowing more time to achieve ventilation in an optimally oxygenated patient. Although the NIV may be more useful in ensuring better positive pressure ventilation, HFNO delivery seems to be more practical in view of the nature of its interface.[28]

CONTRAINDICATIONS

Similar to any non-invasive oxygen therapy, its use in critically ill patients is limited. The HFNO is contraindicated in patients who are unconscious or agitated and uncooperative. It is also not for patients with airway obstruction, facial injury or malformation, patients with a lot of secretions and to those with risk of aspiration. It is definitely not suitable for patients in respiratory arrest and unstable hemodynamics for example in shock, intractable arrhythmia or post-CPR.

Few important issues remain to be resolved, such as its indication, timing of starting and stopping HFNO, and escalating the oxygen treatment. Despite these, HFNO therapy is an innovative and effective method for the early treatment of adults with respiratory failure with diverse underlying diseases.

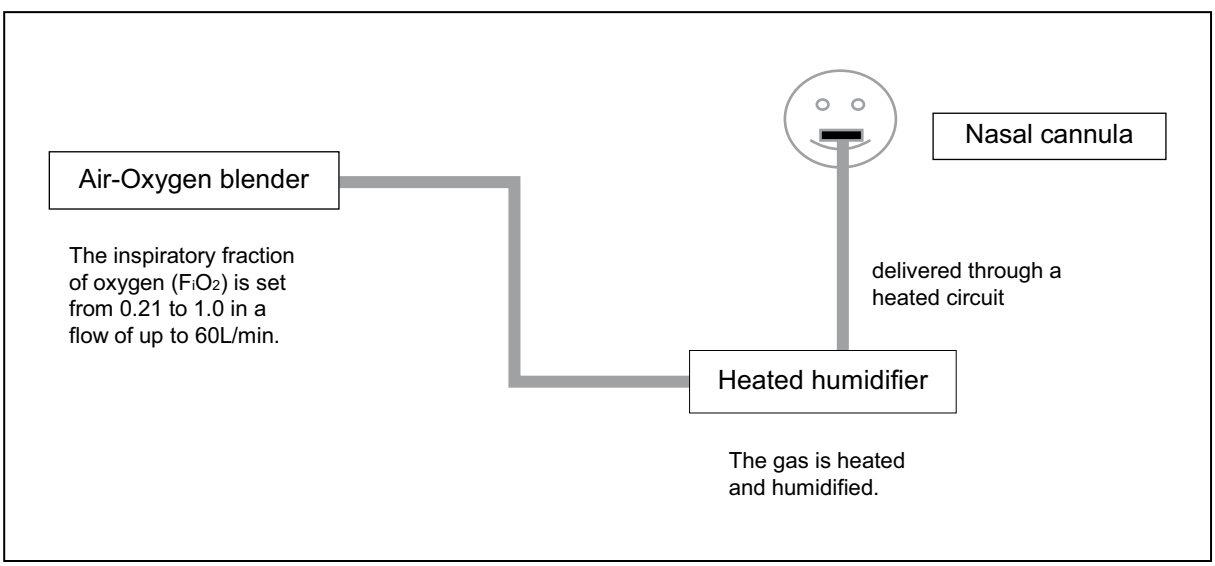

Figure 1: HFNC oxygen delivery system

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Anaesthesia And The Developing Brain

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INTRODUCTION

Anaesthesia is widely applied in surgery, imaging and invasive procedures in the paediatric population. Doctors refer to general anaesthesia as "sleep" to avoid upsetting patients but in reality it alters brainwave activity and is best described as a "reversible, drug-induced coma," according to a paper published in the New England Journal of Medicine (NEJM) 2010.[1]

"How do we determine what are physical, chemical and psychologic hazards of occupation and in particular those that are rare and not easily recognized?" and "…the available human studies… cannot exclude the possibility that the anaesthesia-induced neurotoxicity observed in many animal studies may also occur in children" ……..Sir Austin Bradford Hill, at a meeting of the Royal Society of Medicine in 1965.[2]

53 years on since that quote and more than 20 years of studies about the effects of general anaesthesia on infant animals have led to serious concerns about anaesthesia-induced neurotoxicity in the developing human brain. Yet its short and long term effects in paediatric patients remains poorly understood.

It may be pertinent to note that anaesthetics are just one of many potential sources of perioperative neurotoxicities. Other possible contributors are genetic anomalies, prematurity, sepsis, infection, vascular diseases, hemodynamic disturbances, hypoxia, hypo-/hypercapnia, hypo-/hyperglycemia, electrolyte imbalances and temperature variations that occur due to anaesthesia.[3]

So, should anaesthetic application be reduced in the paediatric age group or perhaps even be denied in the neonates?

It has already been proven that neonates and premies have neuroanatomical and synaptic prerequisites to perceive nociception. Insufficient analgesia can have long term repercussions.

Neonatal circumcision without analgesia has pronounced pain experience to later immunization injections compared to those who received active analgesia (EMLA).[4,5]

WHO MODEL LIST OF ESSENTIAL MEDICINE FOR CHILDREN DEC 2012

Aim for safe anaesthesia in neonates (0-28 days) by providing

- Analgesia
- Amnesia
- Depress stress responses
- Maintain CVS stability
- Return them to baseline status

Neonates carry 10 times more mortality and morbidity risk compared to other paediatic age group, mostly involving the cardiovascular and respiratory systems.[6] The practitioner's experience, the presence of existing respiratory, cardiac or muscular disease are the key factors that determine the risk of morbidity and mortality.[7]

TERMINOLOGIES

Neurotoxicity

In experimental studies, this means a reduction in neural density and apoptosis whereas in clinical studies this constitutes disturbances in memory, attention, learning and motor activity.

Pain is neurotoxic…hence anaesthesia-analgesia application in painful conditions have a net neuroprotective effect.[8,9]

Apoptosis (Greek: apo - 'from' : ptosis - 'fallings')

Cell death which occurs as a normal and controlled part of an organism's growth and development.

Apoptosis physiologically occurs in the developing brain at a rate of approximately 1%. However, apoptosis that occurs following pathological processes like hypoxia and ischemia is of great concern. Several experimental studies have shown that apoptosis is increased following anaesthesia exposure. However, it is not possible to conduct such studies in humans.

Neuroplasticity

It is the ability in intercellular connections to reorganize itself by learning, forgetting and forming new synapses. It is also the ability to recover from an injury and develop abnormal adaptations following adverse experiences e.g. repetitive pain during early brain development.

Pathogenesis

Neonates are born with approximately 100 billion neurons. A newborn infant has about 50 trillion synapses, increasing to 1000 trillion within the first year of life and decreasing to 500 trillion in adulthood. Critical periods for brain development are the intrauterine period, the first 3 years of life and puberty.

In the fetal stage, neuronal differentiation leads to neuronal migration and thence synaptogenesis, which continues into postnatal life. During the postnatal period, myelination, synaptogenesis and plasticity peak during first two years of life. Synaptogenesis encompasses the area of interest in all of the current studies.

