THE EFFECTS OF INTRAVENOUS DEXMEDETOMIDINE PREMEDICATION ON INDUCTION OF ANAESTHESIA USING TARGET-CONTROLLED INFUSION OF PROPOFOL AND REMIFENTANIL

DR SITI NUR AMANI AB AZIZ

DISSERTATION SUBMITTED IN

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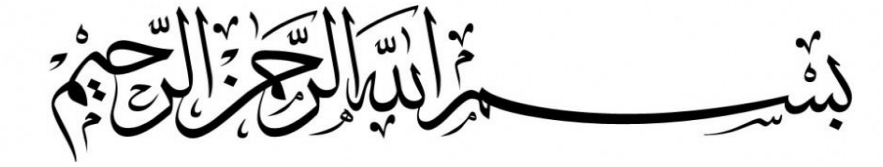

With the name of Allah, Most Gracious Most Merciful again, for His blessings in the completion of this thesis to fulfil the requirement for the degree in anaesthesiology.

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ABBREVIATIONS

ANOVA	Analysis variance
ASA	American Society of Anaesthesiologist
ABA	American Board of Anaesthesiology
BIS	Bispectral index score
BP	Blood pressure
bpm	beat per minute
CI	Confidence interval
Cpt	Target plasma concentration
Ce	Effect-site concentration
ECG	Electrocardiogram
EEG	Electroencephalography
ENT	Ear, Nose and Throat
GABA	Gamma-aminobutyric acid
GA	general anaesthesia
HR	Heart rate
IV	Intravenous
MAP	Mean arterial pressure
SD	Standard deviation
TCI	Target-controlled infusion
TIVA	Total intravenous anaesthesia

ABSTRAK

KESAN SUNTIKAN UBAT DEXMEDETOMIDINE SEBAGAI UBAT PENDAHULUAN KE ATAS PEMBIUSAN YANG MENGGUNAKAN UBAT PROPOFOL DAN REMIFENTANIL SECARA SUNTIKAN BERTERUSAN (INFUSI KAWALAN SASARAN)

Tujuan: Kajian ini dijalankan untuk melihat kesan pendahuluan ubat dexmedetomidine semasa pembiusan bersama infusi kawalan sasaran propofol dan remifentanil ke atas proses induksi dan juga ke atas perubahan hemodinamik.

Tatacara: Seramai lima-puluh empat orang pesakit berstatus ASA I dan II yang dijadualkan untuk pembedahan elektif secara pembiusan am dengan intubasi pada trakea telah dipilih. Kajian ini dijalankan dalam berbentuk prospektif, rawak, pemerhati-buta, cubaan dalam terkawal. Para pesakit dibahagikan kepada dua kumpulan secara rawak. Para pesakit kumpulan dex (n=27) menerima dos pendahuluan dexmedetomidine 1 mcg/kg yang dialirkan selama 10 minit. Para pesakit kumpulan kontrol (n=27) menerima cecair 0.9% normal saline mengikut jumlah isipadu (iaitu bagi 1 mcg/kg dexmedetomidine), yang dialirkan selama 10 minit. Pembiusan am kemudiannya dimulakan untuk semua pesakit, dimulai dengan aliran infusi kawalan sasaran remifentanil sebagai permulaan 2 ng/ml selama satu minit. Seterusnya diikuti dengan aliran infusi kawalan sasaran propofol sebagai permulaan 2 mcg/ml. Selepas satu minit, dos propofol akan dinaikkan sebanyak 0.5 mcg/ml setiap 30 saat sehingga pesakit mencapai pembiusan optimum; tidur/tidak sedar. Selepas

itu pesakit akan diberi suntikan rocuronium sebanyak 0.9 mg/kg dan saluran pernafasannya diintubasi selepas satu minit pemberian rocuronium. Selepas proses intubasi, infusi kawalan sasaran remifentanil akan dinaikkan sebanyak 1 ng/ml setiap kali, sekiranya kadar degupan jantung semakin laju atau/dan tekanan darah semakin meningkat. Kenaikan ini dilakukan sehingga kadar degupan jantung dan tekanan darah menjadi lebih stabil. Kepekatan propofol di dalam darah, kepekatan propofol pada organ-sasaran, masa untuk proses induksi iaitu bermula aliran propofol sehingga pesakit tidur dan jumlah remifentanil yang diperlukan untuk menstabilkan parameter jantung selepas intubasi dicatatkan. Tekanan darah, purata tekanan darah, kadar degupan jantung dan skor kesedaran dicatatkan pada T permulaan, T selepas dos ubat pendahuluan, T selepas remifentanil, T selepas pesakit mencapai tidur, T sebelum intubasi, T 1 minit selepas intubasi dan T 5 minit selepas intubasi.

Keputusan: Kumpulan dex menunjukkan kepekatan propofol di dalam darah yang lebih rendah berbanding kumpulan kontrol [2.44 (0.54) vs 4.20 (1.11) mcg/ml, masing-masing; $p<0.001$]. Kepekatan propofol pada organ sasaran juga lebih rendah dalam kumpulan dex berbanding kumpulan kontrol [1.60 (0.67) vs 0.67) mcg/ml, masing-masing; $p<0.001$]. Masa induksi lebih singkat dalam kumpulan dex berbanding kumpulan kontrol [71.59 (38.13) vs 182.48 (62.64) saat, masing-masing; $p<0.001$]. Semasa induksi, terdapat perbezaan yang bererti dalam purata tekanan darah antara dua kumpulan bersandarkan masa; ($F=35.64$, $p<0.001$). Purata tekanan darah kumpulan dex adalah signifikan lebih rendah berbanding kumpulan kontrol pada T selepas remifentanil; [85.93 (CI 95% 80.85, 91.01) vs 94.89 (CI 95% 89.81, 99.97) mmHg]. Kadar degupan jantung juga menunjukkan perbezaan bererti antara dua kumpulan tanpa mengira masa ($p=0.002$) dan juga perbezaan bererti dalam-antara kumpulan bersandarkan masa ($F=22.38$, $p<0.001$). Purata kadar degupan jantung dalam kumpulan dex adalah signifikan lebih rendah berbanding kumpulan kontrol pada T selepas dos ubat pendahuluan; [64.48 (CI 95% 59.94, 69.03) vs 81.22 (CI 95% 76.68, 85.79) bpm] dan pada T selepas remifentanil; [64.00 (CI 95% 59.16, 68.83) vs 79.37 (CI

