EFFECTS OF DEXMEDETOMIDINE ON CEREBRAL BLOOD FLOW AUTOREGULATION AND CEREBRAL HEMODYNAMICS IN PATIENTS WITH INTRACRANIAL TUMOURS

Thesis submitted for the partial fulfillment for the requirement of the degree of DM (Neuroanesthesiology)

by

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DECLARATION

I hereby declare that this thesis entitled '**Effects of Dexmedetomidine on cerebral blood flow autoregulation and cerebral hemodynamics in patients with intracranial tumours'**, has been prepared by me under the guidance of Dr. Manikandan.S, Additional Professor, Department of Anaesthesiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram.

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CERTIFICATE

This is to certify that this thesis entitled **'Effects of Dexmedetomidine on cerebral blood flow autoregulation and cerebral hemodynamics in patients with intracranial tumours'** is a bonafide work of **Dr. ARULVELAN. A,** D.M. - Neuroanaesthesia Resident, and has been done under my guidance and supervision in Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram. He has shown keen interest in preparing this dissertation.

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INTRODUCTION

INTRODUCTION

The adult human brain weights approximately 1300 grams and represents around 2% of the body weight. However it receives approximately 15% of the cardiac output. Whole brain oxygen consumption represents about 20% of total body oxygen utilisation. The brain's substantial demand for substrate must be met by adequate delivery of oxygen and glucose. However the space constraints imposed by non compliant cranium and meninges require that blood flow not be excessive. There are various physiological mechanisms including metabolic, myogenic and autonomic nervous system control by which blood flow to the brain is maintained constant over a range of physiological variables.

Myogenic control, also called as cerebrovascular autoregulation plays an important role in control of cerebral blood flow. Autoregulation by definition refers to the capacity of the cerebral circulation to adjust its resistance so that it can maintain CBF constant over a wide range of mean arterial pressure values. Cerebrovascular autoregulation has been shown to be altered in various pathological conditions involving brain including, trauma, stroke, and vascular malformations. Apart from local causes cerebral autoregulation is also shown to alter in systemic illness like diabetes mellitus, hypertension, sepsis and cirrhosis of liver. Drugs used in

anaesthesia and intensive care settings like sedatives, inhalational agents and vasoactive medications can also alter the cerebrovascular autoregulation. Gross impairment in autoregulation can cause cerebral ischemia or hyperaemia depending upon the blood pressure, which can cause damage to neurons and can exaggerate ongoing ischemic damage leading to poor clinical outcome. Drugs used in neuroanaesthesia and neurocritical care should have minimal alteration in neurophysiological functions. The favourable characteristics of an ideal drug should include, uniform metabolic suppression, blood flow reduction in accordance to metabolic suppression, reduction of ICP, reduction of CSF pressure, maintaining cerebrovascular autoregulation and without epileptogenic potential.

Alpha-2 adrenoceptor agonists are being increasingly used in Anaesthesia and critical care. Clonidine which was initially used as an antihypertensive drug, now widely used as an adjunct in general and regional anaesthesia procedures. Dexmedetomidine is a new intravenous drug gaining popularity among α_2 adrenoceptor agonists. Beause of its high α_2 selectivity it produces cooperative sedation, anxioloysis, analgesia and attenuates the stress response to surgery and anaesthesia interventions. These clinical characteristics make this intravenous agent a potentially attractive adjunct for neuroanaesthesia and neurocritical care interventions.

Dexmedetomidine acts mainly in subcortical structures in-contrary to conventional anaesthetic agents which predominantly cause cortical metabolic suppression. Few studies with Dexmedetomidine showed intact flow metabolism coupling whereas some studies showed altered flow metabolism coupling with relative hyperaemia. Administration of Dexmedetomidine has resulted in decreased global and regional blood flow and also reduced blood flow velocity. Systemic effects of Dexmedetomidine like hypotension and bradycardia can play a role, but the exact mechanism is not identified. Dexmedetomidine has been shown to produce minimal reduction of ICP and CSF pressure. It has been shown that Dexmedetomidine has no epileptogenic potential in humans. Although literatures on cerebral blood flow effects of Dexmedetomidine are available, there is scarcity of data on the effect on cerebral autoregulation, which maintains the blood flow over a variable range of cerebral perfusion pressure.

Factors controlling cerebral blood flow include cerebral metabolism, PCO_2, PO_2, viscosity and myogenic regulation (autoregulation). The limits of autoregulation have been shown to be within mean arterial pressure of 50 to 150mmHg. But studies have shown that inter individual variability is very high and the limits of autoregulation can be altered by cerebral and systemic pathological processes. In critical care or anaesthesia setting where

patients are sedated and on ventilator support, where the metabolism and partial pressure of blood gases are under control, the autoregulation can play an important role in maintaining cerebral blood flow. Thus it should be ensured that drugs used in neuroanaesthesia and critical care setting should have minimal or no effect on cerebral hemodynamics and autoregulation.

Various methods have been described to assess the phenomenon of autoregulation including Transcranial Doppler (TCD) based assessment of flow velocities, imaging based assessment (MRI, PET, SPECT) and cerebral oxygenation based techniques (NIRS, $PbtO_2$). TCD has major advantage over other methods because of the simplicity, low cost, repeatability, bed side assessment and without any radiation hazards. The new improvement in transcranial Doppler, like colour duplex imaging has increased the sensitivity and accuracy. Apart from autoregulatory assessment, several other indices derived from flow velocity assessment like Pulsatility index (PI), Resistant index (RI), Estimated zero flow pressure (ZFP) and estimated effective cerebral perfusion pressure (eCPP) can be useful in assessing the response of distal cerebral vasculature to variety of stimuli including drugs and pathological processes.

BASIC SCIENCE

&

REVIEV OF LITERATURE

CEREBRAL BLOOD FLOW AND REGULATION

The adult human brain weights around 2% of the body weight. However it receives approximately 15% of the cardiac output and consumes about 20% of total body oxygen utilisation. As the neurons are highly active and energy is needed for ionic flux and structural integrity, the demand for oxygen and glucose is high compared to other organs and the substantial demand for substrate must be met by adequate delivery.

The global cerebral blood flow has been estimated to be around 50ml/100g/min. This global measure is representative of flow to two different regions: the gray matter, where neuronal cell bodies and synapses are located and metabolically highly active, has a blood flow of 75-80ml/100g/min and the white matter, where fibre tracts are located has blood flow of around 20ml/100g/min. Spinal cord blood flow is less extensively studied. The grey matter has a rate of 60ml/100g/min and white matter has rate of around 20ml/100g/min.

There are various mechanisms by which blood flow to the brain is maintained constant over a range of physiological variables.[1] They are chemical regulation, neurogenic regulation and myogenic regulation.

a) CHEMICAL REGULATION

Metabolism and Cerebral blood flow (CBF) :

Flow and metabolism coupling in the brain is a complex physiologic process that is regulated by combination of metabolic, neural, glial and vascular factors.[2] Increased neuronal activity results in increased cerebral metabolic rate (CMR). This increase in CMR is associated with a well matched proportional change in CBF. Although the exact mechanism is not identified, the available data implicate that the local by products of metabolism like K^+, H^+, lactate, adenosine and nitric oxide (NO) can play role in blood flow autoregulation. Nerves innervating cerebral vasculature release peptides like VIP, Neuro peptide, substance P and CGRP, which can also modulate the neuro vascular coupling.

PaO_2 and Cerebral blood flow:

The changes in PaO_2 from 60 to 300mmHg have little influence on CBF. Below a PaO_2 of 60mmHg however CBF increases rapidly.[3] Neuronal NO and hypoxia induced opening of ATP dependent K^+ channels can play a role in vasodilatation. Recent studies have shown that stimulation of rostral ventrolateral medulla by hypoxia results in an increase in CBF. At high PaO_2 values CBF decreases modestly. At 1 atm pressure of oxygen 12% decrease in CBF is observed.

$PaCO_2$ and Cerebral blood flow:

The changes in CBF directly varies with changes in $PaCO_2$. Within the physiological range, CBF changes 1 to 2ml/100g/min for each 1mmHg change on $PaCO_2$. This sensitivity to change in CBF is also positively correlated to resting level of CBF.[1,4]

The changes caused by $PaCO_2$ are apparently dependent on pH alteration in extra cellular fluid of the brain. In adults, NO and prostaglandins may play important role in CO_2 induced vasodilatation, whereas in infants this phenomenon may be mediated by cAMP and prostaglandins.[5] Although the $PaCO_2$ mediated vascular response are occur rapid, the CBF tends to return to the baseline over a period of 6 to 8 hours.