Synaptogenesis is the most important period of brain development, also described as the "fragile period" or "critical period." It consists of five phases. The greatest leap in synapse formation occurs in phase 3 ('big bang') which corresponds to the neonatal period and continues at the same speed during phase 4 ('plateau phase'). Synaptogenesis continues during phase 5 but is limited and localized, corresponds to adulthood. The brain's sensitivity to environmental stimuli is at maximum during the neonatal and infancy period when synaptogenesis is also maximized.[10]

MECHANISM OF THE ANAESTHETIC AGENTS

Anaesthetics elicit their effects by enhancing the activity of major inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and glycine (e.g. benzodiazepines, barbiturates, propofol, etomidate, isoflurane) OR antagonizing the N-methyl-D-aspartate (NMDA) receptors of the major excitatory neurotransmitter glutamate (e.g. ketamine, nitrous oxide, xenon). During brain development, GABA facilitates cell proliferation, neuroblast migration, and dendritic maturation and, unlike in adults, it acts as an excitatory neurotransmitter during infancy rather than an inhibitory neurotransmitter.[11,12] Glutamate and aspartate direct synaptic signaling at nerve terminals and control ion intake to neurons. They have been found to influence synaptogenesis, neuronal plasticity, learning and memory.[13,14] Although the excitatory neurotransmitters are normally responsible for nerve conduction, they are also potential sources of neurotoxicity.

An abnormal decrease in glutamate may disturb normal excitation, and abnormal increases may cause excitotoxicity and cell death by disturbing calcium homeostasis. Glutamate and similar amino acids have been shown to cause acute swelling in the neuron body, dendrites and glia and also promote neuronal degeneration over extended periods of time. For this reason, there is a delicate mechanism acting in normal conditions to regulate glutamate levels in the synaptic gap involving reuptake of excess glutamate from the synaptic gap through receptors present in presynaptic end of nerve terminal and glial cells. Anaesthesia applications are believed to disrupt the balance between excitatory and inhibitory neurotransmission and thus cause neuronal injury.[13,14]

Experimental studies have shown that anaesthesia induces apoptosis via intrinsic and extrinsic pathways. Anaesthetics during the

neurodevelopmental period causes translocation of BCL-2 associated X protein to the mitochondria, leading to mitochondrial membrane disruption and permeability and leakage of cytochrome c into the cytosol. This in turn activates the apaf-1 and caspase pathways, resulting in lipid peroxidation via release of free oxygen radicals.[15]

EXPERIMENTAL STUDIES

Inhalation Anaesthetics

Sevoflurane was applied to neonatal (PND3, PND7, and PND14) and adult rats (PNW7) at concentrations ranging from 1% to 4%. Spatial memory was then assessed in adulthood using the Morris water maze (MWM) test. The PNW7 rats were less sensitive to sevoflurane than neonatal rats. Memory defects were apparent in groups treated with repeated low doses or a single high-dose anaesthetic. Shen et. al.[16] concluded that neonatal exposure to sevoflurane can result in memory defects in adulthood, with greater deficits seen in animals treated with *multiple doses in a short period of time*. They recommend that exposure to anaesthesia during the neonatal period should be limited in dose and duration. Another study has shown that 4-hour sevoflurane exposure (2.5%) resulted in reduced hippocampal postsynaptic density protein-95 expression without causing any neuronal loss and was associated with learning and memory disturbances.[17]

Another experimental study reported that 0.5% minimum alveolar concentration (MAC) sevoflurane applied for 6 hours had no significant effect on apoptosis and S100ß levels. Conversely, *isoflurane*, which is given in the same circumstances, was shown to increase the level of apoptosis and S100ß levels.[18] Another study, which evaluated the effects of inhalation anaesthetics in neonatal rats, demonstrated that sevoflurane, isoflurane, and desflurane increased caspase-3 levels. Interestingly, *nitrous oxide* application (up to 150% concentration) for 6 hours did not cause neuroapoptosis; however, apoptosis was increased when nitrous oxide was applied with isoflurane.[19]

Xenon, the currently preferred anaesthetic, does not cause neuroapoptosis when used alone; on the contrary, it reduced the effects of other inhalation anaesthetics when administered first.[20]

Intravenous Anaesthetics

Ketamine

Zou et. al.[21] have examined the effect of *ketamine* anaesthesia duration in newborn rhesus monkeys. Three hours exposure to ketamine did not produce any significant histochemical change, whereas profound brain cell death was observed in the frontal cortex among subjects that were under the effect of ketamine for 9 or 24 hours. In cell culture study of Bosnjak et. al.[22] they demonstrated that ketamine decreases neuronal viability time and dose, dependently, induces apoptotic pathway.

Propofol

Yu et. al. examined neuroapoptosis and long-term behavioural changes in PND7 rats that were given single and repetitive doses of propofol. These effects were more pronounced among the group that was subject to *repeated doses* of propofol.[23]

Benzodiazepines (clonazepam, diazepam, and midazolam) have controversial effects on apoptosis; however, barbiturates (pentobarbital, phenobarbital) clearly increase apoptosis. The few studies that have examined the effects of sodium p-thiopental reported that exposure did not result in increased apoptosis.[24-28] *Dexmeditomidine* has been shown to reduce prenatal toxicity caused by propofol.[29]

CLINICAL STUDIES

Despite the many experimental studies conducted, there is insufficient evidence to conclude that general anaesthetics have a neurotoxic effect on the developing human within mammals, species vary widely in the rate and timing of brain development.

Total maturation of the rat brain takes only a few weeks whereas maturation of the human

brain occurs over many years. Hence 6 hours of anaesthesia in a rat may correspond to 1 month of a human life span. The dose and duration of anaesthetics used in experimental models is not directly proportional to the procedures used in patients. Experimental doses may be as much as 20 times the standard clinical dose.

Retrospective birth cohort study that used New York State Medicaid data collected between the years 1999 and 2002, 383 children who underwent inguinal hernia repair with anaesthesia before the age of 3 were evaluated along with 5050 children who did not undergo an operation. Hazard ratios regarding behavioural and developmental disorders were reported to be 2.3 with exposure to anaesthesia, 1.0 for age, 2.7 for gender, 1.2 for race, and 1.6 for birth complications.[30] Considering that elective surgeries can be postponed, exposure to anaesthesia is an avoidable risk for most infants.

In another report, patients who had been overexposed to anaesthesia had more learning difficulties than those who were treated with appropriate doses. The risk of learning difficulties was progressively increased with repeated exposure to anaesthesia.[31,32] The effects of anaesthesia used during Ceasarean procedures were examined in children. Infants born under regional anaesthesia exhibited fewer learning difficulties in the later stages of their life.[33,34]

One retrospective study examined 10,450 siblings born between the years 1999 and 2005 and evaluated developmental and behavioural disorders among those who did and did not receive anaesthesia prior to the age of 3. The incidence of developmental and behavioural disorder was 128.2/1000/year among those who were exposed to anaesthesia and 56.3/1000/year among those who were not exposed to anaesthesia. Therefore, behavioural disorders were 60% more frequent among those who received anaesthesia in comparison to those who did not. The estimated hazard ratio for developmental and behavioural disorders was 1:1 for those who received anaesthesia once before the age of 3, 2:9 for those exposed twice, and 4 for those who had been exposed to anaesthesia three or more times.[35]

The 2012 Bayesian meta-analysis[36] examined exposure to anaesthesia in children aged <3 years and deficits at age 10 by using a battery of directly administered neuropsychological assessments with deficits found in language and abstract reasoning, cognitive function, motor skills and behaviour.

Average exposed children had lower scores than unexposed peers in receptive (CELF-R) and expressive language (CELF-E).

CELF-R - receptive language (measures listening comprehension)

CELF-E - expressive language score (tracks speaking ability)

Adjusted for demographic characteristics, exposure to anaesthesia was associated with an increased risk of disability in language (95% CI) and cognition (95%).

aRR 1.87 (CELF-R)
aRR 1.72 (CELF-E)

An increased aRR for disability in language and cognition persisted even with a single exposure. Children in this cohort had a higher relative risk of language and abstract reasoning deficits at age 10 than unexposed children.