95% 74.53, 84.21) bpm]. Selepas intubasi, terdapat perbezaan bererti dalam purata tekanan darah antara dua kumpulan tanpa mengira masa ($p<0.001$). Bagi kadar degupan jantung pula, terdapat perbezaan bererti dalam purata kadar degupan jantung tanpa mengira masa ($p=0.004$). Manakala untuk skor kesedaran, terdapat perbezaan bererti dalam purata skor kesedaran untuk dalam-antara dua kumpulan bersandarkan masa ($F=22.40$, $p<0.001$). Purata skor kesedaran kumpulan dex adalah signifikan lebih rendah berbanding kumpulan kontrol pada T selepas dos ubat pendahuluan; [87.36, (CI 95% 85.75, 89.90) vs 97.71 (95.68, 99.74)] dan pada T selepas remifentanil; [83.61 (CI 95% 79.96, 87.26) vs 95.38 (CI 95% 91.80, 98.95)]. Purata skor kesedaran kumpulan dex adalah signifikan lebih tinggi berbanding kumpulan kontrol pada T selepas pesakit mencapai tidur; [72.04 (CI 95% 67.65, 76.44) vs 63.46 (CI 95% 59.16, 67.76)] dan pada T 5 minit selepas intubasi; [54.00 (CI 95% 49.36, 58.64) vs 41.54 (CI 95% 37.00, 46.08)]. Tiada perbezaan yang bererti dilihat pada: purata tekanan darah antara kedua-dua kumpulan dan kadar degupan jantung pada ‘dalam-antara’ kumpulan semasa proses induksi, kadar degupan jantung pada ‘dalam-antara’ kumpulan selepas proses intubasi dan skor kesedaran antara dua kumpulan.

Kesimpulan: Pemberian ubat permulaan dexmedetomidine mengurangkan dos kepekatan propofol di dalam darah dan kepekatan propofol pada organ-sasaran semasa proses induksi. Ia juga menurunkan parameter hemodinamik yang stabil semasa proses induksi dan proses intubasi saluran pernafasan dan juga memendekkan masa pembiusan.

ABSTRACT

THE EFFECTS OF INTRAVENOUS DEXMEDETOMIDINE PREMEDICATION ON INDUCTION OF ANAESTHESIA USING TARGET-CONTROLLED INFUSION OF PROPOFOL AND REMIFENTANIL

Objective: The aims of this study were to determine the effects of intravenous dexmedetomidine premedication on induction of anaesthesia and intubation using TCI propofol and TCI remifentanil.

Methods: 54 respondents, aged 18 to 60 year-old, ASA I – II patients scheduled for elective surgeries under general anaesthesia with endotracheal intubation were enrolled in this prospective, randomized, observer blinded, controlled clinical trial. They were randomly allocated into two groups. Group I: Dex Group (n=27) received infusion loading dexmedetomidine 1 mcg/kg over ten minute. Group II: Control Group (n=27) received the same calculated volume of 0.9% normal saline solution over ten minute. General anaesthesia was induced in both groups with TCI remifentanil starting at 2 ng/ml over one minute followed by TCI propofol at target plasma concentration of 2 mcg/ml. After one minute, the TCI propofol will be titrated every 0.5 mcg/ml in every 30 second until loss of consciousness achieved. After successful induction, intravenous rocuronium 0.9 mg/kg was given and intubation done after one minute. After intubation, TCI remifentanil must be tapper up by 1 ng/ml if there were any tachycardia and hypertension until stable. The following data were recorded; target plasma concentration and effect-site concentration of propofol at

successful of induction, the induction time from starting of TCI propofol to loss of consciousness and any supplementation of TCI remifentanil after intubation. The following parameters were recorded; blood pressure (BP), mean arterial pressure (MAP), heart rate (HR) and bispectral index score (BIS) at T baseline, T after completed loading drug study, T after TCI remifentanil, T after successful TCI propofol, T before intubate, T 1 minute after intubate and T 5 minute after intubate.

Results: Dex Group showed significantly lower target plasma concentration of propofol than control group [2.44 (0.54) vs 4.20 (1.11) mcg/ml; p<0.001]. The effect-site concentration of propofol also significantly lower in Dex Group than control group [1.60 (0.67) vs 3.43 (1.09) mcg/ml; p<0.001]. Dex Group had significantly shorter induction time compared to control group [71.59 (38.13) vs 182.48 (62.64) second; p<0.001]. During induction of anaesthesia, there was a significant difference of mean MAP between the two groups based on time; (F=35.64, p<0.001). Mean of MAP in Dex Group was significantly lower than control group at T after TCI remifentanil; [85.93 (CI 95% 80.85, 91.01) vs 94.89 (CI 95% 89.81, 99.97) mmHg]. In term of HR on induction, there were significant differences between the groups (p=0.002) regardless of time and within-between the group based on time (F=22.38, p<0.001). Mean of HR in Dex Group was significantly lower than control group at T after intravenous loading dex; [64.48 (CI 95% 59.94, 69.03) vs 81.22 (CI 95% 76.68, 85.79) bpm] and at T after TCI remifentanil; [64.00 (CI 95% 59.16, 68.83) vs 79.37 (CI 95% 74.53, 84.21) bpm]. After endotracheal intubation, there were significant differences of mean MAP between the two groups (p<0.001) regardless of time. In term of HR after endotracheal intubation, there were significant differences of mean HR between the two groups (p=0.004) regardless of time. The BIS core was significantly lower in Dex Group compared to control group after intravenous loading of dexmedetomidine, [87.83 (7.06) vs 97.70 (0.47); p<0.001]. In term of the BIS score changes there was a significant difference of mean BIS score within-between the two groups based on time (F=22.40, p<0.001). Mean of BIS score in Dex Group was significantly lower than control group at T after intravenous loading

dexmedetomidine; [87.36, (CI 95% 85.75, 89.90) vs 97.71 (95.68, 99.74)] and at T after TCI remifentanil; [83.61 (CI 95% 79.96, 87.26) vs 95.38 (CI 95% 91.80, 98.95)]. Mean of BIS score in Dex Group was significantly higher than control group at T after successful induction; [72.04 (CI 95% 67.65, 76.44) vs 63.46 (CI 95% 59.16, 67.76)] and at T 5 minute after intubation; [54.00 (CI 95% 49.36, 58.64) vs 41.54 (CI 95% 37.00, 46.08)]. No other significant different seen in other parameter; mean of MAP between the two groups and mean of HR within-between the group during induction of anaesthesia, mean HR within-between the group after endotracheal intubation and mean BIS score between the two groups.