Temperature and Cerebral blood flow:

CBF decreases by 6 to 7% per °C of temperature reduction parallel to decrease in $CMRO_2$. Hypothermia reduces energy utilisation with both electrophysiological function and basal component associated with maintenance of cellular integrity. Hyperthermia has an opposite effect on cerebral physiology. Between 37°C and 42°C CBF and CMR increase. However above 42°C a dramatic reduction in CMR and CBF occurs, due to protein degradation and cellular energy failure.[6]

b) NEUROGENIC REGULATION

Considerable evidence has shown that the cerebral vasculature is extensively innervated including cholinergic (parasympathetic and non parasympathetic), adrenergic (sympathetic and non sympathetic), serotoninergic and VIPergic systems of both intracranial and extracranial origin. Extracranial innervations is through superior cervical ganglion and sphenopalatine ganglion.. The intra axial pathways include innervations from locus ceruleus, vestigeal nuclei, dorsal raphe nucleus, and the basal of Myenert. Hemorrhagic shock, a state with high sympathetic tone results in a lower CBF compared with hypotension produced by sympatholytic drugs. Activation of cerebral sympathetic innervations shifts the upper limit of autoregulation and offers some protection against hypertensive breakthrough of blood brain barrier.[7]

c) VISCOSITY AND CEREBRAL BLOOD FLOW

In healthy subjects variation of hematocrit within the normal range of 33 to 45% probably results trivial change in CBF. In anaemia CBF is increased, this can be due to reduced viscosity and also due to the reduced oxygen carrying capacity of blood. It is shown that in the setting of focal cerebral ischemia, a hematocrit of 30 to 34% will result in optimal oxygen delivery.[8]

d) MYOGENIC REGULATION (AUTOREGULATION)

Autoregulation refers to the capacity of the cerebral circulation to adjust its resistance so that it can maintain CBF constant over a wide range of mean arterial pressure values.[9]

Classically the limits of autoregulation are described between 50 to 150mmHg of mean arterial pressure. Above and below the autoregulatory plateau CBF is pressure independent and varies linearly with CPP. These limits are not strictly fixed and especially the lower end of autoregulation shows considerable variation among individuals and in various disease processes.

The mechanisms of autoregulation in the brain are not completely understood. When pressure fluctuates at the high end of the autoregulatory curve the blood flow regulation is most likely due to the myogenic behavior (Bayliss effect) of the vascular smooth muscles that constrict in response to elevated pressure and dilate in response to decreased pressure, which may involve Ca_2^+ or K^+ channels. Autoregulation at pressures below the limits of autoreguloatory curve is likely due to hypoxia and release of metabolic factors like NO, H^+, K^+ and adenosine leading to vasodilatation.[10]

The ‘speed of autoregulation’ is not exactly defined. It is described to operate between 30 to 150 seconds, thus indicating that even in healthy

individual there is transient absence of autoregulation and pressure passive flow. In brain and brain stem region regional, segmental and temporal heterogeneity is observed in autoregulatory phenomenon due to variable response of pial blood vessels.[11] Apart from cerebrum, cerebellum and spinal cord also shows autoregulatory phenomenon.

Impairment of autoregulation leads to pressure passive blood flow leading to hypoperfusion and ischemia during hypotension and hyperaemia during hypertension. As both hypo and hyper perfusion is detrimental in cerebral vascular system, autoregulation and its disturbances have got particular attention.

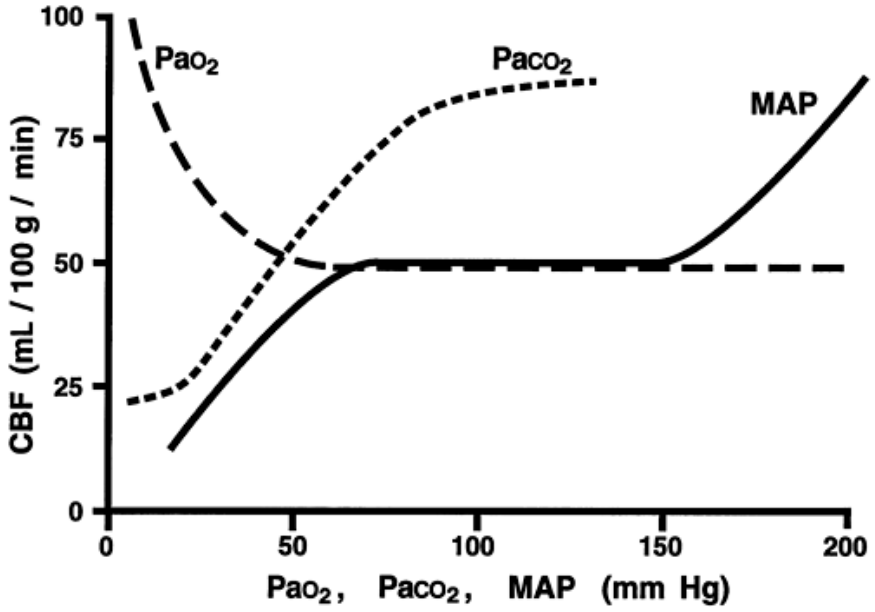


Figure 1 : Regulation of cerebral blood flow

AUTOREGULATION IN PHYSIOLOGICAL CONDITIONS

Cerebral autoregulatory phenomenon is seen in term neonates along with intact CO_2 reactivity. However in preterm neonates autoregulatory phenomenon is not well developed but CO_2 reactivity is maintained.[12] In adolescent age group flow velocity gradually increases, but the autoregulation is strictly maintained.

In elderly patients studies have proven that although magnitude of autoregulation is preserved, speed of onset may be delayed when compared to young healthy adults.[13]

In pregnant women, increased CBF velocities are observed, but autoregulation and CO_2 reactivity are strictly maintained comparable to age matched non pregnant females.[14]

AUTOREGULATION IN PATHOLOGICAL CONDITIONS

Cerebral autoregulation can be altered in variety of pathological conditions either localised to central nervous system or involving other organ systems.

The autoregulation is lost in severe head injury or acute ischemic stroke leaving surviving brain tissue to the potentially harmful effects of changing blood pressure. Impaired autoregulation can lead to increase in ICP because of increased blood volume, thus accelerating the ischemic injury.[15] Assessment of autoregulation in head injury and stroke helps in better management of blood pressure and ICP changes related to it.

Autoregulation is shown to be impaired in minor head injury patients and in paediatric head injury patients.[16,17] Impairment of autoregulation is shown to be worse in ipsilateral side of lesion and recovery of the normal autoregulatory control can take more than 2 weeks. These finding suggested that perfusion pressure management should be considered in some of the patients for a period of at least 2 weeks.

Studies have shown that autoregulation can also be impaired after aneurismal subarachnoid haemorrhage particularly after the vasospasm has occurred and can lead to delayed ischemic neurological deficits (DIND).[18]

Autoregulation can be impaired around any space occupying lesion including tumors, hematoma or abscess. Remote regional CBF abnormality can occur in patients with intra cranial tumours due to local tissue compression against unyielding anatomical structures, namely, the tentorium and the falx.[19,20]

Cerebral vasculature distal to Arterio-Venous malformation (AVM) shows the phenomenon of adaptive autoregulatory displacement. After resection of AVM, this adaptive displacement may lead to occlusive hyperaemia or normal perfusion pressure break through after restoration of normal perfusion pressure.[20] Similarly patients with chronic carotid artery occlusion show altered autoregulatory phenomenon.[22]

Reduced vasomotor reactivity is also demonstrated in patients with cerebral microangiopathy leading to lacunar infarct and demyelination of white matter.[23] Animal experiments have shown that autoregulation is impaired in asymptomatic cerebral venous occlusion, neonatal cerebral ischemic injury and infections involving the central nervous system.[24,25]

In patients with migraine, because of altered automic control the phase and gain of dynamic autoregulation can be different from normal people. [26]

Although the autoregulation is impaired in many pathological conditions involving the central nervous system, blood flow can be at least partially corrected by altering the $PaCO_2$ as in majority of conditions CO_2 reactivity is maintained.

Cerebral autoregulation can also be affected in systemic illness without any intracranial pathology.

In patients with chronic uncontrolled hypertension the autoregulatory limits are shifted to the right and these patients are prone for cerebral ischemia in hypotensive conditions where normal individuals can tolerate without any ill effect.[9]

In patients with chronic uncontrolled diabetes, because of abnormal glycosylated proteins in blood vessels, abnormal NO response and co-existing neuropathy the autoregulation can be impaired and it can manifest even before the clinical expression of nephropathy, retinopathy and cardio vascular autonomic neuropathy.[27]

Cerebral autoregulation can be impaired in patients with fulminant hepatic failure and in patients with hepatic encephalopathy.[28] Patients with end stage renal failure also show abnormal MCA flow velocity pattern and

altered autoregulation which can be restored by hemodialysis.[29] Studies have shown that autoregulation could be impaired in patients with sepsis and septic shock and this altered vascular response might contribute for the development of septic encephalopathy.[30] Impaired autoregulation is also demonstrated in patients with symptomatic orthostatic hypotension and in patients with obstructive sleep apnoea.[31]

DRUGS AND CEREBRAL VASCULAR AUTOREGULATION

Anaesthetic agents can affect cerebral hemodynamics by direct effect on vasculature or by indirect effect on cerebral metabolism or by changes in systemic hemodynamics.[32]

Sevoflurane is widely used during inducton and maintenance phase of general anaesthesia. In common with other volatile agents Sevoflurane shows an intrinsic dose dependent vasodilatory effect and this effect can lead to impaired autoregultion. But studies conducted with Sevoflurane in adults and paediatric patients showed that up to a MAC of 2, autoregulatory phenomenon is well preserved along with intact CO_2 reactivity.[33]

Study conducted by Strebel *et al* demonstrated that up to 1 MAC, Isoflurane and Desflurane altered the rate and strength of dynamic autoregulation and concentration of 1.5 MAC and above, abolished the

autoregulatory response.[34] Studies have shown that use of nitrous oxide increases the cerebral blood flow and impairs cerebral autoregulation.[35]

Propofol has shown to preserve autoregulation both at high and low doses in healthy individuals.[36] However, high doses of Propofol have been shown to impair cerebrovascular autoregulation in head-injured patients. The combined use of Propofol and Remifentanil anesthesia has been shown to preserve cerebral vascular resistance and cerebrovascular autoregulation.[38]

Study conducted by Ogawa *et al* with thigh cuff method, showed that Dexmedetomidine, an α_2 agonist, widely used as a sedative agent may weaken the dynamic cerebral autoregulation.[39]

Apart from anaesthetic agents vasoactive agents used during anaesthesia and in Intensive care setting can also affect cerebral autoregulation.