MOVING TOWARDS THE FUTURE

As clinical studies in the literature are often retrospective, and even strong correlations are not evidence of causality, the Mayo Anesthesia Safety in Kids (MASK) study was launched by Mayo Clinic at the suggestion of the FDA to evaluate neurotoxicity in children exposed to anaesthesia. This included children born in Olmsted County between 1997 and 2007 and who still lived there when they reached 8 years old. Those who received general anaesthesia before the age of 3 were excluded from the study. Children classified as having single, multiple, or no anaesthesia exposure were evaluated between the years 2007 and 2016, when they were at the age of 8-12 or 15-19 with a single session that

lasted for 4 hours using the National Center for Toxicological Research-Operant Test Battery (NCTR-OTB). The NCTR-OTB test evaluates processing speed; cognitive/intellectual memory; attention, language, motor and visual-spatial, and cognitive processing; and executive functions.[37] The Pediatric Anesthesia and Neurodevelopmental Assessment (PANDA), which was conducted by the University of Columbia followed sibling pairs under the age of 3 who underwent inguinal operation up to the age of 8-15, published four symposia in 2-year interval. The first meeting in 2008 established the goals of the study. The second meeting in 2010 was interdisciplinary. The third meeting in 2012 was attended by different disciplines, parents, clinicians, FDA workers, and patient's rights advocates. In this meeting, attendees agreed to collaborate on advanced preclinical, clinical and translational studies.[38,39]

Additionally in 2012, paediatric anaesthesiologists and paediatric surgeons met to discuss the neurotoxicity risk of some elective procedures and anaesthesia applications performed in children and specifically to discuss questions and concerns of parents. Meeting attendees, including paediatric general surgeons, urologists, plastic surgeons, and ophthalmologists, reviewed inguinal hernia, hypospadias-undescended testis, cleft lip, craniosynostosis, cataracts and strabismus applications in early childhood. They emphasized that the amount of volatile anaesthetics and sedation levels could be reduced by using balanced anaesthesia methods, regional anaesthesia methods, and the use of opioid and non-opioid analgesics, but the group was unable to reach a consensus on best practices.[40] At the 2014 meeting, the existing clinical studies, General Anesthesia Study (GAS), MASK, and PANDA, were evaluated, and Strategies for Mitigating Anesthesia-Related neuroToxicity in Tots (SmartTots) presented along with the future targets of this organization. SmartTots is a public-private partnership that investigates the effects of anaesthetic agents on neural development in infants and children. The 2014 report indicated that the collected data was insufficient to draw any conclusions. However, it stated 2 years later that the results would be considered as a public health problem, leading to greater awareness.[41]

The GAS Study (2007-2013) which is a prospective randomized controlled trial enrolled a total of 722 patients. Patients ranged from less than 60 weeks from conception and greater than 26 weeks gestational age. This study was conducted in 28 hospitals from Australia, Italy, the USA, the UK, and Canada. 363 infants in the awake-regional group, and 359 infants in the sevoflurane general anaesthetic plus a regional block in neonates undergoing hernia repair. No opioids or nitrous oxide was used. Regional techniques and intravenous acetaminophen were used for postoperative analgesia. Protocols were applied in order to prevent development of adverse states that would contribute in neurotoxicity, such as hypoglycemia, hypotension, and hypoxia. Children were assessed using the composite cognitive score of the Bayley Scales of Infant and Toddler Development III test at the age of 2 and with the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) Full Scale Intelligence Quotient score at the age of 5. According to the study results, the median general anaesthesia duration was 54 minutes. No significant difference was found between the groups regarding cognitive composite score at 2 years of age. This study provides strong evidence that sevoflurane anaesthesia lasting <1 hour in infants does not produce more severe neurotoxicity at the second year of age than awake-regional treatment. Nonetheless, the primary outcome of this study is the evaluation of neurodevelopmental state at 5 years of age in 2018 and this result has not been published yet. It was also reported in this study that early-period apnoea development (<30 minutes) was less frequent in the regional anaesthesia group.[42]

Other discussed topics are applied anaesthesia techniques to mothers during childbirth. Flick et. al. determined that neuraxial labor analgesia for vaginal delivery did not cause learning disabilities in childhood.[33]

As it was not possible to reach a consensus based on the current data, it was concluded that it would not be appropriate to inform parents and establish a protocol yet.[43]

CONCLUSION

U.S. Food and Drug Administration in December 2016 issued a black box warning on the label of general anaesthetic and sedative drugs to warn of potential risk of these drugs when used repeatedly or for prolonged surgical hours in children.

The FDA warning has drawn criticism from doctors who say it is based on inconclusive data and may cause undue alarm among parents of children who must undergo general anaesthesia. "Given that anaesthetic exposure in early life has not been consistently linked to adverse changes from clinical studies to date, no changes in anaesthetic clinical practice are recommended currently," advised Professor Andrew Wolf on behalf of the Association of Paediatric Anaesthetists of Great Britain and Ireland 2015.[44]

As of April 2017, children's hospitals across Canada are advising parents not to delay necessary surgeries out of fears raised by the U.S. FDA. "Right now, there is really no strong evidence that we should delay surgeries because of the anaesthetic risk," said Dr Jason Maynes, Director of Research in Anaesthesia and Pain Medicine at the Hospital for Sick Children in Toronto, Canada's largest paediatric hospital.[45]

Anaesthesia and surgery is only undertaken when absolutely necessary in children. Short anaesthetics of less than 1 hour are associated with minimal if any effects on the brain development. Sequelae of longer anaesthetics and multiple exposure is still being questioned. Most studies only show an association. GAS, PANDA and MASK are prospective, randomized studies that aim to provide proof and shed light on this matter.

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Managing Acute Post Operative Pain In Opioid Tolerant Patients

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INTRODUCTION

The perioperative management of opioid tolerant patients can be very challenging. Patients who have been exposed to long-term opioids include those on long term prescription opioids; patients with cancer pain or chronic non cancer pain (CNCP); and those using street drugs. In comparison to opioid naïve patients, opioid tolerant patients express higher resting and dynamic (movement) pain scores and 2 to 3 times greater opioids requirement via patient-controlled analgesia (PCA).[1] Medical and nursing staff unfamiliar with these patients may be apprehensive in prescribing or administering large doses of opioids for fear of causing harm.[1] Under-treatment of pain may result in opioid-seeking behaviour with the patient perceived as 'manipulative' and 'non-cooperative'. This can have a negative impact on the doctor-patient relationship and overall patient care.[1]

DEFINITIONS AND TERMINOLOGY

Tolerance
A predictable physiological decrease in the effect of a drug over time resulting in progressive increase in the amount of that drug required to achieve the same effect.

Physical dependence
A physiological adaptation to a drug whereby abrupt discontinuation or reversal of that drug, or a sudden reduction in its dose, leads to a withdrawal (abstinence) syndrome.

Withdrawal can be terminated by administration of the same or similar drug.

Addiction
A disease characterized by aberrant drug-seeking and maladaptive drug-taking behaviours including cravings, compulsive drug use and loss of control over drug use despite the risk of physical, social and psychological harm.

Unlike tolerance and physical dependence, addiction is not a predictable effect of a drug.

Substance use disorder
A cluster of cognitive, behavioural and psychological symptoms indicating that the individual continues using the substance despite significant substance related problems.

Pseudo-addiction
Behaviours that may seem inappropriately drug-seeking but are a result of under-treatment of pain and resolve when pain relief is adequate.

Diversion
Sharing, selling or trading prescribed drugs to someone for whom they are not prescribed.

Opioid Induced Hyperalgesia (OIH)
State of nociceptive sensitization caused by exposure to opioids. (Ramasubbu 2011).

Source: *Adapted from AAPM 2001*

GROUPS OF PATIENTS

Four main groups of opioid-tolerant patients are encountered in acute pain settings.