Summary: Premedication of dexmedetomidine reduced the requirement of target plasma concentration and effect-site concentration of TCI propofol for induction. It also produced shortened induction time and more stable haemodynamic changes during induction, as well as intubation.

CHAPTER 1: INTRODUCTION

Nowadays there are many ways and options to conduct general anaesthesia. Other than bolus intravenous induction and inhalational induction, the introduction of total intravenous anaesthesia (TIVA) offered another step of induction. The introduction of TIVA gives a better understanding on pharmacokinetics of the drugs. This eventually led to the introduction of target controlled infusion (TCI). Why the techniques of induction and maintenance of anaesthesia is expanding? The aims remain to provide smooth induction with minimum haemodynamic changes, at the same time maintaining the adequate depth of anaesthesia during the induction and intubation as well as throughout the maintenance and extubation period.

Laryngoscopy and tracheal intubation is a known procedure that most often associated with elevation of heart rate and blood pressure due to sympathetic response to the manipulation of the airway. These surge of responses have been described by King et al. (1951) more than 60 years ago (King *et al.*, 1951). Even though the surge of these parameters are transient and might only cause minimum consequence in ASA physical status I and young patients, it can cause negative effect in the vulnerable patient (Kovac, 1996). For the examples are; patients with long standing diabetes mellitus, hypertension, high intracranial pressure and cardiac disease. Studies in anaesthetized patients proved that sympathetic nerve activity and blood pressure rose rapidly during laryngoscopy and intubation (Ebert *et al.*, 1990; Ebert *et al.*, 1992; Sellgren *et al.*, 1992) and it also indirectly affected the renal system; as it caused alpha-adrenergic renal vasoconstriction in response

to the physiological stress (Conboy *et al.*, 2010; Momen *et al.*, 2005; Momen *et al.*, 2003; Sauder *et al.*, 2008). Therefore stimulation of sympathetic excitatory response during laryngoscopy and intubation may contribute significantly to perioperative cardiovascular morbidity and mortality as well as carry significant risk to other vital organ (Muller *et al.*, 2013).

How does this sympathetic response occur during induction, laryngoscopy and intubation? In the pharynx, the sensations are innervated by glossopharyngeal nerve and the motor aspect is innervated by vagus nerve. For the larynx, the sensory is innervated by internal laryngeal nerve and recurrent laryngeal nerve. Its motor innervation is also by recurrent laryngeal nerve except for cricothyroid muscle (Ellis, 2004). The mechanism of intubation response is based on sympathetic and parasympathetic responses. The sympathetic response is a polysynaptic pathway with the glossopharyngeal and vagus nerve forming the afferent arch to the sympathetic nervous system via the brainstem and spinal cord. Then produced autonomic response at the efferent by increased the firing of the cardioaccelerator fibres and release of adrenergic mediator including catecholamine. Therefore the summation effects are the rise in blood pressure, heart rate and pulmonary artery wedge pressure as well as the decreased in the ejection fraction. The parasympathetic reflex is monosynaptic. It is common in children but can still occur in adults. The reflex is mediated by increased in vagal tone at the sino-atrial node (*Blunting the intubation response: Fact or Fiction* 2011)**.** Many other studies showed significant haemodynamic response throughout laryngoscopy and intubation (Hassan *et al.*, 1991; Shribman *et al.*, 1987; Singh and Smith, 2003; Takahashi *et al.*, 2002) with the increment of systolic BP up to 41-53mmHg, HR up to 20-23bpm and MAP up to 100% from the baseline (King *et al.*, 1951; Perkins *et al.*, 2013).

In 1992, during the World Congress at The Hague, a European task force for TIVA was initiated. Since then there was huge expansion of the usage of TIVA into the clinical practise parallel with better understanding of pharmacokinetic of intravenous induction agent. This eventually led to the introduction of TCI in 1996 according to European Society of Intravenous Anaesthesia (EuroSIVA). TIVA is a technique of general anaesthesia using combination of agents given solely by the continuous intravenous route and in the absence of inhalational agent. In the TIVA it is focused on the concentration of the drugs in the plasma. The TCI is also given continuous intravenous route, but it is more precise. TCI is an infusion controlled in such manner as to attempt to achieve a user defined drug concentration in a body compartment of interest known as effect site concentration (Sivasubramaniam, 2007). The software calculates continuously the patient's expected drug concentration and administers a bolus-elimination-transfer regimen and adjusting the pump infusion rates based on weight, height, age and sex of the patient to achieve effect-site concentration; in our practice the effect site is the brain. There are many TCI models and TCI pumps available (Absalom *et al.*, 2009; Sivasubramaniam, 2007). In this study, we used Marsh model targeting plasma concentration for the propofol and Minto model targeting effect-site concentration for the remifentanil. The TCI pumps for both drugs are an Injectomat TIVA Agilia, manufactured by Fresenius Kabi, Germany. TIVA and TCI techniques offer markedly reduce incidence of post-operative nausea and vomiting, more predictable with rapid recovery and greater hemodynamic stability. Other than that, it also reduces atmospheric pollution, easier to titrate, preservation of hypoxic pulmonary vasoconstriction and reduction in intracereberal pressure (College of Anaesthesiologists, 2013; Yuill and Simpson, 2002).