Investigation done by Endoh *et al* in patients under Propofol-Fentanyl anaesthesia, Nicardipine caused impaired cerebral autoregulation. In the same investigation autoregulation was maintained with use of Nitroglycerine and Prostaglandin E_1.[40]

Moppett *et al* demonstrated in healthy volunteers that, Glycerol tri-nitrate increases the effective CPP by reduction in cerebral vessel tone without impairment in cerebrovascular autoregulation. In the same experiment, use of Norepinephrine did not cause increase in CPP despite

increasing the arterial pressure.[41] Another study conducted by Moppett *et al* showed that no significant change in autoregulation or reactivity to CO_2 with the use of sympathomimetic agents like Ephedrine, Dopamine and Dobutamine even with clinically significant increase in cardiac index.[42]

In a study conducted by Bouma *et al*. it was shown that when autoregulation was impaired administration of Mannitol may cause increase in cerebral blood flow up to 40%, but the effect of Mannitol on autoregulation was not assessed.[43]

ASSESSMENT OF AUTOREGULATION

All the methods assessing cerebral autoregulation assess the changes in flow velocity secondary to changes in CPP.[44] The autoregulatory phenomenon has different properties, which forms the basis of these tests; these properties are :

- *Limits of autoregulation* – the upper and lower values of CPP where the blood flow is kept constant
- *Speed of autoregulation* – the time interval within the blood flow was restored when there is change in CPP.
- *Gradient of autoregulation* - degree to which FV remains constant despite changes in perfusion pressure within the limits of autoregulation

Trans cranial Doppler (TCD) is commonly used bedside equipment for assessment of autoregulation. Currently use of newer modalities like MRI, PET scan and NIRS are also described with varying sensitivity and specificity.

TCD assisted autoregulation assessment

Theoretically when the diameter of the large cerebral vessels remains constant changes in the flow velocity correlates with changes in blood flow. TCD assessment of flow velocity will be carried out with varying cerebral perfusion.[45] Change in Cerebral perfusion pressure can be induced by variety

of methods including, use of vasoactive agents, changes in position (sit-to-stand, bed tilt), valsalva manoeuvre, immersion of hand in ice water (cold pressor test), isometric exercise of upper limb, lower body negative pressure, rapid deflation of inflated thigh cuffs and compression of common carotid arteries in neck. Changes in cerebral blood flow velocity (CBFV) are continuously monitored with TCD and various techniques and indices are described for assessment of autoregulation.

Static autoregulation

This refers to the assessment of autoregulatory plateau over a small range of arterial pressure change.[45] Using TCD, middle cerebral artery flow velocity is measured under normal physiological conditions and then repeated after 20-30mmHg steady state increase in MAP induced by Phenylephrine infusion. The index of autoregulation is calculated as percent change in the CVR per percent change in the MAP. If autoregulation is intact, the index should be 1 and a value of less than 0.4 suggests impaired autoregulation.

Dynamic autoregulation

These tests describe the flow velocity (FV) response to sudden changes in perfusion pressure, induced by number of methods.

Thigh cuff method, first described by Aaslid in 1989, has been extensively used in anaesthesia and intensive care.[46] In this method, the MCA flow velocity is continuously measured while the arterial pressure is lowered transiently by rapidly deflating bilateral thigh tourniquets. Normally, both MAP and FV decreases initially, but because of intact autoregulation, FV recovers quicker than the MAP. If autoregulation is impaired, FV recovery follows passively the recovery of the mean arterial pressure. An autoregulation index (ARI) is calculated based on the goodness of fit between the observed changes in FV and those predicted if autoregulation is as fast as possible (ARI=9) or absent (ARI=0). A normal value has been quoted as 5±1. The main advantages are the ARI is minimally affected by age and transient change of MAP without use of any vasoactive agents.

Transient hyperaemic response test, first described by Giller, has been extensively used in research and clinical arena.[47] This test involves continuous record of middle cerebral artery flow velocity (MCA FV). A brief (3 to 10 seconds) compression of ipsilateral common carotid artery is commenced, which results in a sudden reduction in the MCA FV and presumably perfusion pressure. If autoregulation is intact this provokes

vasodilatation in the vascular bed distal to MCA. Thus a transient increase in MCA FV is seen on release of compression. Two indices are assessed – Transient hyperaemic response ratio (THRR) and Strength of autoregulation (SA). This test has been validated against measurement of static autoregulation and dynamic autoregulation with thigh cuff method.[48,49] In theory the THR test assess both the gradient as well as the limits of autoregulatory plateau without differentiating between the two.

Transfer function analysis

Computer generated models using continuous assessment of cerebral perfusion pressure, TCD flow velocities and the moving correlation (Mx) between the two factors are used to assess autoregulation.[50]

The transfer function between the oscillations in BP and CBFV is characterized by three parameters: gain (or magnitude), phase shift, and coherence.

a) Gain: The gain represents the damping effect of autoregulation on the magnitude of the BP oscillations. A low gain indicates an efficient autoregulation, whereas an increase in gain represents a diminished efficiency of the dynamic process of autoregulation.

b) Phase shift: Synchronous waveforms are 'in phase'. In case intact autoregulation, changes in CBFV recover faster than the changes in BP,

which causes CBFV oscillations appear before BP oscillations called as 'phase lead'. The phase shift can be expressed in degrees from 0° to 360°, or in radians from 0 to 2 π. In patients with a complete loss of autoregulation, the phase shift between CBFV and BP is expected to be close to 0° as CBFV parallels BP change i.e. in phase.

c) Coherence function: It tests the linearity of the relation between input and output (BP/CBFV). Coherence approaching unity in a specific frequency range suggests a linear relationship in this domain, whereas coherence approximating zero may indicate no relationship between the signals. For the calculation of phase shifts and gain values, thresholds of coherence of > 0.4 or > 0.5 have been used by most researchers.

OTHER MODALITIES OF AUTOREGULATORY ASSESSMENT

LASER Doppler flowmetry (LDF):

This technique uses low power solid state LASER diode as coherent light source.[51] Infrared light of 760-800nm wavelength is directed to tissues and this light is scattered by moving blood cells and stationary tissue cells, causing a Doppler shift. A portion of the scattered photons generates electrical signal on the surface of a photo detector which contains frequency and power information. Frequency information is related to blood cell

velocity, and the power information is related to blood volume. The correlation coefficient between arterial blood pressure and blood flow can be calculated and autoregulation can be assessed. The disadvantages of LDF are need of invasive access to brain tissue and limited area of assessment.

Near Infra red spectroscopy (NIRS) :

With the help of light emitting diodes 700 to 1300 nm frequency light is transmitted and regional saturation of haemoglobin is assessed using Beer Lamberts law. The changes in CBF are reflected by the changes in cerebral intravascular oxygenation (HbD), regional cerebral oxygen saturation (rSO_2) and cerebral tissue oxygenation.[52] The concordance between the change in Mean arterial pressure and cerebral blood flow values can be studied using correlation, coherence and partial coherence methods and autoregulation can be assessed. The disadvantage being, assessment of regional blood flow and signal interference from extra cerebral tissues, non metabolising tissues and non haeme chromophores. NIRS based autoregulatory assessment is commonly used in neonates and infants.

Brain tissue oxygen tension

Regional saturation of brain tissue can be assessed by thermal diffusion probe, brain tissue oxygen monitoring probe or microdialysis probe.[53] As the saturation of brain tissue is found to correlate with cerebral blood flow,

moving correlation between the arterial blood pressure and brain tissue oxygen tension can be used to measure cerebrovascular autoregulatory response.

ICP waveform

Intra cranial pressure and blood flow have a close link particularly in head injured patients. The moving correlation index between mean arterial blood pressure and intracranial pressure called PRx can be used to monitor and quantify cerebral vascular reactivity.[54] A PRx value of less than 0.3 indicates intact autoregulation and more than 0.3 indicates impaired reactivity.

TRANSIENT HYPERAEMIC RESPONSE TEST

This technique of autoregulatory assessment was first described by Giller, has been extensively used in research and clinical arena.

Physiology

This test involves continuous record of middle cerebral artery flow velocities (MCA FV). A brief (3 to 10 seconds) compression of ipsilateral common carotid artery is commenced, which results in a sudden reduction in the MCA FV and presumably perfusion pressure. If autoregulation is intact this provokes vasodilatation in the vascular bed distal to MCA. This vasodilatation causes decreased cerebral vascular resistance and transient increase in MCA FV on release of compression.