1. *Patients with chronic non-cancer pain treated with opioids either weak or strong*, where acute presentations may be due to a newly acute painful condition e.g. surgery, trauma or to exacerbation of the underlying chronic conditions e.g. pancreatitis.

2. *Patients with cancer pain treated with opioids*, who may be at various stages of their illness ranging from active treatment or palliation to remission.

3. *Patients with a substance use disorder*, who are either using illicit opioids or on an opioid maintenance treatment programme.

4. *Patients with acute or subacute opioid tolerance or OIH*, due to perioperative or postoperative opioid administration especially opioids of high potency (not covered here).

PRINCIPLES OF ACUTE PAIN MANAGEMENT

Management of opioid tolerant patient should commence at the time of preoperative assessment. The main aims are:

1. Effective analgesia
2. Prevention of withdrawal
3. Strategies to attenuate tolerance
4. Appropriate discharge plan to ensure continuity of long term care.

PREOPERATIVE MANAGEMENT

Preoperative assessment is important to identify risk factors and reduce the patient's surgical and anaesthetic perioperative morbidity or mortality.

Key points for preoperative management are:

1. *Patient identification and detailed opioid history*

   Recognition of patients who are opioid tolerant can be difficult. In some patients the diagnosis can be made during preoperative assessment whereas in others may only be apparent when postoperative pain control is difficult to achieve. Some patients offered their opioid use history willingly while others may be reluctant to do so. A clue that may be indicate the possibility of opioid tolerant is the abuse of non opioid substances e.g. alcohol, marijuana or nicotine. These patients are more likely to have opioid dependency compared to the general population.[3] A urine toxicology test can also be performed to screen for opioid and also other drug of abuse.[4]

   Obtain the details of type, duration of use and the timing of the last dose of opioid. Verify the relevant doses of prescribed drugs but it may not be possible in emergency settings. Therefore, as a temporary measure to prevent the risk of opioid withdrawal, the reported daily opioid amount can be given in two to four divided doses with the response including level of sedation and respiratory rate. Admission to high dependency unit should be considered if the reported "usual" dose is deemed high. Issues of diversion and uncertainty of actual use of verified dose can be addressed by administering a reduced reported dose and repeated over a few days as needed.[5]

2. *Early recognition of opioid withdrawal*

   Withdrawal symptoms (Table I) may occur upon abrupt discontinuation of opioids or when opioid antagonists are administered. The timing of the last dose is extremely important. Additionally, acute withdrawal time frames are substance specific. For instance, morphine and heroine withdrawal occur at 6 to 18 hours compared to 24 to 48 hours for methadone. Opioid users should be encouraged to take their usual dose of prescribed opioid on the morning of elective surgery.[6] For opioid abuser patients the baseline assessment of quantity of opioid use can be difficult to obtain, therefore they may need rapid titration of opioid dose if the initial doses are ineffective.[7]

3. *Perform relevant assessment including history, physical examination, and investigations*

   Opioid tolerant patients undergoing elective surgery have increased risk of postoperative mortality and morbidity. In addition to a routine preoperative history, targeted information should be sought (Table II).

4. *Evaluation of co-morbidities associated with opioid tolerant patient*

   Cardiovascular disease: hypertension, dilated cardiomyopathy.

   Gastrointestinal disease: reduced gastrointestinal motility, gastro-esophageal

reflux disease (GERD), which increases the risk of aspiration during endotracheal intubation, dysphagia, constipation, and bowel discomfort.

Infectious disease: hepatitis, HIV, sexually transmitted disease

Concomitant drug usage: anxiolytics, benzodiazepines, alcohol

Possible coexisting psychiatric disorders: depression, anxiety, psychosis, and personality disorders. Consider referral to psychiatrist and addiction specialist for evaluation.

Difficult intravenous access.

Table I: Sign and Symptoms of opioid withdrawal

Signs	Symptoms
Sweating	Restlessness
Pupillary dilatation	Irritability
Tachycardia	Nausea
Hypertension	Abdominal cramps
Vomiting	Increased sensitivity to pain
Diarrhoea	Myalgia
Yawning	Dysphoria
Fevers/Chills	Insomnia
Rhinorrhoea	Anxiety
Lacrimation	Craving for opioids
Piloerection	

Table II: Pain related assessment in opioid-tolerant patients

Information from all opioid tolerant patients
Current treatment providers
Opioid and non-opioid medications
Dose verification of all relevant medications
Non-prescribed drugs (e.g. over-the-counter and illicit drugs, alcohol, nicotine)
Drug allergies and reactions
Experiences and expectations of acute pain management
Support systems after discharge
Additional information in patients with CNCP or cancer pain
Pain diagnosis
Usual pain scores
Functional status
Prognosis (cancer pain)
Psycho-spiritual issues (including end-of-life issues, anxiety, depression, coping style and strategies)
Where relevant, the authorised prescriber of any opioids
Presence of invasive pain treatment (e.g. Intrathecal pump, spinal cord stimulator)
Medication misuse, evidence of aberrant drug-related behaviour or addiction
Expectations about their admission (e.g. expectation that chronic back pain will be improved after spinal surgery; palliative vs curative surgery in patients with cancer)
Additional information in patients with an addiction
Opioid substitution therapies and doses (methadone)
Other prescribed or illicit substance use (poly abuse is common)
Routes of administration
Where relevant, registered prescriber and dispensing pharmacy
Medical and psychiatric co-morbidities (e.g. blood-borne viruses, hepatic disease, other infections, chronic pain, personality disorder)

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Table III: Recommendations and Equianalgesic Dose Conversion Ratios for Perioperative Pain Management

Commonly used oral / transdermal opioids	Recommendations	Conversion Ratio
Methadone	Continue if allowed orally Convert to oral morphine and then to IV if NBM	Oral methadone: Oral Morphine 1:2-3 *When changing opioids, reduce by 50% for cross tolerance*
Morphine	Continue if allowed orally Convert to IV Morphine and maintain continuous baseline if NBM Additional morphine PCA if required	Oral morphine: IV Morphine 2-3:1
Oxycodone	Continue if allowed orally Convert to IV Morphine and maintain baseline if NBM Additional morphine as indicated	Oral oxycodone: IV Morphine 1:0.5-0.6
Tramadol	Continue if allowed orally Convert to IV morphine and maintain baseline if NBM Additional morphine as indicated	Oral Tramadol: Oral Morphine 5:1
Fentanyl Patch	Continue Additional morphine as indicated	
Buprenorphine patch	Continue Additional morphine as indicated	

5. *Avoidance of prejudice and patient reassurance*

   Opioid tolerant patients fear the risks of under-treatment due to prejudices, and dependence relapse. Consider patients expectation related to their postoperative pain management and investigate the possible correlation with previous experiences. Patients should be reassured that despite a previous or an ongoing history of opioid dependency, effective pain control is an achievable goal. Moreover, the risk of relapses can be minimized.

6. *A perioperative pain plan*

   Investigate and evaluate management strategies used in previous procedures. Discuss with the patient the analgesic strategy (multimodal approach, regional techniques when suitable, PCA).

7. *Continuation of all regular opioids and other drugs prescribed for pain management on the day of surgery, even if the patient is fasting, unless contraindicated*

Those enrolled in an opioid substitution programme, who are to be admitted on the day of surgery, may be able to arrange a 'take-away' dose that can be self-administered preoperatively.