Dexmedetomidine is a centrally acting alpha 2-adrenergic receptor agonist. Initially manufacturer suggests dexmedetomidine is indicated for two conditions; for conscious-sedation in non-intubated patient during minor surgical procedures such as cataract surgery

and dental surgery or any other clinical procedure such as awake fibreoptic intubation, and colonoscopy. Second condition is for sedation in mechanically ventilated patient in intensive care for less than 24hours sedation. Nowadays the use of dexmedetomidine has been expanding into operation theatre environment as an adjunct in anaesthesia particularly during TIVA (García Botero *et al.*, 2011). In general, it has been proven to have the ability to blunt the stress response associated with anaesthesia procedures (Talke *et al.*, 2000). When dexmedetomidine is infused at doses ranging from 0.25 to 2 mcg/kg over two minute, it produced dose dependent sedation with peak sedative effect seen at tenth minute after drug administration (Belleville *et al.*, 1992). The main concern of dexmedetomidine effect is on cardiovascular system. An infusion of dexmedetomidine from 0.25 to 2 mcg/kg over two minute caused a dose dependant decreased about 14% to 27% in arterial BP (Bloor *et al.*, 1992). There were also decreased in heart rate and cardiac output at the dosage above 0.5 mcg/kg with reduction of 20% at 1 mcg/kg and 40% at 2 mcg/kg doses (Bloor *et al.*, 1992). Dexmedetomidine produces a reduction in systemic sympathetic tone with preserved baroreceptor activity and sensitivity (Hogue Jr *et al.*, 2002). Other advantages of dexmedetomidine; it has shown efficacy in decreasing the needs for opioids, benzodiazepines and propofol (Arcangeli *et al.*, 2009).

Propofol, 2,6-diisopropylphenol, is an intravenous anaesthetic agent, used primarily for induction in general anaesthesia and for the maintenance of anaesthesia. The context-sensitive half- time is 20min even after eight hour of infusion (Evers *et al.*, 2011). The context-sensitive half-time of propofol is minimally influenced by the duration of infusion because of rapid metabolic clearance after infusion is discontinued. Infusion propofol in combination with short acting opioid has proved to be a valuable adjuvant during short ambulatory procedures. General anaesthesia with propofol associated with very minimal post-operative nausea and vomiting and minimal residual sedative effects. The effect of propofol on the cardiovascular system, i.e significantly decreases systemic BP, is more than

that evoked by comparable doses of thiopental. There is no protective effects on the haemodynamics during stimulation from direct laryngoscopy and intubation. According to the College of Anaesthesiologist (2013) the recommended target concentration for induction of anaesthesia for propofol starts at 4 mcg/ml and titrable till up to loss of consciousness and followed by maintenance 2 to 6 mcg/ml. This target concentration is applicable for individual less than 90kg, not more than 65 years old and ASA I and II.

Remifentanil is a mu-agonist opioid. It is an ultra-short acting opioid. It is rapidly hydrolysed by red cell and tissue esterases. Remifentanil has a low volume of distribution, 400ml/kg but the clearance is high, 40-45ml/kg/min. Therefore its elimination half-life is extremely short, eight to ten minute without accumulative effects. The context-sensitive half-time is three to five minute, more rapid than any other opioid. Since it has rapid offset, it must be given by continuous infusion (Calvey and Williams, 2009). Anaesthesia can be induced by administration of 1 mcg/kg over 60 to 90 second (Stoelting and Hillier, 2006). If rapid bolus given, it can cause marked bradycardia, hypotension and chest wall rigidity. Based on College of Anaesthesiologist (2013), for the TCI to start at 2 ng/ml and increase to 3 ng/ml before intubation and maintenance 1 to 8 ng/ml. For the TIVA, 1 mcg/kg over 60 to 90 second then maintenance 0.1 to 1 mcg/kg/min.

For this study, we wanted to assess the effects of intravenous dexmedetomidine premedication on induction of anaesthesia using target-controlled infusion of propofol and remifentanil and haemodynamic changes during intubation in patient undergoing surgical procedure under general anaesthesia. Specifically, we would like to look into the target plasma concentration and effect-site concentration of propofol at successful induction of anaesthesia after intravenous loading dose of dexmedetomidine between the two groups and the induction time between the two groups. We also wish to see the haemodynamic changes during induction of anaesthesia and after endotracheal intubation. The last objective in this study is to observe the BIS score changes throughout induction and intubation procedures.

CHAPTER 2: LITERATURE REVIEW

2.0 INTRODUCTION OF ANAESTHESIA

In the community perspective, going for surgery is equivalent to going for sleep due to the anaesthetic medications and its technique.

2.0.1 THE HISTORY AND DEFINITION OF ANAESTHESIA

Modern anaesthesia is said to have begun with the successful demonstration of etherization by William Morten in October 16, 1846 at the Massachusetts General Hospital, Boston. He as a dentist, administered diethyl ether to Edward Abbott for the excision of a tumor for his neck. Together with William Marton were Hickman, Wells, Davy and Long (Bovill, 2008; Cottineau *et al.*, 1998).

Inhalational anaesthesia rapidly became common for surgery; with ether, nitrous oxide and chloroform. These agents predominated the anaesthetic world until the development of organic fluorine chemistry in the 1950s. Introduction of fluorine paved the way for the synthesis of the fluorinated anaesthetic alkanes and ethers used in modern anaesthesia.

The word ‘etherization’ was used during initial introduction of anaesthesia. It then replaced with the terms anaesthesia and narcosis (a Greek word for loss of sensation or without feeling and stupor or paralysis, respectively) (Bovill, 2008; Urban and Bleckwenn,

2002). The expansion of definitions then well-established later by Woodbridge Antognini and Overton (Urban and Bleckwenn, 2002).

In the modern era, the definition of anaesthesiology provided by American Board of Anaesthesiology (ABA), states that anaesthesiology is the practice of medicine providing insensibility to pain during surgical, obstetric, therapeutic and diagnostic procedures. The insensibility to pain may be provided by local anaesthetic, regional anaesthetic or general anaesthesia (GA).

According to ABA, GA is defined as a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilator function is often impaired. Patients often require assistance in maintaining a patent airway, with positive pressure ventilation required due to depressed spontaneous ventilation or drug induced depression of neuromuscular function. The cardiovascular function may also be impaired.

2.0.2 TYPES OF ANAESTHESIA AND THE AIMS DURING GENERAL ANAESTHESIA

There are many types of anaesthesia as seen in Figure 2.3.1.