Factors analysed:

Standard criteria should be used to identify the MCA with TCD. After a good recording of waveform is obtained, ipsilateral common carotid artery is compressed for 3 to 10 seconds and then suddenly released. Flow velocity waveforms are continuously recorded throughout the study.

The THR test is accepted when it fulfils the following criteria:

- Onset of compression results in sudden decrease of flow velocity
- Heart rate and Blood pressure remains stable during the procedure
- Flow transits after the compression are absent
- The power of the reflected Doppler signal is constant (It indicates that the MCA diameter remains constant)

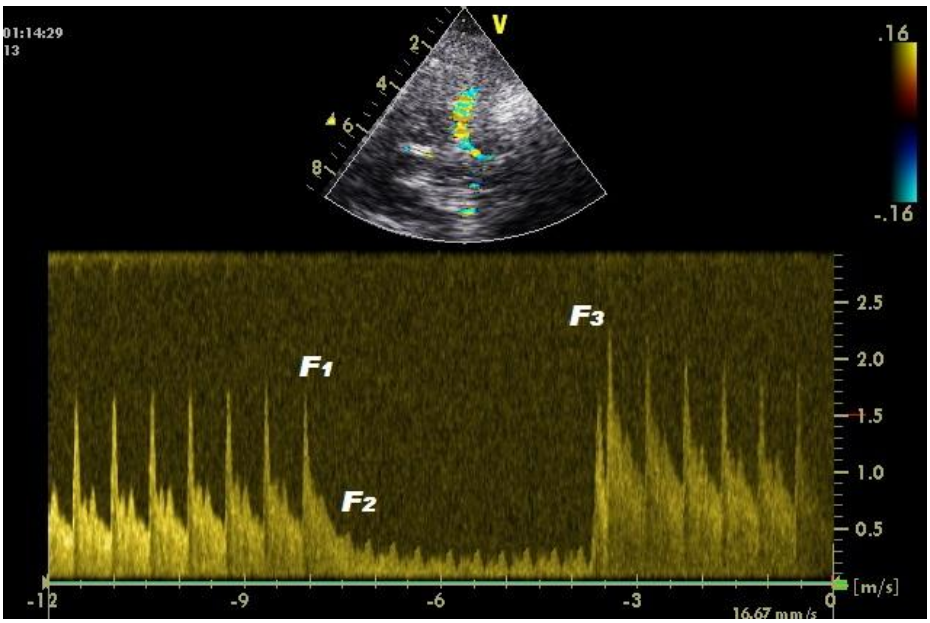


Figure 2 : THRR analysis

For analysis time-averaged mean of the outer envelope of the flow velocity profile preceding the compression (F_1), immediately after compression (F_2), and immediately after the release of compression (F_3) are selected.

As a measure of magnitude of decrease in blood flow velocity during common carotid artery compression the Compression ratio (CR) is calculated.

$$CR = \frac{(F_1 - F_2) \times 100}{F_1}$$

Studies have shown that compression ratio around 40% is ideal for getting a valid THRR and SA values.[55]

The following two autoregulatory indices have been described.

Transient hyperaemic response ratio (THRR): The THR ratio is the ratio between the flow velocity after release of compression and flow velocity before the onset of compression.

$$THRR = \frac{F_3}{F_1}$$

Validation studies and clinical studies have shown that the normal value for THRR is around 1.36±0.09. More than 2 standard deviation change signifies clinically altered autoregulatory response.[44,55]

Strength of Autoregulation (SA): The strength of autoregulation is calculated by normalizing the THRR for changes in mean arterial pressure of the MCA at the onset of compression.

$$SA = \frac{F_3 \times P_2}{MAP \times F_1}$$

Where $\mathbf{P_2 = MAP \times F_2/F_1}$ or 60mmHg whichever is greater (assumed lower limit of autoregulation).

Normal value for strength of autoregulation is around 0.8 – 1.1. Decrease in SA index denotes impaired autoregulation.[44,55]

Validity of THRR based autoregulation assessment

This test has been validated against measurement of static and dynamic autoregulation.[48,49] Smielewsky and colleagues have shown that the Transient hyperaemic response ratio is valid index and has similar sensitivity to leg-cuff method, as described by Aaslid *et al* in detecting the changes in cerebral autoregulation produced by different systemic carbon dioxide concentrations.[49] In theory the THR test assess both the gradient as well as the limits of autoregulatory plateau without differentiating between the two. The variability (coefficient of variation<10%) is much lower than the other tests, making it suitable for comparisons.

The advantages of THRR based autoregultory assessment are reproducibility, simplicity and lack of pharmacological intervention. The main disadvantage is risk of embolisation of carotid artery atheroma.

Experimental factors like duration of carotid artery compression and magnitude of decrease in blood flow velocity during compression can affect THR ratio. Various studies have applied 5 seconds to 15 seconds of compression. Study conducted by Cavill *et al* in healthy volunteers suggested that at least 10 seconds of compression should be used to get an ideal response as the inherent autoregulatory delay can be 6 to 10 seconds.[55]

Values of compression ratio (CR) in the modelling study for THRR by Smielewski *et al* were 36 to 57 %. Assuming normal blood pressure in all volunteers the CR of 36-57% could reduced the MCA perfusion pressure approximately 40 to 64 mmHg which is well below the lower limit of autoregulation (~ 60mmHg).[49] Study conducted by Cavill *et al* demonstrated that relationship between CR and THRR starts to plateau when CR exceeds 40%, and the authors suggested that a CR of 40% or more approximates to the point at which the autoregulatory capacity is tested to the maximum in normotensive healthy volunteers.[55]

DEXMEDETOMIDINE

HISTORY

Dexmedetomidine was developed in the 1990s by Abbott Laboratories as a sedative agent, predominantly for use in the intensive care unit setting.[56] In 1999, FDA approved to market Dexmedetomidine, in the United States for sedation in mechanically ventilated adult intensive care patients. In 2008, FDA approved Dexmedetomidine to use as a procedural sedative. Dexmedetomidine is not approved by FDA for use in any paediatric setting.

PHARMACOKINETICS

Dexmedetomidine like Clonidine, belongs to imidazole subclass of α_2 adrenoceptor agonists. It is the S-enantiomer of Medetomidine which is an anaesthetic agent used in veterinary procedures.[56] Dexmedetomidine is freely soluble in water, has molecular weight of 236.7.

Dexmedetomidine is chemically described as (+)-4-(S)-[1-(2-3-dimethylphenyl)ethyl]-1H-imidazole monohydrochloride ($C_{13}H_{16}N_2$.HCL).

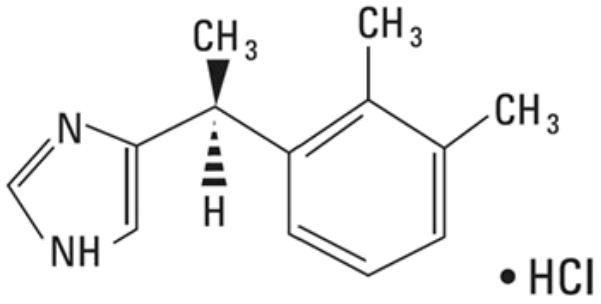


Figure 3 : Chemical structure of Dexmedetomidine hydrochloride

As Dexmedetomidine is given through intravenous route the bio-availability reaches near 100%. The volume of distribution (Vd) is approximately 2-3 L/Kg. It is 94% protein bound and displays non linear pharmacokinetics.

Dexmedetomidine is rapidly metabolised in liver by cytochrome P450 enzyme system. It undergoes conjugation (41%), n-methylation (21%) or hydroxylation followed by conjugation. The rate of clearance is around 10-30 ml/Kg/min and elimination $t_{½}$ around 2-3 hours. Metabolites of Dexmedetomidine possess no intrinsic activity and 95% excreted in urine and 1% through faeces. Pharmacokinetics of Dexmedetomidine is best described by three-compartment model. These pharmacokinetic properties apparently unaltered by age, sex, weight or renal function but clearance of Dexmedetomidine correlates with height of the subjects.[57]

PHARMACODYNAMICS

Dexmedetomidine shows a high ratio of specificity for α_2 adrenoceptor (α_2:α_1- 1600:1) compared to clonidine (α_2:α_1- 200:1), making it as a complete α_2 agonist.[100]

Three subtypes of α_2 receptors are described - α_2A, α_2B, α_2C.[58] The α_2A receptors are primarily distributed in periphery and α_2B, α_2C are in brain and spinal cord. Stimulation of α_2 adrenergic receptors that activates a pertussis toxin sensitive guanine nucleotide regulatory protein (G protein) resulting in inhibitory feedback and decreased activity of adenyl cyclise. This results in reduction of intracellular cyclic adenosine monophosphate (cAMP) and cAMP dependent protein kinase activity leading to dephosphorylation of ion channels. Changes in ion channels subsequently modify ion translocation and membrane conductance leading to various clinical effects depending on the site of action.