8. *Conversion of oral opioids to its corresponding intravenous (IV) dose of morphine for patients unable to be fed orally*

   The oral morphine equivalent dose (MED) of the current opioid can be calculated by determining the total 24 hours dose of current oral opioids and then converted to equivalent intravenous (IV) morphine dose using equianalgesic tables. (Table III and IV)

Table IV: Example of Opioid rotation from oral methadone to IV morphine

Scenario: An emergency laparotomy is required in a patient taking 100 mg of oral methadone and whom will be nil by mouth after operation
Issues: Patient is unable to take oral methadone, this is converted to a suitable IV morphine to prevent withdrawal
Management: Conversion of oral opioids to IV morphine
Conversion ratio for oral methadone to oral morphine 1:2 or 3
Using a 1:3 ratio 100mg of oral methadone is equivalent to 300mg of oral morphine
300mg of oral morphine is equivalent to a 100mg of IV morphine
Due to incomplete cross-tolerance between opioids, a 50% reduction in the calculated equianalgesic dose is recommended
The dose of IV morphine required to prevent withdrawal is 50mg over 24h
This can be provided via PCA with either (a) an increased bolus dose of between 1.5 and 2mg or (b) a standard PCA bolus of 1mg but with a background infusion of $2mgh^{-1}$

INTRA OPERATIVE MANAGEMENT

There are no preference for a specific intraoperative opioid over another in opioid tolerant patients.[6] The attending anaesthetist needs to be aware of the possibility of a larger dose requirement for adequate pain control. The opioid of choice is to be titrated following the usual method. Dosage and requirements in different surgical settings should be guided by vital signs. Regional analgesia and ketamine infusion are helpful to reduce intraoperative opioid requirements. The surgical wound should also be infiltrated with local anaesthetic at the end of surgery.

Opioid tolerant patients are at increased risk of awareness therefore depth of anaesthesia monitoring may be indicated.

Care should be taken with the placement of warming devices in those with transdermal drug delivery systems, as the heat may accelerate drug release.

POSTOPERATIVE MANAGEMENT

Postoperative pain scores may be higher initially and decrease more slowly than in the opioid-naïve.[4] The interpretation of high pain score can be difficult especially if considered in isolation, therefore comparison with pre-existing 'usual' pain scores can be helpful. It is also important to assess dynamic pain scores and function (ability to take a deep breath, cough and ambulate). If pain scores escalate or fail to decline in the postoperative period, other reasons for pain (e.g. surgical complications) must be considered.[4]

The presence of postoperative triad of elevated pain scores, high opioid use and low incidence of side-effects (apart from sedation) should trigger suspicion of tolerance in those not previously identified as at risk of opioids tolerance.[4]

DRUGS OF CHOICE

Multimodal analgesia is mandatory to reduce opioid consumption. These opioid sparing techniques are:

1. Regularly prescribe **non-opioid analgesics** such as paracetamol, non-steroidal anti-inflammatory drugs, or COX-2 inhibitors unless contraindicated.

2. **PCA** allows instant self administration of mediation as needed (PRN) basis. It decreases the risk of under medication and breakthrough pain while increasing patient satisfaction. It also reduces the nursing staff workload of administering medication. A basal rate of opioid may be administered to opioid-dependent patients to supply baseline requirements in patients not able to take oral medications. Once oral medication is tolerated and satisfactory analgesia achieved with PCA the patient may be switched to oral opioids.

3. The use of **local anaesthetic** techniques including wound infiltration, regional, or neuroaxial block should be employed where possible to improve postoperative analgesia and decrease opioid requirements. Local anaesthetic catheters can prolong the benefits of regional anaesthesia well into the postoperative period.

4. **Ketamine** is recommended in the acute pain management of opioid-tolerant patients as it has been shown to reduce postoperative opioid use and pain scores. Activation of the N-methylaspartate (NMDA) receptor is believed to be one of the mechanisms for the development of opioid tolerance and opioid-induced hyperalgesia (OIH).[4] Ketamine is a non-competitive antagonist of the NMDA receptor and can attenuate both of these phenomena. Low dose ketamine administered as a continuous IV or subcutaneous infusion for 1-5 days can be a useful adjunct for opioid tolerant patients. There are a number of dosing regimes available. An example is 200mg in 50cc=4mg/ml concentration running at initial dose 1ml/hr and can be increased up to 4mls/hr depending on the side effects.

5. **Gabapentinoids** (gabapentin, pregabalin) may have a role in opioid-tolerant patients as an opioid-sparing adjunct. The usage is recommended in patients who persist with poorly managed pain despite maximizing other opioid-sparing techniques and using appropriate doses of opioid. The dose for gabapentin is 300mg TDS or pregabalin 75mg BD, titrated according to efficacy and side-effects.[1]

DISCHARGE PLAN AND MANAGEMENT

The goal prior to discharging patients would be maintaining or resuming the usual medications as soon as possible, with any changes being for short term only.[4] Therefore it is important to formulate and communicate a plan for onward care after discharge. Several factors need to be considered including time expected to the resolution of the acute episode, choice of analgesic agents used, potential complication and its management and the duration of the treatment during the acute phase. Equally crucial are communication with the patients' treating doctors regarding the post discharge care, follow up arrangements as well as patient education and support.

CONCLUSION

The perioperative management of opioid tolerant patients can be tricky. Management starts with identification of at-risk individuals, extends to pre, intra and post operative care and eventually to the establishment of a post-hospital discharge care plan. There are various interventions at each stage essential in preventing pain related complication while ensuring satisfactory pain relief to these patients. The fundamental aspects of management include continuing baseline opioid requirements and maximizing other opioid-sparing techniques. A multi-disciplinary and multi-modal approach to analgesia is essential, as well as ensuring there is a continuing plan in place for onward care in the community.

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The Role Of Peripheral Nerve Blocks In High Risk Adult Patients For Non-Cardiac Surgeries

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INTRODUCTION

In this review article, we discuss the role of peripheral nerve blocks (PNB) in high-risk adult patients with diminished functional capacities, multiple comorbidities and are scheduled for surgeries where PNB can be favourably used as either a component of multimodal analgesia strategy or as the sole anaesthetic technique. General anaesthesia is the gold standard for anaesthetising patients for surgeries such as open aortic, major vascular, neuro, head and neck, pulmonary or abdominal surgeries. PNB can be utilized in procedures involving extremities, and to a lesser extent in thoraco-abdominal surgeries. A recent guideline on the management for postoperative pain strongly recommends that clinicians should consider use of surgical site-specific PNB as part of multimodal analgesia, particularly in patients who undergo lower extremity and upper extremity surgical procedures (high-quality evidence).[1]

HIGH-RISK PATIENTS - RISK STRATIFICATION

High-risk patients require risk stratification for anaesthesia. Appropriate selection of high risk patients for regional anaesthesia may result in the most favourable patient outcome. There are various scoring systems to risk stratify patients perioperatively. The American Society of Anaesthesiologists (ASA) physical status, Lee's Revised Cardiac Risk Index (RCRI) and the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM) scores are some commonly used scoring systems.[2] The scoring systems are fraught with limitations as patients are stratified into expected population risk categories but do not address individualised risk for a single patient. Often, the scores are useful to stratify low risk patients. However, it is poorly discriminatory between high and extremely high risk patients. It is not the intent of this manuscript to discuss in detail perioperative risk stratification for anaesthesia.