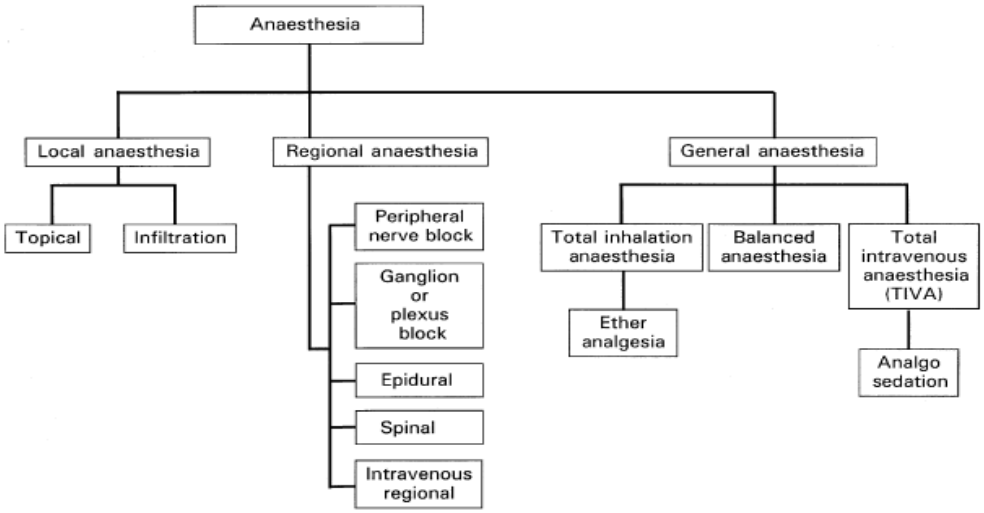

Figure 2.0.2.1: Types of anaesthetic procedures

From: Urban and Bleckwenn 2002. Concepts and correlation relevant to general anaesthesia. ***British Journal of Anaesthesia***, 89 (1):3-16

In our study, we focus on GA that requires endotracheal intubation. The concern is to achieve and keep smooth induction and maintain stable haemodynamic changes (Urban and Bleckwenn, 2002). Figure 2.0.2.2 summarized the aim during GA, hence minimizing the potentially harmful direct and indirect effects of anaesthetic agents and techniques and at the same time, sustaining physiologic homeostasis during surgical procedures for good post-operative outcomes.

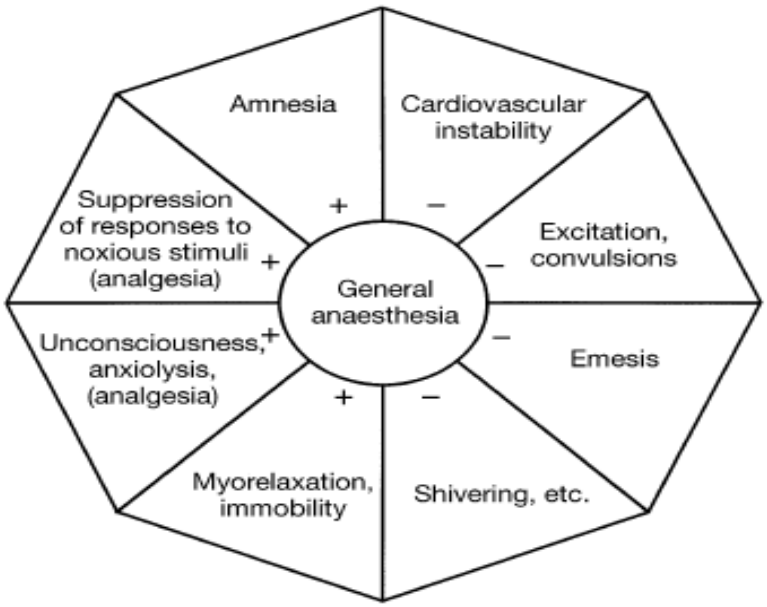

Figure 2.0.2.2: Components of general anaesthesia, those to be achieved and those to be avoided.

Analgesia has been put in brackets because it is already included in other categories; if pain is defined as conscious awareness of a noxious stimulus, then unconscious patient may not perceive pain. Immobility includes the abolition of spontaneous movement.

From: Urban and Bleckwenn 2002. Concepts and correlation relevant to general anaesthesia. ***British Journal of Anaesthesia***, 89 (1):3-16

2.0.3 GENERAL ANAESTHETIC AGENTS IN CLINICAL USE

Since introduction of ether, there have been other varieties of anaesthetic drugs that have been introduced, as seen in Figure 2.0.3.1 They consist of halogenated ethers; sevoflurane, desflurane, isoflurane, enflurane, the halogenated alkane; halothane, nitrous oxide, intravenous induction agents; barbiturates, benzodiazepines, etomidate and analgesic (Evers *et al.*, 2011; Urban and Bleckwenn, 2002).

None of the above agents can be used as a single agent to provide anaesthesia. The inhalational agents lack analgesia potency and may even possess hyperalgesic properties (Zhang *et al.*, 2000). The intravenous anaesthetic agent also lack analgesia potency; with

propofol being known to cause pain during injection. As a result, multiple co-administration of drugs are given to provide good GA; the hypnotic drug, the analgesic drug and a muscle relaxant.