DOSAGE

Dexmedetomidine hydrochloride supplied as 1 ml or 2 ml vials with concentration of 100mcg/ml. For infusions it is reconstituted in Normal saline and can be administered through a peripheral or central venous access. Dexmedetomidine is initiated with a loading dose of 1mcg/Kg/10 min followed by 0.2 to 1 mcg/Kg/hr titrated to clinical effects.[56]

CENTRAL NERVOUS SYSTEM EFFECTS

Sedation and anxiolysis:

Dexmedetomidine exerts its sedative and anxiolytic effects by activation in sub cortical structures especially locus coeruleus, a major site of non adrenergic innervation and a key modulator for a variety of brain functions including sleep, arousal, anxiety and drug withdrawal symptoms.[59] Dexmedetomidine produces a decrease in activity of the projections of the locus coeruleus to the ventrolateral preoptic nucleus. This increases GABA and galanin release in the tuberomammillary nucleus, producing a decrease in histamine release in cortical and subcortical projections. The α_2 agonists seem to inhibit ion conductance through L-type or P-type calcium channels and facilitate conductance through voltage-gated calcium-activated potassium channels.

The action of Dexmedetomidine in locus coeruleus mimics natural sleep, clinically manifesting as cooperative form of sedation, in which the patients easily transform from sleep to wakefulness and task performance when aroused and back to sleep when not sedated. This phenomenon also leads to less cognitive impairment and disinhibition during prolonged sedation. Dexmedetomidine has also been shown to ablate memory in a dose-dependent manner.[60]

Analgesia:

In the spinal cord, stimulation of α_2-receptors in substantia gelatinosa of the dorsal horn leads to inhibition of the firing of nociceptive neurons and inhibition of the release of substance-P. In addition, the locus coeruleus is the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. Stimulation of the α_2 adrenoceptors in this area terminates the propagation of pain signals leading to analgesia. Alpha-2 adrenoceptors located at the nerve endings may also have a possible role in the analgesic mechanisms of by preventing norepinephrine release.[61]

Some of the systemic analgesic effects of Dexmedetomidine have been attributed to the confounding sedative effects.[59]

Systemic use of Dexmedetomidine shows narcotic sparing. Although 30 – 50% reduction in opioid use has been demonstrated in studies, the potency does not approximate that of opioids. In the clinical setting, when pain is likely to occur, if Dexmedetomidine is used, the addition of a narcotic seems warranted.[62]

In animals, Dexmedetomidine, in contrast to opioids, does not result in hyperalgesia or allodynia after withdrawal.[56]

Stress response:

The centrally acting α_2 adrenergic agonists, including Dexmedetomidine activate receptors in the medullary vasomotor center, reducing norepinephrine turnover and decreasing central sympathetic outflow. In addition action on locus coeruleus also leads to central stimulation of parasympathetic outflow and inhibition of sympathetic outflow. This phenomenon helps in preventing sympathetic surges during airway management, skull pin fixation and surgical stimuli leading to stable perioperative hemodynamics.[63]

NEUROPHYSIOLOGICAL EFFECTS

Cerebral metabolism and Cerebral blood flow:

Brain has a high metabolic rate and the delivery of substrate is dependent on cerebral blood flow and, in the setting of ischemia, even modest alterations in CBF can substantially influence neuronal outcome.[1]. So, in neuro anaesthesia and neuro critical care, considerable emphasis is placed on the manner by which anesthetic agents and techniques influence CBF.

Apart from major blood vessels noradrenergic receptors are found in microarterioles and capillaries also. As Dexmedetomidine decreases the firing of locus coeruleus neurons and decreases norepinephrine release, vasodilatory increase in CBF is expected. However, Dexmedetomidine can also cause

decrease in cerebral blood flow via direct α_2 mediated vascular smooth muscle constriction.

Transcranial Doppler based assessment of flow velocities showed significant decrease after administration Clonidine as well as Dexmedetomidine.[64,65] The decrease in flow velocity with Dexmedetomidine was dose dependent and the effect was persistent for approximately 20 minutes after stopping the infusion. Significant decrease in regional and global blood flow was also observed with Dexmedetomidine in PET based studies.[66]

Cerebral Microcirculation :

In animal experiments topical application of α_2 agonists including Clonidine and Dexmedetomidine constricts large and small blood vessels by action on α_2 receptors.[67] In a study by Asano *et al* in rats, topically applied and systemically administered Dexmedetomidine constricted pial vessels.[68] As the vasoconstrictive effect of systemically administerd Dexmedetomidine was not totally reversed by topical application of Altipemazole, The authors suggested that apart from direct vasoconstrictive action, Dexmedetomidine may exert its effect by acting on other sites of CNS.

Metabolic regulation of cerebral blood flow :

Canine experiments by Karlsson *et al* and Zornow *et al* showed that 10mcg/kg of Dexmedetomidine caused a reduction in CBF (40,45%), which without a proportional decrease in cerebral metabolic rate ($CMRO_2$). Despite this observation there was no evidence of global ischemia in this investigation.[69,70]

In a study by McPherson *et al* central administration of Dexmedetomidine decreased CBF during normoxia and hypoxia.[71] During normoxia $CMRO_2$ values were maintained despite reduction in CBF and during hypoxia $CMRO_2$ values were decreased along with decreased CBF. The authors concluded that $CMRO_2$ reduction is due to reduced supply of Oxygen because of vasoconstriction and not due to Dexmedetomidine induced metabolic suppression. This study also shows that flow metabolism coupling is not well defined with Dexmedetomidine. However, in human volunteer studies and in neurosurgical patients undergoing tumour resection, administration of Dexmedetomidine has shown to preserve cerebral metabolism and blood flow relationship.[72,73]

$PaCO_2$ and PO_2 dependent regulation of cerebral blood flow :

Fale *et al* demonstrated that systemic administration of Dexmedetomidine prevented normocapnic and hypercapnic increase CBF in dogs anesthetized with isoflurane.[74] In vivo experiment by Ganjoo *et al* in rats with laser Doppler flowmetry demonstrated that vasoconstrictive effect of Dexmedetomidine can be aggravated by hypocarbia.[67]

McPherson *et al* evaluated the effect of Dexmedetomidine on CBF response to hypoxia in Isoflurane-anesthetized dogs and found that the vasodilatory response to hypoxia was maintained. But the vasodilatory response was still lower than in controls.[71]

Myogenic regulation (Autoregulation) :

Myogenic autoregulation after Dexmedetomidine administration was studied by Ogava *et al.*[39] Two doses of Dexmedetomidine were used and autoregulaion assessed with thigh cuff method and transfer function analysis. In very low frequency range Transfer function gain increased and phase decreased significantly, suggesting alterations in dynamic cerebral autoregulation. The authors concluded that Dexmedetomidine weakens dynamic cerebral autoregulation and delays restoration in CBF velocity during conditions of decreased steady state CBF velocity.

Cerebral protection:

Cerebral ischemia is associated with an increase in circulating and extracellular brain catecholamine concentrations. Interventions to reduce sympathetic tone had shown to improve outcome.[75] Thus theoretically the treatment with agents that decrease the release of norepinephrine in the brain may provide protection against the damaging effect of cerebral ischemia.

Studies have shown that Dexmedetomidine reduced the intracerebral catecholamine outflow during injury and resulted in less neural tissue damage with better neurologic outcome after transient global or focal cerebral ischemia in the rats.[76,77]

Animal studies have shown that α_2 adrenoreceptor (especially α_2A) agonists reduce excitatory neurotransmitter glutamate release and enhances glutamine disposal by oxidative metabolism in astrocytes.[78,79] Studies have shown that the neuro protective effects can also be due to alteration in balance between proapoptotic and antiapoptotic proteins or expression of growth factors like BDNF.[80]

The exact mechanism of the neuroprotective effect of α_2 agonists, however, is unclear. The neuroprotective properties of Dexmedetomidine in humans have not been proved.

Intra cranial pressure:

Increased ICP can cause reduction in cerebral perfusion pressure and may lead to global or regional ischemia. Internal pressure gradients may be created, producing internal or external herniation of the brain substance.

Alpha-2 agonists are more potent vasoconstrictors on the venous than on the arteriolar side of the cerebral vasculature.[81] Because the venous compartment comprises most of the cerebral blood volume, α_2 agonists could presumably decrease ICP without greatly increasing arteriolar cerebrovascular resistance. Animal experiments with Xylazine (α2 agonist) and Dexmedetomidine have shown to decrease ICP. In rabbit model of cryogenically induced space occupying lesion, administration of Dexmedetomidine resulted in no increase of ICP.[82]

A minimal variation in ICP was reported during intubation, Mayfield clamp application and skin incision when Clonidine was used before induction in patients with brain tumours posted for resection.[83] Talke *et al*. found that in patients after trans-sphenoidal hypophysectomy a target concentration of 600 ng/mL of Dexmedetomidine resulted in no increase in lumbar CSF pressure.[84]

Seizure:

Dexmedetomidine reduces seizure threshold in animal models, suggesting facilitation of seizure expression by the inhibition of central noradrenergic transmission.[85] Yet, there have been no report of seizures in humans. Dexmedetomidine is being used successfully in patients with known epilepsy for awake craniotomy for provision of sedation without any seizure incidences.[86,87]

Electro corticogram:

The anesthetic agents suitable for perioperative monitoring of ischemia and seizures should have minimal effects on the electroencephalogram (EEG).