Ultimately, the main purpose of patient risk assessment is to include well informed patients to participate in shared decision making about whether surgery represents their best treatment option. Apart from inherent patient risk factors, the effectiveness of perioperative care, surgery-specific risks, operative urgency and intraoperative events are factors that can affect the postoperative outcome.[2] Predictors of 1-year mortality such as increasing numbers of co-morbidities, ASA physical status, age above 65 years, history of major hepatic or cardiovascular diseases, cumulative deep hypnotic, surgical and intra-operative hypotension duration as well as intra-cavitary operations should be taken into consideration in the overall decision-making.[3]

CRITERIA FOR SELECTING REGIONAL ANAESTHESIA[4]

Patients who are deemed to be at high risk for difficult mask ventilation or intubation may be eligible for regional anaesthesia, avoiding the need to instrument their airways. Likewise patients with severe respiratory disease which the use of general anaesthesia and positive pressure ventilation may result in respiratory complications shall be considered. Care should be taken in selecting eligible patients, taking into consideration both the type of surgery and patient factors.

Regional anaesthesia may be considered for short procedures without major expected blood loss. These surgeries include orthopaedic arthroscopies, many urologic procedures, and even some peripheral vascular cases, such as the creation

of an arteriovenous fistula. PNB and neuraxial anaesthesia should also be considered when the risk of general anaesthesia outweighs that of regional anaesthesia and the commonest example will be caesarean deliveries. General anaesthesia may be more appropriate for cases with major fluid shifts or high expected blood loss, or when regional techniques will not provide adequate analgesia.

Patient positioning and airway access should also be considered, as long cases may affect patient comfort in the operating room and may preclude the use of regional anaesthesia as the primary anaesthetic. Nevertheless combined general anaesthesia and regional technique can always be an option if no contraindication. Balanced anaesthesia and multimodal analgesia is the keyword.

Patient selection is also crucial in deciding whether regional anaesthesia should be chosen instead of general anaesthesia. Absolute contraindications to peripheral nerve blockade include patient refusal, infection at the injection site, and true allergy to local anaesthetics. Relative contraindications to peripheral nerve blockade include injury to the injection site, a bleeding disorder, or pre-existing neuropathy. For spinal or epidural anaesthesia, absolute contraindications include coagulopathy, severe and untreated hypovolemia, and increased intracranial pressure. Relative contraindications to neuraxial anaesthesia include an uncooperative patient, sepsis, pre-existing neuropathies or demyelinating diseases, and severe cardiac valve pathologies, such as aortic stenosis or mitral stenosis. Spinal deformities or prior back surgery may also preclude a patient from receiving neuraxial anaesthesia.

Good candidates for regional anaesthesia should be able to remain calm and motionless enough to tolerate both nerve or neuraxial blockade and surgical procedures while awake. Monitored sedation shall be incorporated with regional techniques as primary anaesthetic to improve patient comfort and cooperative whenever possible.

In making the decision to proceed with regional anaesthesia as primary anaesthetic technique for a high risk patient with a recognized difficult airway, the anaesthesia environment should be optimized. The anaesthesiologist should have expertise in regional anaesthesia techniques and difficult airway management, as well as be immediately available in case of emergency. Equipment for difficult airway management and support should be readily accessible. Both the surgical and anaesthesia teams must be in full communication and fully cooperate to ensure patient safety. Ideally, there should be easy and direct access to the head should there be any need for an unplanned endotracheal intubation or advanced airway management. Before proceeding, the patient with a difficult airway should be made aware of the possible conversion to general anaesthesia and the potential placement of a surgical airway.

PNB AND ITS CLINICAL BENEFITS

A. Morbidity and Mortality

The notion that regional anaesthesia may be beneficial over general anaesthesia was mooted by Rodgers et. al. who concluded that neuraxial block reduces postoperative mortality and serious complications; namely deep vein thrombosis, pulmonary embolism, transfusion requirements, pneumonia and respiratory depression.[5] This was supported by data from the systematic review[5] and a few studies on hip and knee athroplasties.[6-8]

In comparison to neuraxial anaesthesia, population-level studies investigating the impact of PNB on perioperative outcomes are still lacking. Memtsoudis et. al.[9] investigated the association between PNB use and outcomes from retrospective data on 1,062, 152 recipients of hip and knee arthroplasties between 2006 and 2013. Their results showed that the use of PNBs were associated with lower odds for most adverse outcomes mainly among patients with total hip arthroplasty (THA). Notable beneficial effects were seen for wound

complications among THA patients and pulmonary complications in total knee arthroplasty (TKA) patients. Use of PNBs was significantly associated with reduction in opioid consumption for patients with THA (16.2%) and TKA (12.7%) respectively.

Patients undergoing non-traumatic major lower extremity amputation commonly have multiple comorbidities like diabetes mellitus, cardiovascular and renal disorders and they are at risk of significant postoperative morbidity and mortality.[10,11] Scott et. al.[10] found no association between the choices of anaesthetic technique (neuraxial versus general anaesthesia) with survival after major lower extremity amputation surgery, when corrected for other variables. The overall 30-day mortality was 12.4%, and was slightly higher in patients with ASA grade IV or V at 23.2%. Chandran et. al.[11] reported a large case series of 57 ASA grade IV patients who underwent above knee amputation with PNB as primary anaesthetic. 91% successfully underwent the surgery with PNB and the overall 30-day mortality was 12.4%. Majority had stable haemodynamic during the surgery and no intraoperative mortality. At present, there are no studies directly comparing PNB with other anaesthetic technique for major lower extremity amputation surgeries in terms of mortality benefit and it is ethically unjustified to conduct such study in high-risk cases.

Generally speaking, many of us experienced the benefits of using regional anaesthesia in high risk patients and the evidences are growing. Therefore, it is reasonable to associate PNB with the potential for reduction in morbidity and mortality.[12,13]

B. Haemodynamic Stability

PNB provide greater haemodynamic stability than any other anaesthesia technique.[11,14-17] This advantage is highly favourable when handling high risk patients known to have limited cardiovascular reserve. For lower extremity surgery, neuraxial technique such as continuous spinal anaesthesia (CSA) can also provide stable haemodynamic when administered judiciously. Nonetheless, CSA is limited in high-risk patients with deranged coagulation or those on anticoagulant/antiplatelet medications without adequate duration of drug(s) cessation.

Aksoy et. al.[16] conducted a small comparative study involved 70 patients on haemodynamic effects of combined psoas compartment-sciatic nerve block (PCSNB) versus CSA in elderly high-risk patients undergoing hip replacement surgery. Both CSA and PCSNB produced satisfactory quality of anaesthesia. The marked stability of haemodynamic profiles in those who had PCSNB were significant when compared with CSA cases.

C. Postoperative Pain (Acute and Chronic)

PNB as a component of multimodal postoperative analgesia regimen leads to improvement in postoperative pain control and reduction in the use of opioids.[18-23] Other notable benefits were reduced incidence of postoperative nausea vomiting,[19,23] earlier step-downs to phase II recovery and/or bypass of post anaesthesia care unit (PACU),[24] reduction in delays of physical therapies initiation,[25] better patients' satisfaction[19] and reduction in hospital length of stay.[25,26]

One potential adverse outcome following surgery is chronic pain. Patients with severe acute postoperative pain are at greater risk of developing chronic pain.[27] Incidence of chronic pain is well documented after amputation, inguinal hernia, lung, breast and gallbladder surgeries.[28] The incidence of chronic post-operative pain is widely variable at 10-55%. This is probably due to differences in surgical and anaesthesia techniques, study design, the affected tissues types, patient populations and difficulties at prompt identification of chronic pain states. PNB as part of the multimodal analgesic strategy for high risk patients undergoing major surgery effectively reduces acute postoperative pain, thus effectively minimising the risk of chronic pain progression.