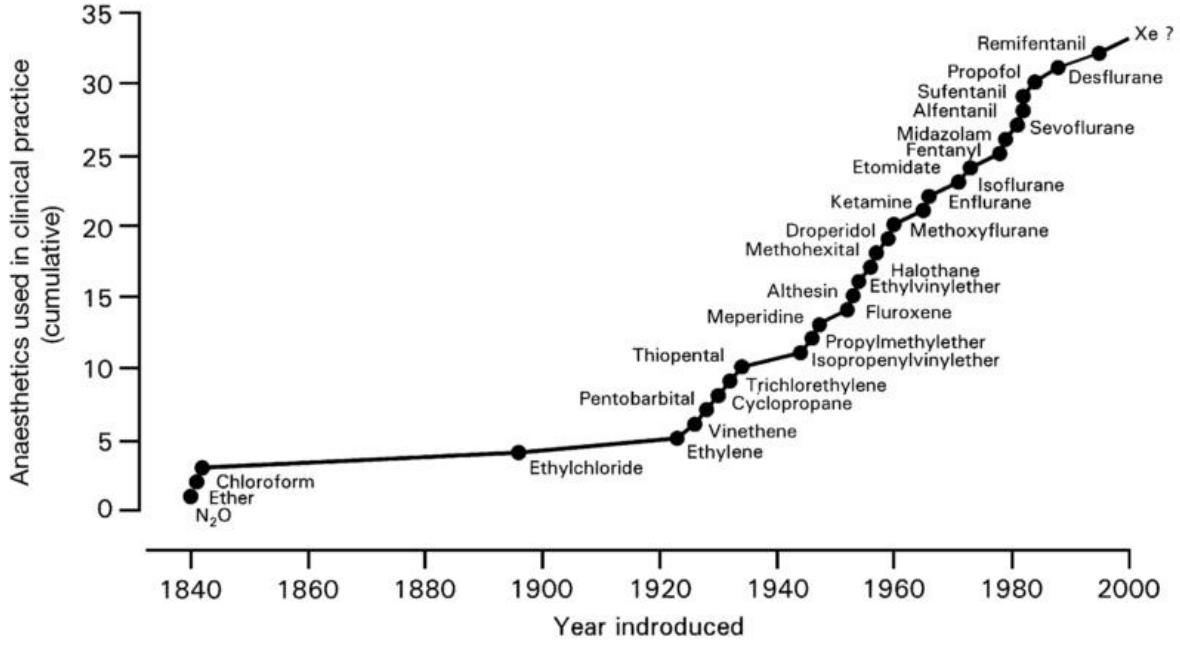

Figure 2.0.3.1 Dates of introduction of anaesthetic drugs

From Urban and Bleckwenn 2002. Concepts and correlation relevant to general anaesthesia. ***British Journal of Anaesthesia***, 89 (1):3-16

2.0.4 MECHANISM OF HAEMODYNAMIC RESPONSE TO LARYNGOSCOPY

Let us revise the anatomy of the airways and the mechanism of intubation response. In the pharynx, the sensory is innervated by glossopharyngeal nerve and the motor is innervated by vagus nerve. In the larynx the sensory is innervated by internal laryngeal nerve and recurrent laryngeal nerve. The motor innervation of the larynx is also by recurrent laryngeal nerve except for cricothyroid muscle (Ellis, 2004). The mechanism of intubation response is based on sympathetic and parasympathetic response. The sympathetic response is a polysynaptic pathway with the glossopharyngeal and vagus nerve forming the afferent arch to the sympathetic nervous system via the brainstem and spinal cord. Then they produced autonomic response at the efferent by increased the firing of the cardioaccelerator fibres and release of adrenergic mediators including catecholamine. Therefore the summation effects are rise in BP, HR and pulmonary artery wedge pressure with decreased ejection fraction. The parasympathetic reflex is monosynaptic. It is common in children population but still can occur in adult population. The reflex is mediated by increased in vagal tone at the sino-atrial node (*Blunting the intubation response: Fact or Fiction* 2011).

According to King et al. (1951) the haemodynamic changes was due to either decreased vagal tone or increased sympathoadrenal activity. They found that it was easier to block the response of BP than the increment in the HR. The laryngoscopy without intubation alone can increased BP effect and this response augmented with intubation is unfortunately capable of produce arrhythmia (King *et al.*, 1951).

The cardiovascular response to the laryngoscopy and intubation not only involves central nervous system (CNS) but also by increased adrenomedullary catecholamine activity (Bedford, 1988; Derbyshire *et al.*, 1983; Derbyshire *et al.*, 1987). Apart from explanation of

the CNS role, there also effects of polysynaptic pathways which cause the release of noradrenaline from adrenergic nerve terminals in vascular beds and release of adrenaline from the adrenal medulla. Derbyshire et al. (1983) also highlighted the possible involvement of renal role: release of renin from the juxtaglomerular apparatus cause activation of renin-angiotensin system which may contribute to the hypertensive response during tracheal intubation.

There was a study done separating the response to laryngoscopy and the act of endotracheal intubation (Ovassapian *et al.*, 1983). The study reported maximum increase in BP and HR occurred during placement of endotracheal tube in the trachea. Another similar study also found significant elevation of BP and catecholamine in laryngoscopy with or without intubation with HR increased further during intubation (Shribman *et al.*, 1987).

2.0.5 THE EFFECTS OF GENERAL ANAESTHESIA ON HAEMODYNAMIC DURING INDUCTION AND INTUBATION

Many studies had been done regarding haemodynamic impact during induction and intubation in relation to either pharmacological agents or techniques of anaesthesia and intubation.

2.0.5.1 Effects from the drugs manipulation

A comparison was made between opioid and beta blocker to obtund the sympathetic reflex during intubation. Bolus injection of fentanyl 2 mg/kg failed to prevent elevation of HR and BP, whereas esmolol 2 mg/kg was able to maintain HR but not the BP (Hussain and Sultan, 2005). In study by Rathore et al. (2002) with different doses of esmolol to obtund sympathetic reflex during laryngoscopy showed a rise in HR and systolic pressure at two minute intubation in all groups. The only significant group was esmolol 150mg, which was the highest dose in the study, to keep minimum elevation in haemodynamic changes at two minute intubation (Rathore *et al.*, 2002). A comparative study between two opioids on haemodynamic changes during intubation was done (Sharma and Parikh, 2014). There is increased in systolic pressure, diastolic pressure and HR at intubation in both groups; nalbuphine and fentanyl. However the rise was more in nalbuphine group than fentanyl group for the BP, but not in the HR. They concluded the elevation of HR was not significant in both groups (Sharma and Parikh, 2014).

2.0.5.2 Effects from the technique of anaesthesia

A study from Thailand on effect of propofol induction by manual bolus injection versus target controlled-infusion (Taweesangsuksakul, 2010). He reported that there were no significance difference in haemodynamic parameters during intubation by target-controlled infusion and manual bolus infusion despite dose of induction by target controlled infusion was much more than manual bolus infusion.

2.0.5.3 Effects from the technique of intubation

Airway manipulation by direct laryngoscopy and intubation are known to induce clinical changes in haemodynamic parameter. These procedures are among the most painful process during anaesthesia associated with haemodynamic response which can last at least 10 minute (Barak *et al.*, 2003; Bruder *et al.*, 1991; Malde and Sarode, 2007; McNicol *et al.*, 2011). Throughout these procedures, there is sympathoadrenal stimulation and causing release of catecholamine which cause surge of HR and BP. This causes alteration in hemodynamic up to more than 30% from the baseline (Edwards *et al.*, 1994; Kovac, 1996).

Tabari et al. (2013), comparing intubation by direct laryngoscopy and intubating laryngeal mask showed: there were rises of BP and MAP in both groups but no differences seen in both group when compared to after intubation (Tabari *et al.*, 2013). Bennett et al. (2004) reported MAP increased at intubation in the tracheal intubation group and in the intubating LMA (ILMA) group but not in the LMA group. There were also rises in HR but the changes were not significant (Bennett *et al.*, 2004).