The α_2 agonists attenuate α and β fractions and total power of an EEG as well as increased slow-wave activity.[88] Although the EEG changes produced by α_2 agonists are qualitatively similar to those produced by other agents, there is an important difference in their mechanisms of action. The preponderance of the lower frequency θ and δ bands, typically seen with increasing depth of inhalational anaesthesia is primarily the result of a direct suppression of the cortical activity. Alpha-2 agonists, however, act by interrupting noradrenergic neurotransmission and, subsequently, by disinhibiting the inhibitory interneurons in the locus coeruleus.

Dexmedetomidine (20 μg/kg) and Halothane (1–2%) produced quantitatively similar EEG changes in chronically instrumented cats.[89]

In humans, the infusion of Dexmedetomidine at 0.6 μg/kg/h produced EEG changes that correspond to a bispectral index scale of 60 (moderate to deep sedation), but the volunteers were readily awakened simply by talking to them. The results of these studies suggest that processed EEG parameters may be inadequate to assess the depth of sedation.[87] However, Maksimow *et al* showed depth of Dexmedetomidine induced sedation can be monitored with EEG based spectral entropy.[90]

Intra-operative electrocorticography requires that an anaesthetic should not interfere with EEG monitoring of seizure spikes, and agents that reduce seizure threshold may result in false positive localization of seizure focus.

In a study by Sturaitis *et al*, combined Dexmedetomidine and Sufentanil infusions resulted in marked alterations in background activity, and suppression of epileptiform activity. However, small bolus doses of Etomidate elicited epileptiform activity over epileptogenic cortex in most patients.[91] In contrast, in patients undergoing EEG monitoring, under sedation with Dexmedetomidine alone, epileptiform activity did not seem to be suppressed and in some patients the activity was exaggerated. Thus, adjuvant anesthetic agents, dose, rate of administration, and possibly the awake state may modify the EEG and seizure threshold with Dexmedetomidine.

Evoked potentials:

The ideal anaesthetic agent useful in neurosurgery should not interfere with perioperative neurophysiological monitoring. Study by Li *et al* in rats confirmed the preservation of the cortical somatosensory evoked potential at clinical and supraclinical concentrations of Dexmedetomidine.[92] In volunteer studies and in spine surgery patients use of Dexmedetomidine did not cause significant change in somatosensory or motor evoked potential responses.[93,94]

Minimal effect on cortical SSEP amplitudes and latencies were also observed with Dexmedetomidine during tumour and aneurysm surgeries.[95] Dexmedetomidine is also shown to have minimal effect on flash electroretinogram and visual evoked potential monitoring during ophthalmic artery aneurysm coiling or clipping procedures.[96]

CARDIOVASCULAR SYSTEM EFFECTS

The hemodynamic effects of Dexmedetomidine result from both peripheral and central mechanisms.

The hemodynamic effects of a bolus of Dexmedetomidine in humans have shown a biphasic response.[97] A bolus intravenous injection of 2µg/kg resulted in an initial increase in blood pressure (22%) and decrease in heart rate (27%) from baseline. This initial increase in blood pressure is probably due to the vasoconstrictive effects of Dexmedetomidine when directly stimulating

peripheral α_2 receptors. Effect of Dexmedetomidine on central nervous system leads to a reduction in sympathetic outflow and an increase in vagal activity leading to decrease in heart rate and blood pressure. In addition, Dexmedetomidine also has some action as a peripheral ganglionic blocker, further enhancing the sympatholytic effect.

Although hypotension has been described in patients receiving Dexmedetomidine, this exaggerated physiological effect seems to have a frequent temporal relationship to the use of a loading dose and/or pre-existing hypovolemia.[98,99] Omitting the loading dose or not giving more than 0.4 μg/kg reduces the incidence of hypotension, or makes it less pronounced. Giving the loading dose over 20 minutes also minimizes the transient hypertension.

In animal models, Dexmedetomidine showed some beneficial effects on the ischemic heart through decreased oxygen consumption and redistribution of coronary flow from nonischemic zones to ischemic zones after acute brief occlusion.[100] In human studies, the perioperative use of α_2 agonists have shown to reduce the incidence of myocardial ischemia.[101] No rebound effects have been found when discontinuing Dexmedetomidine infusion, even when it is given for more than 24 hours.[102]

RESPIRATORY SYSTEM EFFECTS

Alpha-2 adrenoreceptor agonists have minimal effects on ventilation. In healthy volunteers, as well as during procedural sedation, even very high doses of Dexmedetomidine did not compromise respiratory function.[99,103] There was no significant difference between placebo and Dexmedetomidine in measures of respiratory function after extubation in the group of ICU patients.[103]

Dexmedetomidine has shown to preserve the hypercapnic ventilatory response and hypercapnic arousal phenomenon, which has been described during normal sleep and is a safety feature.[104,105] Intravenous and inhaled Dexmedetomidine has been implicated in blocking histamine-induced bronchoconstriction in dogs.[106]

MUSCULOSKELETAL EFFECTS

It is shown that Dexmedetomidine increases duration of block and decreases the muscle force when used with Vecuroneum and Rocuroneum respectively. Although these changes were statistically significant, the investigators concluded that they were not clinically relevant.[108] Dexmedetomidine also is able to reduce muscle rigidity after high-dose opioid administration.[109]

GASTRO INTESTINAL EFFECTS

Alterations in gastrointestinal motility and delays in gastric emptying are of particular concern in the perioperative period and in critically ill ICU patients, in whom it may interfere with enteral feeding, may lead to aspiration or can cause and promote bacterial translocation.

In a whole-animal model (rat), Asai *et al* compared the effects of Clonidine, Dexmedetomidine, and Morphine on GI transit time and gastric emptying using radio labelled sodium chromate.[110] Clonidine and Dexmedetomidine weakly inhibited gastric emptying time and Morphine's effect was greater. Effects of Dexmedetomidine on gastric pH and on lower oesophageal sphincter tone have not yet studied according to the current literature.

ENDOCRINE EFFECTS

Alpha-2 adrenoreceptor agonists attenuate responses to stress, including neurohumoral responses. Because of the chemical resemblance of the drug to Etomidate, the concern arose that Dexmedetomidine use can suppress corticosteroid synthesis, but it is not proven in clinical studies.[111] Venn *et al* have compared the effects of Dexmedetomidine and Propofol on endocrine, metabolic and inflammatory responses in patients in the intensive care unit after major surgery.[112] There were no differences in cortisol, ACTH, prolactin and

glucose concentrations between the two groups. The insulin concentration was significantly lower and growth hormone level significantly higher in the Dexmedetomidine, but circulating concentrations remained in the physiological range. Although long-term data are not yet available, Dexmedetomidine administration for up to 7 days in dogs failed to suggest any adrenal shock or severe impairment of the hypothalamic-pituitary axis.[111]

RENAL SYSTEM EFFECTS

Dexmedetomidine induces diuresis in animal models studied, possibly through an ability to reduce efferent sympathetic outflow of the renal nerve.[113] Dexmedetomidine has been shown to suppress antidiuretic hormone and increases secretion of atrial natriuretic peptide, resulting in natriuresis and increased urine output.[114]

MISCELLANEOUS EFFECTS

In-vitro and in-vivo studies have shown that, Dexmedetomidine has no effect on WBC chemotaxis, phagocytosis, and superoxide anion production.[115] Dexmedetomidine when used for sedation during mechanical ventilation, there was a decrease in interleukin-6 levels from baseline.[116] When Dexmedetomidine was used for sedation in spinal cord injured patients, TNF-α and IL-6 levels were significantly decreased with less neutrophil infiltration at the site of injury. [117]

DEXMEDETOMIDINE- CLINICAL USES

INTENSIVE CARE UNIT

Dexmedetomidine has been approved for use as sedative in the ICU setting. Several studies has shown that Dexmedetomidine significantly reduces the need of other sedatives and analgesics especially opiods, provides stable hemodynamics and has minimal effect on respiratory funcition.

Sedation :

Dexmedetomidine was compared with Propofol for sedation in mechanically ventilated postoperative patients. In Dexmedetomidine group heart rate was low, MAP was similar and PaO2/FiO2 ratio was higher compared to Propofol group. Time to extubation was similar in both groups. Patients receiving Dexmedetomidine seemed to have greater recall of their stay in the ICU, but all described this as pleasant overall.[118]

In two different studies by Arain *et al* and Hsu *et al*, Dexmedetomidine has been shown to consistently reduce opioid requirements in postoperative patients requiring sedation in the ICU.[119,120]

The FDA approved the use of Dexmedetomidine infusions for 24 hours or less. However, multiple studies have shown the safety of using this drug for longer periods.

In data collected from prescribing patterns in 10 institutions, it was found that Dexmedetomidine was used for longer than 24 hours in 33.8% of cases. It also was noted that 33% of patients received a loading dose, 27% of patients received a dose higher than the recommended maximum, and 60% of patients remained on the infusion after extubation.[121] Literature review of 11 clinical trials including 6 adult groups and 5 paediatric groups by Guinter *et al* showed that prolonged infusion of Dexmedetomidine for more than 24 hours is safe without any adverse effects and rebound effects.[122] The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) randomized trial reported an earlier return to a delirium-free cognitive state and more ventilator-free days with Dexmedetomidine when used for 24 to 120 hours.[123] These studies indicate that it can be used long-term (>24 h) in critically ill patients.