Regional anaesthesia technique specifically epidural anaesthesia and paravertebral block may prevent

persistent postoperative pain after thoracotomy in every fourth patient and breast cancer surgery in every fifth patient respectively.[29] In addition, continuous peripheral nerve blocks (cPNB) have been described for the treatment of chronic pain such as cancer-induced pain,[30,31] complex regional pain syndrome,[32,33] ischemia-induced pain,[34] ulcer derived pain[35] and phantom limb pain.[36,37]

D. Improved Limb Perfusion

The sympathectomy effect from brachial plexus blockade results in vasodilatation which improves regional vascular flow and thus primary patency rate.[38-40] In addition, brachial plexus blockade can provide effective anaesthesia and analgesia without airway manipulation and is associated with minimal haemodynamic changes. PNB is the preferred anaesthetic technique for vascular access surgery in patients with end stage renal disease.

E. Postoperative Rehabilitation

Superior pain relief can be provided through continuous PNB (cPNB) utilising postoperative perineural catheters for several days.[41,42] This facilitates aggressive rehabilitation, reduction in adverse effects related to systemic analgesia and leads to greater patient satisfaction.[43-45]

PNB FOR HIGH-RISK CASES - SITE SPECIFIC SURGERIES & EVIDENCES

Studies assessing PNB as sole anaesthetic technique in high risk patients are scarce and usually published as case reports, case series or small observational studies.[10,11,46-50] Performing PNB on a high-risk patient is challenging as the anaesthetic options are limited in the event of block failure due to poor physiological reserves. Technical difficulties encountered during block performance may be due to patient, operator or equipment factors. Some of the difficulties encountered are; obese patients with deeper target neural structure relative to usual anatomical location, oedematous soft tissue with poor sono-anatomy view, reduced sensitivity in evoked electrical motor response in diabetic neuropathy, local anaesthetic failure or unpredictable onset from tissue acidosis.[51]

A. Upper Extremity Surgeries

Ultrasound guided brachial plexus block can provide sole surgical anaesthesia for upper extremity surgeries with a success rate of 90-100%.[52] It results in faster block performance, fewer needle passes, reduced incidence of vascular puncture and faster sensory block onset.[53] Knowledge of brachial plexus anatomy facilitates the technical aspects of block placement as various approaches exert different anaesthetic coverage. Knowledge of anatomy also helps to optimize patient-specific block selection. In addition to the anaesthetic coverage, the block selection should take into consideration other factors, such as patient comfort, pre-existing respiratory dysfunction and practitioner experience.[54]

B. Lower Extremity Surgeries

Unlike the upper extremity, it is not possible to anaesthetise the lower extremity with a single PNB injection and the injections are generally deeper than those required for upper extremity block. In addition, the preferential neuraxial techniques provides reliable lower-extremity anaesthesia.[55] Achieving quality anaesthesia and analgesia of the lower limb with PNB is more challenging due to dual innervation from two major plexuses; lumbar and sacral.[54] Most indications for elective lower limb blockades involve either hip or knee joint surgeries. Hence, complete anaesthesia will require at least two nerve blocks. Alternatively, the clinician may choose to perform a single nerve block which covers major innervation of the surgical site for analgesia. The use of ultrasound guidance for lower extremity PNB in comparison with other nerve localization techniques has shown decreased block performance time, decreased block onset time, increased rate of complete sensory block and increased analgesic efficacy.[56]

It is still possible to use PNB as surgical anaesthesia for certain types of hip surgery. However, it can be challenging and commonly requires additional local

infiltration at the proximal site of the skin incision together with deep sedation.[57,58] On occasion, the variable innervation of the surgical site from T12 and L1 dermatomes makes combined lumbar and sacral plexus block an unpredictable method for anaesthesia for hip surgery.[59] Nevertheless, there is a definite role for PNB to provide analgesia after hip and knee surgeries.[60]

C. Truncal Surgeries

PNB of the trunk have been used to provide analgesia for surgical procedures and painful conditions of the thorax or abdomen. Local anaesthetic solution is injected into tissue planes, in which the injectate spreads and reaches variable target nerves that innervate the chest or abdominal wall. There is no need to identify specific nerves or plexi. The most commonly performed truncal blocks are paravertebral, transversus abdominis plane (TAP), rectus sheath, ilioinguinal and iliohypogastric (II/IH) nerve blocks. These blocks were underutilised in the past as the success rates with traditional landmark approaches were operator dependent and associated with serious complications.[61-64] Ultrasound guidance has renewed interest in truncal blocks by reliably guiding the placement of local anaesthetic in the desired location while avoiding inadvertent needle trauma to surrounding structures.[65] Currently, newer ultrasound guided truncal blocks such as PECS I/II, transversalis fascia, quadratus lumborum, serratus plane and erector spinae plane blocks have emerged.[66-71]

Truncal blocks as sole anaesthetic technique for chest or abdominal wall surgery are much less reported and usually considered for patients deemed at high risk for general anaesthesia.[72-78] It is difficult for truncal blocks to provide effective surgical anaesthesia. Intravenous sedation analgesia (multimodal) are often required, especially for blocks which do not cover visceral pain.[79]

Paravertebral block is the most reliable truncal block for surgical anaesthesia. Based on the systematic review by Thavaneswaran,[80] there were 6 randomised controlled trials which used paravertebral blocks as surgical anaesthesia during breast surgery and another 2 trials conducted during open herniorrhaphy. Patients who received paravertebral blocks for surgical anaesthesia at the level of the thoracic and lumbar vertebrae had less pain and postoperative nausea and vomiting in the immediate postoperative period, and reported overall greater patient satisfaction when compared with general anaesthesia.[80] However, it should be emphasized that surgical anaesthesia can only be achieved from multilevel paravertebral blocks, as it is impossible to predictably block all roots in the surgical field using single injection techniques.[81]

D. Increasing The Success Rate of PNB in High Risk Patients

At present, the definition of a successful PNB remains widely variable. There is a lack of universally adopted block success indicators for PNB.[82] Some determinants of PNB efficacy are based on PNB onset time, extent of block, degree of block (surgical or analgesic block), duration of block, requirement of additional rescue PNB or sedative/analgesia adjuncts, presence of block related complications and satisfaction amongst patients, anaesthesiologists, surgeons or institutional executives.[82] It is important to properly delineate the determinants of block success as they relate to key performance indicators in the delivery of optimal healthcare.[83]

In the context of this article, block success is defined by reliable onset, adequate dermatomal coverage and duration of PNB necessary for the completion of operative procedures. These "successful" PNB can be tailored as sole surgical blocks of choice or as analgesic adjuncts in combination with balanced general anaesthesia. Some common and relevant considerations[84] which promote success of PNB are listed in Table III.

Regular practice in regional anaesthesia ensures patient safety and its associated benefits. In the hands of proficient anaesthesiologist, PNB in high-risk patients are more likely to be successful. There are

recommendations for regular training and practice in regional anaesthesia in order to safeguard quality in this service.[87] A team-based approached, led by accredited instructors for the purpose of guiding and supervising doctors during their learning curve in regional anaesthesia is highly encouraged.