2.0.6 IMPACT OF INDUCTION AND INTUBATION TO THE HAEMODYNAMIC INSTABILITY

Even though haemodynamic response does not present a problem for most of the patients, in subgroup particularly with cardiovascular and cerebral diseases may increase risk of mortality and morbidity from acute tachycardia and hypertension resulting from the stress of laryngoscopy and endotracheal intubation (Roy *et al.*, 1979; Thomson, 1989). Kovac (1996) in his report mentioned that few studies support that controlling peri-operative stress, induction and intubation included, improved outcomes in high risk patients (Giles *et al.*, 1982; Moffitt *et al.*, 1985; Slogoff and Keats, 1985).

Activation of sympathetic response can cause hypertension, tachycardia, arryhtmia, increased intracranial pressure and increased intraocular pressure (Divatia and Bhowmick, 2005; Mort, 2004). The hypertensive response during endotracheal intubation possessed harmful effects in patient with cardiovascular disease, high intracranial pressure, hypertension and anomalies of cerebral vessels (Gurulingappa *et al.*, 2012). These populations, they might predispose to hypertensive crisis and emergency, cerebral haemorrhage, myocardial ischemia and infarct, arrhythmia, cardiac failure and pulmonary edema. Slogoff & Keats (1985) also reported that most ischaemic episode during anaesthesia were associated with intubation and surgical stimulation especially if presence of tachycardia. Tachycardia and hypertension were two dynamic predictors for perioperative cardiac morbidity (Kaplan, 1987). It is because both HR and BP are primary determinant of balance between myocardial oxygen supply and demand (Kaplan, 1987; Moffitt *et al.*, 1985). Stimulation of HR and BP during laryngoscopy and intubation affect the myocardial oxygen supply and oxygen demand by increased the demand which unable to meet the supply. Additional effect by acute hypertension; peak systolic ventricle pressure increases, producing commensurate increase in ventricular demand which further increase myocardial oxygen consumption (Giles *et al.*, 1982; Kaplan, 1987).

A study was done to see the haemodynamic changes and catecholamine response during intubation in spinal cord injury patient (Yoo *et al.*, 2001). The spinal cord injuries then divided into different level of injury. After tracheal intubation, systolic arterial pressure was increased significantly in control group (33%), high paraplegic (28%) and low paraplegic (39%) and the rose was persisted until two minute after intubation. HR also increased significantly after induction and further increased in response to tracheal intubation. However incidence of hypotension and bradycardia was very small and not significant. The level of plasma noradrenaline concentration in all group were increased significantly but no significant changes in plasma adrenaline concentration after intubation (Yoo *et al.*, 2001).

2.0.7 THE EFFECTS OF TOTAL INTRAVENOUS ANAESTHESIA AND TARGET-CONTROLLED INFUSION ON GENERAL ANAESTHESIA

The TIVA infusion system allows us to select the target blood or site concentration required for a particular effect individually. Such as, to achieved loss of consciousness, to achieve adequate analgesia level and to keep patient calm and cooperative during monitored-sedation anaesthesia.

Russell (1998) comparing manual infusion scheme and target-controlled infusion (TCI) system for propofol. Anaesthesia is induced more rapidly with the TCI system and the laryngeal mask airway insertion is inserted earlier in these patients. Patient anaesthetized with TCI tended to move less both in the response to the initial surgical stimulus and subsequent procedure (Russell, 1998).

Level of anaesthesia is deeper in TCI system compared to manual infusion. This can be due to larger amount of propofol administration during induction and maintenance in TCI. However this will lead to increased respiratory depression compared to manual infusion. Otherwise the haemodynamic variables are similar in both groups (Russell, 1998).

An intervention review in TCI versus manual continuous infusion of propofol for GA and sedation in adult does not find sufficient evidences to see any difference in the quality of anaesthesia and sedation or the adverse events (Leslie *et al.*, 2008).

2.0.8 THE SYSTEMIC EFFECTS OF ANAESTHETIC DRUGS ON PHYSIOLOGICAL CHANGES

GA can lead to variable physiological changes involving multi-systems. The changes vary with the drugs used. Therefore different agents possess different clinical outcome. In general, intravenous and volatile agents all reduce BP as a result of vasodilatation and negative inotropy and chronotrophy (Calvey and Williams, 2009; Stoelting and Hillier, 2012).

The intubation procedure can stimulate sympathetic reflex and release the catecholamine which can lead to acute hypertension and tachycardia. The positive pressure ventilation can impede venous return to the heart, therefore reducing the preload and cardiac output.

The drugs also cause respiratory depressant and depress the airway reflexes particularly by intravenous induction agents and volatile agents. Propofol is very effective at inducing apnoe and depressing the airway reflexes, facilitating placement of supraglotic airway devices (Bovill, 2008).

Other than depressant effect, some drugs can be used as cardiovascular preservation. Ketamine maintain cardiovascular stability, preserve the muscular tone and preserve the airway patency. Etomidate also useful in cardiovascular instability however its depression effect on adrenal limits its use.

2.0.9 CHOICES OF ADJUNCT DURING INDUCTION AND INTUBATION

2.0.9.1 Lignocaine

Lignocaine is a local anaesthetic (LA). It also used as antiarrhythmic agent, bronchodilator, intravenous analgesia and airway anaesthesia (Stoelting and Hillier, 2012). A systematic review of randomized control trial was done on efficacy of intravenous lignocaine versus placebo on attenuating cardiovascular response to laryngospasm and tracheal intubation (Qi *et al.*, 2013). The intravenous lignocaine is useful to attenuate the cardiovascular response to intubation compared to placebo group. The decrease in pressure response induced by lignocaine is about 20 mmHg and HR is about 15 bpm.

2.0.9.2 Benzodizepine

Benzodizepines are used for sedation rather than GA due to its prolonged amnesia and sedation effects. As adjuvant, benzodiazepines are used for anxiolytics, amnestic and sedation pre induction or even during induction. The commonly used benzodiazepine is midazolam.