The similarity between natural sleep (N-REM) and Dexmedetomidine induced hypnosis has been speculated to maintain cognitive and immunologic function in the sleep-deprived states as in the ICU.[124]

Delirium:

Delirium in the ICU is a risk factor for increased length of stay and increased mortality. In a study comparing Dexmedetomidine and Lorazepam, with comparable sedation scores, Dexmedetomidine infusion was associated with less incidences of delirium.[123] Dexmedetomidine when used with

benzodiazepines significantly reduced incidence of delirium and autonomic hyperactivity in patients with alcohol withdrawal syndrome.[125] Dexmedetomidine has been successfully used in the treatment of withdrawal of narcotics, benzodiazepines and recreational drugs.[126]

Weaning:

Dexmedetomidine offers unique quality of sedation similar to normal sleep which allows evaluation of neuropsychological status of mechanically ventilated patients. Daily wake up test and spontaneous breathing trial can be done even with continuing infusion of Dexmedetomidine with less sympathetic stimulation and better patient cooperation. This result in early weaning, decreased ventilator associated complications and decreased ICU stay.[127]

Although multiple trials have evaluated the use of Dexmedetomidine in the ICU setting, there are very few studies evaluating this drug in the neurosurgical population. Pandharipande *et al* compared Dexmedetomidine and Lorazepam for sedating patients with acute brain dysfuntion during mechanical ventilation. Clinical outcome showed no significant differences in ventilator free days, length of stay in the ICU and rate of mortality after 28 days.[123] A pilot study by James *et al* in head injured patients showed that, both Dexmedetomidine and Propofol based sedation resulted in comparable systemic and cerebral physiological parameters. [128]

ANAESTHESIA & PAIN MANAGEMENT

Premedication :

Premedication with Dexmedetomidine not only offers anxiolysis, sedation and analgesia, but also helps in attenuating the haemodynamic responses during laryngoscopy and intubation, thus reducing opioid and anaesthetic requirements.[129,130] Dexmedetomidine is also used as premedication through relatively noninvasive buccal or nasal route. The buccal and nasal route ensures better absorption, more compliance in younger children and better parentral separation when compared with Midazolam..[131,132]

Antiemetic :

Dexmedetomidine produces emesis in cats which is reduced by co-administration of Ondensetron.[133] However, in human studies it has been shown that with the use of Dexmedetomidine, vomiting episodes are significantly reduced in laproscopic procedures, gynaecological surgeries and bariatric surgeries.[134,135]

Airway management :

A phase III-b, randomised double blinded, placebo controlled trial showed that Dexmedetomidine is effective in patient undergoing awake fibre optic guided intubation for difficult airway management.[136] Another multicentre placebo controlled study also concluded that Dexmedetomidine can

be an alternative for sedation during awake airway management procedures in patient with cervical spine injury and difficult airway scenarios.[137] Better patient cooperation and hemodynamic stability was observed in these studies with the use of Dexmedetomidine.

Adjunct to general anaesthesia :

For maintenance of anaesthesia, Dexmedetomidine has been used as adjunct in patients undergoing multiple types of surgery.[138] As an adjunct, it has minimum alveolar concentration (MAC) and opioid sparing properties, which helps in decreasing the inhalational anaesthetic and opioid requirements, which can be advantage in situations where high anaesthetic concentration is either undesirable or not tolerated. Randomized controlled trials in bariatric surgical patients have found that intraoperative use of Dexmedetomidine as an adjunct reduces postoperative pain scores and Morphine consumption, and maintains stable hemodynamics.[135]

The intense surgical stimuli associated with craniotomy frequently leads to sympathetic activation and marked changes in systemic arterial pressure, CBF, and ICP. Perioperative hypertension in neurosurgical patients is associated with intracranial bleeds and prolonged hospital stay. Even with current neuroanesthesia management, hemodynamic stability may be challenging, especially in hypertensive patients.

Uyar *et al*, in a randomized, double-blinded, placebo-controlled study, showed that single bolus dose of Dexmedetomidine (1 mcg/kg) intravenously over 10 minutes before induction of anaesthesia attenuated the hemodynamic and neuroendocrinal responses to skull-pin insertion in patients undergoing craniotomy.[139] In another study by Tanskanen *et al* in patients undergoing craniotomy for supratentorial tumour removal, Dexmedetomidine use blunted the tachycardic response to intubation and the hypertensive response to extubation. The patients were also extubated faster without respiratory depression.[140] In a study by Gunes *et al* in patients undergoing supratentorial craniotomy studied infusion of Dexmedetomidine as an adjuvant decreased Sevoflurane use by 50%, Desflurane use by 36% and Isoflurane use by 40%. In addition Dexmedetomidine provided better brain relaxation and good surgical field exposure.[141]

Monitored anaesthesia care & Awake craniotomy:

FDA has approved the use of Dexmedetomidine as a sedative-analgesic and/or total anaesthetic in adults and paediatric patients undergoing small minimally invasive procedures, with or without the need for tracheal intubation. In a study comparing the efficacy of Dexmedetomidine or Propofol as a sedative agent in patients receiving local anaesthesia or regional blocks, the sedation scores and hemodynamics were comparable between two groups.

However, smaller doses of opioid were needed in the first hour in Dexmedetomidine group.[142]

Review of MRI sedation protocol by Mason *et al* showed that Dexmedetomidine as sole sedative agent provides adequate sedation comparable to benzodiazepines with minimal hemodynamic changes.[143] Same authors reported use of Dexmedetomidine in paediatric patients for CT imaging. Dexmedetomidine has been used in adult patients having parkinsonism undergoing MRI, where stereotactic frame placement and accurate imaging in tremulous patients makes remote location anaesthetic management challenging.[144]

Dexmedetomidine has also been used successfully for sedating patients undergoing awake carotid endarterectomy, permitting intraoperative neurological examination.[145] Patients sedated with Dexmedetomidine were comfortable and cooperative and had a lower incidence of postoperative hypertension than patients in the control group.

The addition of Dexmedetomidine infusions to assist on transoesophageal echocardiography examination has been described, with better hemodynamic profile and improved patient satisfaction than with benzodiazepine and narcotics alone, with no added respiratory depression.[146]

Surgical procedures for pathology involving near eloquent areas pose great challenge. Surgical resection should be balanced between aggressive resection and anticipated neurological dysfunction. Hence, these procedures often require patient cooperation for functional assessment. Drugs used in these procedures should have rapid onset of action, easy titrability and without minimal or no residual action when stopped before functional assessment.

As Dexmedetomidine provides anxiolysis, sedation, analgesia and provides a form of cooperative sedation without respiratory depression, it may be an attractive alternative or adjunct to the currently used anaesthetic techniques.

Use of Dexmedetomidine for intraoperative language mapping during resection of left temporal lesion was first reported by Bekker *et al*. The authors used a sleep-awake-sleep technique. Dexmedetomidine was the sole agent for the awake portion of the procedure. The same authors described the use of Dexmedetomidine for brain mapping of the cortical speech area and resection of the epileptic foci in a 12-year-old child.[87]

Mack *et al* described use of Dexmedetomidine infusion as a supplement to general anesthesia in 10 patients undergoing awake craniotomy and neurocognitive testing.[147] They reported successful completion of neurocognitive testing in all patients. Ard *et al* reported a series of 17 patients who underwent an asleep-awake-asleep technique for awake craniotomy. The

Dexmedetomidine was continued at 0.1 to 0.4 mcg/kg/hour during neurocognitive testing with satisfactory results.[148]

Stereotactic implantation of deep brain stimulators for movement disorders represents a challenge for surgeons and anaesthesiologists. Most commonly used sedatives may suppress tremor (e.g. Propofol) or affect microelectrode recording that is used for precise localization of the surgical target. The use of Dexmedetomidine for deep brain stimulator placement improved patient satisfaction without compromising target localization. It also resulted in stable hemodynamics, minimal use of antihypertensive intervention, ease of neurological examination and patient satisfaction without respiratory compromise.[144]

Atipamezole, a selective α_2 antagonist, at 50µg/kg was effective in reversing the sedation of Dexmedetomidine, when used to provide sedation for brief operative procedures.[149] This reversal of effects resulted in a more rapid recovery than occurred after equisedative doses of Midazolam.

PAIN MANAGEMENT

Although it has been proven that analgesic potency of Dexmedetomidine does not approximate with opioids, the greater α_2 receptor selectivity of Dexmedetomidine enhances the therapeutic window of Dexmedetomidine in the treatment of pain.[150]

Opiate sparing effect of Dexmedetomidine has important implications for the management of acute postoperative pain[151] and adjunct to labour analgesia.[152] Dexmedetomidine is also useful in treatment of chronic pain states, including disorders involving spasticity or myofascial pain, neuropathic pain, sympathetically maintained pain such as complex regional pain syndrome (CRPS) and chronic daily headaches. It is evolving as an adjuvant analgesic, both as intravenous and intrathecal infusion, in cancer pain refractory to multiple treatment modalities.[153]

The use of Dexmedetomidine has dramatically increased. This highly selective α_2 agonist has a set of unique effects that include sedation, sympatholysis and analgesia without significant respiratory depression. Originally approved as a sedative in the ICU, it has found many off-label applications in the ICU, the operating room, and perioperative environment.