Table I: PNB as sole anaesthetic technique in high risk cases for upper and lower extremity surgeries (papers published in indexed journals via Pubmed search)

Author (Year)	Type of PNB	Surgery	Clinical Description
Ferre et. al.[46] (2017)	Interscalene block (ultrasound guidance, short acting LA) plus combined suprascapular and axillary nerve block (ultrasound guidance, long acting LA)	Shoulder	Case report - ASA IV, severe COPD; required NIV during the time of hemi-diaphragmatic paralysis as documented by serial ultrasound examination
Beh et. al.[47] (2017)	Costoclavicular approach infraclavicular brachial plexus block (ultrasound guidance)	2nd stage basilic vein fistula graft transposition	Case report - 2 cases; ASA III, ESRF with morbid obesity, HTN, DM, OSA, difficult airway features, central venous occlusive disease which make conventional supraclavicular brachial plexus block tricky, possible patchy block
Chandran et. al.[11] (2018)	Femoral-obturator-sciatic (67%, 9 cases had lateral femoral cutaneous nerve block), Femoral-sciatic (33%); Ultrasound guidance (65%), dual guidance (35%)	AKA	Large case series: 57 ASA IV patients; 91% successful surgery under PNB
Bang et. al.[48] (2016)	Femoral nerve, lateral femoral cutaneous nerve, and parasacral plexus blocks (ultrasound guidance)	Open reduction internal fixation distal femur	Case report: A 22-year-old male with severe Duchenne muscular dystrophy, no locomotive capability, had symptoms associated with dyspnoea 5 years before and required intermittent ventilation.
Bech et. al.[49] (2009)	PNB (ultrasound guidance or peripheral nerve stimulator)	AKA	Case series: 4 elderly with multiple comorbidities, severe cardiac insufficiencies with LVEF 10-25%

ASA, American Society of Anaesthesiologists; LVEF, left ventricular ejection fraction; DM, Diabetes Mellitus; HTN, hypertension; OSA, obstructive sleep apnoea; AKA, above knee amputation

Table II: PNB as sole anaesthetic technique in high risk cases for abdominal and chest wall surgeries (papers published in indexed journals via Pubmed search)

Author (Year)	Type of Truncal Blocks	Surgery	Clinical Description
Quek et. al.[72] (2014)	Bilateral rectus sheath block (ultrasound guidance) with low dose propofol infusion	Open umbilical hernia surgery	Case report - ASA IV, DM, morbidly obese (BMI 34kgm-2), CCF, LVEF 20%, AF on warfarin therapy
Mishra et. al.[73] (2013)	Bilateral TAP block (ultrasound guidance) with dexmedetomidine infusion	Laparotomy	Case report - ASA IV, COPD with infective exacerbation, type 1 respiratory failure, hypotensive, bowel perforation with peritonitis
Lee et. al.[74] (2015)	Left Subcostal TAP block (ultrasound guidance) with small dose fentanyl supplementation	Open gastrostomy	Case report - Elderly with underlying DM, IHD, previous CVA, spinal stenosis; poor heart function, LVEF 35%; recurrent aspiration pneumonia
Jensen et. al.[75] (2013)	Bilateral Dual TAP block (ultrasound guidance)	Revision of abdominal wall defect	Case report - ASA IV, DM, CCF, IHD, CKD, Obesity, Chronic lung disease
Piccioni et. al.[76] (2010)	Thoracic paravertebral blocks (surface landmark with PNS); Case 1: 5ml ropivacaine 1% each segment for 4 segments; Case 2: 4ml ropivacaine 0.75% each segment for 6 segments	Video assisted thoracoscopy, parietal pleural biopsy and talc pleurodesis	Case report - Case 1: COPD, thyroid cancer with lung, mediastinal lymph node metastasis, hypertension, atrial flutter; Case 2: right lower lobe lung cancer with right paratracheal and hilar lymphatic metastasis, previous DVT
Bizzari et. al.[77] (2015)	Thoracic paravertebral blocks (ultrasound guidance, out of plane); T3 and T4 level, 5ml ropivacaine 0.75% each level; Midazolam 1.5mg intraoperatively	Breast surgery: Right upper outer quadrant quadrantectomy	Case report - ASA II with myasthenia gravis for 20 years - stable phase of disease, mild ocular symptom without respiratory crisis, taking steroid and pyridostigmine
Kerai et. al.[78] (2015)	TAP block (ultrasound guidance, in plane posterior approach), 20ml 0.5% bupivacaine plus 10ml 2% Lignocaine; sedation dexmedetomidine infusion	Inguinal hernioplasty	Case report - 2 patients with complex medical conditions; Case 1: middle age man with congenitally corrected TGA with severe pulmonary stenosis, large VSD with right ventricular dysfunction; Case 2: middle age man with Takayasu arteritis, hypertension

ASA, American Society of Anesthesiologists; LVEF, left ventricular ejection fraction; DM, Diabetes Mellitus; IHD, ischemic heart disease; CVA, cerebrovascular accident; CCF, congestive cardiac failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; TAP, transverse abdominis plane, TGA, transposition of great arteries

Table III: Factors associated with favorable PNB outcomes

Factors	Outcomes	Recommendations
Sedation[85]	Improved patient comfort, cooperation, and tolerance to PNB	End-points of sedation include effect site concentration using target-controlled infusion (TCI) Propofol 0.4-0.8mcg/ml and Remifentanil 0.5-1.0ng/ml. Objective clinical assessment of the level of sedation with validated scales such as observer's assessment of alertness/sedation (OAA/S).
Needle visualization[86]	Definitive and dependable needle visualization	In plane needle-beam alignment can be achieved by careful manipulation of transducer and needle using the freehand technique. The first step in troubleshooting a "disappearing" needle is to visually inspect needle and transducer position and exclude gross malalignment. The transducer should then be moved in a slow and controlled manner, using the 3 basic (sliding, tilting and rotating) movements until the needle shaft and tip have been brought back into view. Avoid moving the transducer and needle at the same time when trying to align them, which makes task more difficult and increases the risk of unintentional needle trauma. As for out of plane needle approach, a "walkdown" technique has been suggested to aid needle tip visualization. Needle manipulation: The visibility of needle can be enhanced by manipulating the needle in several ways including (a) altering the needle-beam angle: a needle-beam angle close to 90 degree offers the best needle visibility when using an in plane approach, (b) needle bevel orientation: needle tip visibility is better when the bevel opening is oriented either directly face the ultrasound beam (0 degree) or to face 180 degree away from the beam, and (c) using needles of larger diameter. Alternative: Use mechanical needle guide attached to the transducer to minimize challenges with needle-beam alignment in the in-plane approach, thus helpful for less experienced operator. However, the utility of mechanical needle guide in US guided PNB requires more investigation. Use echogenic needles to address the poor needle visibility at small needle-beam angle. It is foreseen that the clinical use of echogenic needle may surpass non-echogenic type of needle when the benefits of having good needle visualization outweigh the cost of an echogenic needle. Nevertheless, the needle performance is also manufacturer dependent.

Factors	Outcomes	Recommendations
Proxy indicators of needle tip position[86]	Secondary indicator of needle tip position when actual visualization is challenging	Needle handling can incorporate jiggling movement which create corresponding visible tissue movement at the needle tip. Short-beveled for appreciation of 'pop' sensation between fascial layers. Hydro location: deposition of minimal volume of fluids to confirm needle tip position. Hydro dissection: deposition of beyond minimal volume of fluids to access anatomical space which aids in desired needle advancement.
Ultrasound technology[86]	Utilization of new ultrasound imaging technology to optimize block performance	Spatial compound imaging, which is available on most new ultrasound machine improves needle visibility and should be utilized whenever available. Electronic beam steering is helpful especially for deep PNBs with acute needling angulation.
Proficiency[87]	Quality improvement to achieve targeted key performance indicators (KPI) in PNBs	Standardized and uniform modules for safe and efficient conduct of regional anaesthesia. Modules catered for practice-based pathway for those who completed formal anaesthesiology training. Residency-based pathway as part of ongoing anaesthesiology postgraduate programs.

CONCLUSION

There is a definite role of PNB in high risk patients undergoing non-cardiac surgeries. PNB as the sole anaesthetic technique for high risk cases is a challenge due to patient, operator, equipment factors and the added stress of getting a successful block. PNB should be reserved for those deemed at high risk for general or neuraxial anaesthesia. Additional multimodal sedation analgesia is often required in managing such cases as reported in the literatures.

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