Cressey et al. (2001) studied on effect of midazolam pre-treatment on induction dose requirement of propofol. Pre-treatment with midazolam produced significant reduction in propofol requirement in both young and older age group. The older population required significant lower dose of propofol compared to young population. However no demonstrable benefit seen in cardiovascular stability or the incidence of apnoe (Cressey *et al.*, 2001). Combination of lignocaine with fentanyl did not show any benefit over fentanyl alone in inhibition of haemodynamic response (Hassani *et al.*, 2013).

2.0.9.3 Beta blockers

The common drug uses is esmolol due to its short acting. It can prevent the reflex sympathoadrenal discharge-mediated tachycardia and hypertension during laryngoscopy and intubation (Oxorn *et al.*, 1990). A study was done to compare the effectiveness of single bolus dose of esmolol or fentanyl in attenuating the haemodynamic response during laryngoscopy and endotracheal intubation. Esmolol group provide constant and reliable protection against the HR but not the BP (Hussain and Sultan, 2005).

Same observation seen in the study by Gupta & Tank (2011), on comparing esmolol and fentanyl effects to the haemodynamic parameter. The esmolol single bolus successfully attenuated the parameter response particularly the HR but the BP showed a rise although it was less than in other group after laryngoscopy and endotracheal intubation (Gupta and Tank, 2011).

2.0.9.4 Alpha2-adrenergic receptor agonist

A clonidine exerts its haemodynamic effects on both peripheral and central. Peripheral stimulation of subendothelial receptors causes vasoconstriction and on peripheral sympathetic nervous system nerve endings inhibit release of noredrenaline. Centrally, it stimulate alpha 2-adrenergic inhibitory neuron, therefore reduce sympathetic nervous system outflow from CNS to peripheral tissue. As the result, it produces peripheral vasodilatation and decrease in systemic BP, HR and cardiac output.

Comparing was made between clonidine and fentanyl on attenuating the haemodynamic response during laryngoscopy (Gupta *et al.*, 2013). Clonidine is superior to fentanyl in attenuating the haemodynamic response of laryngoscopy and intraoperative haemodynamic stability.

Agrawal et al. (2014) showed a different perspective of clonidine usage during induction. The study is comparing the efficacy of midazolam and clonidine on BIS guided anaesthetic induction (Agrawal *et al.*, 2014). Both provide a beneficial effect on haemodynamic and reduction in induction of propofol. Clonidine group however offer effective in preventing post-operative shivering.

2.1 TOTAL INTRAVENOUS ANAESTHESIA USING TARGET-CONTROLLED INFUSION

TIVA is based on the principle that a plasma concentration needed to produce anaesthesia has to be reached quickly and maintained over the period of time that anaesthesia is planned. A loading dose is determined by volume of distribution and the initial plasma drug concentration. The infusion rate is determined by the clearance of the drug and the plasma drug concentration in plasma. Lightening of the anaesthetic plane can be overcome by intravenous bolus of additional drug. A TCI is an infusion controlled in such manner as to attempt to achieve a user defined drug concentration in a body compartment of interest or tissue of interest.

2.1.1 THE HISTORY

A report on propofol infusion is available since 1982. Its describing the use of propofol infusions for the maintenance of anaesthesia, then the term TIVA being subsequently applied to this technique (Major *et al.*, 1982). Increased in understanding facilitated the development of guidelines for the manual administration of propofol by intravenous infusion to induce and maintain GA in adult practice (Roberts *et al.*, 1988). The traditional practice of the infusion regime for propofol by the Roberts method: 1.5mg/kg loading followed by infusion of 10mg/kg/hr, reduced to rate of 8 and 6mg/kg/hr at ten minutes interval. The concept of ‘target’ plasma concentration for propofol was introduced in 1989 and this actually expanding the development of TCI system (Tackley *et al.*, 1989).

2.1.2 THE PRINCIPLES OF TCI ANAESTHESIA

The TCI pumps are computer controlled syringe drivers which aim to electronically replicate the principles of bolus-elimination-transfer regimen by constantly adjusting the infusion rate to maintain the desired plasma concentration as selected by the anaesthetist. The pharmacokinetic models in TCI is attempted to describe the relationship between dose and plasma concentration with respect to time. It was a mathematical model, used to predict the blood concentration profile of a drug after a bolus dose or after infusion of varying duration. The TCI devices deliver a similar initial bolus and at high infusion rate but as the duration of infusion increases, the rate of delivery automatically progressively reduces to prevent excess accumulation (McCormack, 2008).

2.1.3 DRUGS USED IN TIVA

Drugs used for TIVA should possess most if not all of the following properties; water soluble to minimized toxicity from the solvent, stable in solution, no perivascular sloughing if extravasated, allowable to be given in concentrated solution to avoid fluid overloading, not absorbed by the plastics, does not promote bacterial growth, rapid onset of action, cleared rapidly from the body for a more rapid and predictable recovery, potent and lipid-soluble and chemically compatible with other drugs. There is no single agent that possesses all these properties. The common induction agent used is propofol and the common opioids are remifentanil, alfentanil and fentanyl.

Thiopental is not suitable for TIVA because of prolonged recovery associated with longer infusions. Ketamine has some active metabolites and will accumulate, resulting in prolonged drug action. Etomidate has good cardiopulmonary function but it possess several

detrimental effects for infusion. It suppresses the production of cortisol. Etomidate has high concentration of propylene glycol causes haemolysis resulting in haemoglobinuria.

2.1.4 ADVANTAGES AND DISADVANTAGES OF TCI

The advantages of TCI are low incidence of post-operative nausea and vomiting (PONV), fast emergence, easier to titrate to desired effects and environmental friendly. The propofol has its own, intrinsic, antiemetic properties and rapid clearance of remifentanil, the incidence of PONV in TCI patients is very small. From the IMPACT study, comparing TIVA and inhalation anaesthetic, the incidence of PONV after inhalational increases with the length of exposure. Whereby the TIVA is low risk of PONV and not influenced by the length of anaesthetic hours. TCI allow fast emergence as the half-time of remifentanil is very short and the propofol itself does not accumulate after infusion.

The disadvantage of TCI is related to practical rather than pharmacological application. In most countries propofol is more expensive than volatile anaesthetic agents. The most obvious disadvantage is the requirement of intravenous access prior to induction of anaesthesia. This is not feasible in difficult intravenous access patient for example; post-radiotherapy and -chemotherapy patient, skin disease patient and pediatric population (McCormack, 2008).