TRANSCRANIAL DOPPLER

Introduction

One-dimensional echo-encephalography (A-mode sonography) was used up to the 1970s to determine midline shift in suspected intracranial mass lesions. However, it soon became redundant with the introduction of computed tomography and magnetic resonance tomography, as it lacked real imaging capabilities and the spatial resolution was limited.[154]

The introduction of transcranial Doppler sonography (TCD) by Aaslid *et al* (1982) gave new impetus to neurosonology, as it provided non-invasive real time method to study intracranial hemodynamics at the patient's bed-side.[155] Numerous studies highlight its value in vasospasm after aneurysmal subarachnoid hemorrhage, acute stroke, and now uses are expanding to non invasive assessment of ICP, cerebral autoregulation and cerebral perfusion pressure.

Transcranial colour-coded duplex sonography (TCCS) is a new technical development that combines non-invasive imaging of intracranial vessels and parenchymal structures at a high spatial resolution.[156]

Physical principle

TCD system employs a pulsed wave ultrasound based instrument that operates at a low frequency of approximately 2 MHz.[154] Medical ultrasound is commonly used to image soft tissue. In TCD analysis the ultrasound beam used to identify blood flow with help of Doppler principle.

The shift in frequency of a wave when either the transmitter or the receiver are moving with respect to the wave propagating medium was described by Doppler in 1843 and is accordingly known as the Doppler effect. The difference between transmitted and received frequency is known as 'Doppler shift'. In TCD imaging the ultrasound beam transmitted from the transducer is being scattered from moving red blood cells and they reradiate the ultrasound back toward the transducer, which is now a stationary receiver.

Doppler shift equation (*f*) is described as,

$$f = \frac{2 \times Vf \times Fsrc \times \cos\theta}{V}$$

Where Vf is the velocity of blood, Fsrc is the transmitted frequency, V is the speed of sound in soft tissue (~ 1540m/s) and θ is the angle of insonation (angle between ultrasound beam and velocity of blood)

Considering that TCD frequency and speed of sound in soft tissue remain constant, the frequency shift depends on the angle of insonation and the velocity of blood flow. The observed velocity is at least 97% of true velocity at small angles ($\leq 15°$).

For TCD analysis a handheld transducer is used, which operates as both transducer and receiver, is range gated and directionally sensitive. Range gating provides depth discrimination and directionality distinguishes signals moving toward or away from the transducer. The ultrasound is focussed with a plastic lens to a delimited sample volume. The sample volume is generally between 3 to 6 mm. A high pass filter within the receiver removes signals produced by wall thumps and probe positioning movements. Within a vessel erythrocytes move at different speeds and Doppler signal obtained is composed of different frequency components. A microprocessor then caries out fast Fourier transform analysis of the signal, enabling real time spectral display which provides two dimensional format, where Velocity is represented in vertical scale, time on the horizontal scale and signal intensity as relative brightness of colour. Corresponding to the maximum signal, a spectral envelope will be created along the wave form. Once the outline is created the different parameters are calculated from the time averaged mean flow velocity values of spectral envelope.

The time averaged mean flow velocity represents the peak signal intensity during that particular cardiac cycle and is different from mean flow velocity (mFV) which is calculated from peak systolic and end diastolic flow velocity values.

TRANSCRANIAL COLOUR DOPPLER IMAGING

Transcranial colour-coded duplex sonography (TCCS) is a new and non-invasive ultrasound application, by which the intracranial vascular structures can be displayed in the anatomical relationships to parenchymal structures. It also allows angle corrected flow velocity measurements.[156]

Flow velocities can be coded dependent on the Doppler shift by two methods, frequency based TCCS and power based TCCS. Frequency-based TCCS provides information on flow direction and velocity and less subjected to motion artefacts. Power-based TCCS provides a better signal to noise ratio, is not subject to the aliasing effects, and is independent of the insonation angle.

To prevent inadequate measurements, angle correction should only be applied to velocity measurements when the sample volume can be located in a straight vessel segment of at least 2 cm length. Increasing the power setting and the colour gain to the appropriate level during TCDI are the probably most important instrument control adjustments. Adjusting the focal zone in the range of 6-8cm will improve the image and colour resolution. The appearance of intracranial arterial blood flow is dependent upon many instrument controls that can affect its presentation. Therefore, estimation of arterial size is inaccurate from colour Doppler display.

TECHNIQUE OF INSONATION

Natural foramina and relatively thin areas of the cranium are used to access the intracranial vasculature. Transtemporal, transorbital, transforaminal and submandibular windows are commonly used for TCD examination.[157]

Transtemporal window is due to thinning in the suprazygomatic portion of the temporal bone. This window is routinely used to study the middie, anterior, and posterior cerebral arteries, along with the anterior and posterior communicating arteries and the terminal portion of the internal carotid artery. About 75-80% of the carotid artery blood flow passes through the ipsilateral MCA, making the MCA a key vessel for TCD analysis. Up to 20% of the population may not have adequate temporal window for TCD examination.[157] The transorbital window is available due to the thinness of the orbital plates of the frontal bones and bony defects caused by the optic foramina and superior orbital fissures. This location is used to study the ophthalmic artery and the three segments of the cavernosal portion (siphon) of the internal carotid artery (parasellar, genu, supraclinoid). The transforaminal window is accessibbe when the patient's head is flexed mildly forward and allows assessment of the intracranial portions of the basilar and vertebral arteries. The submandibular window is used by placing a superiorly directed transducer just below the angle of the mandible and it allows study of the extradural segment of the internal carotid artery.

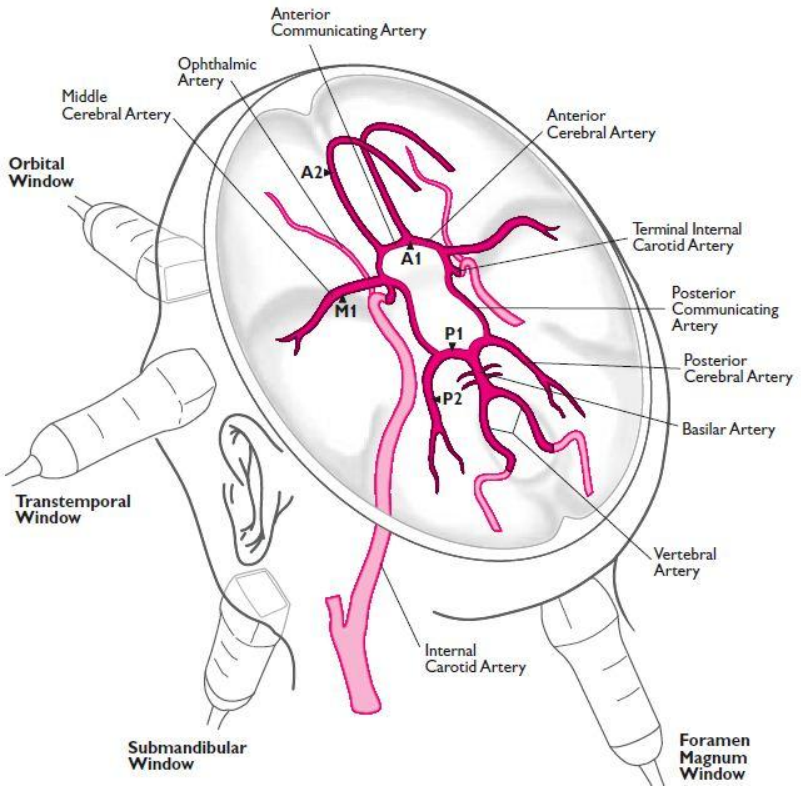


Figure 4 : TCD windows and orientation of basal cerebral vessels

In transcranial Doppler examination, vessels are identified by combination of following criteria [158]

Summary of Vessel Identification Criteria

Artery	Window	Depth (mm)	Direction of Flow (relative to transducer)	Relation to TICA/MCA/ ACA Junction	Velocity (cm/sec)	Response to Carotid Compression
MCA (M1)	Transtemporal	45-65	Toward	At	46-86	↓, 0
MCA/ACA bifurcation	Transtemporal	60-65	Bidirectional	At	. . .	↓, 0
ACA	Transtemporal	60-75	Away	Anterosuperior	41-76	↓, 0, r
PCA (P1)	Transtemporal	60-75	Toward	Posteroinferior	33-64	0, ↓ (fetal origin: ↓, 0)
PCA (P2)	Transtemporal	60-75	Away	Posteroinferior	33-64	0, (fetal origin: ↓, 0)
TICA	Transtemporal	60-65	Toward	Inferior	30-48	0, r
Ophthalmic artery	Transorbital	45-60	Toward	. . .	21-49	0
CS, supraclinoid	Transorbital	60-75	Away	. . .	50-60	0, r
CS, genu	Transorbital	60-75	Bidirectional	. . .	. . .	0, r
CS, parasellar	Transorbital	60-75	Toward	. . .	50-60	0, r
Vertebral artery	Transforaminal	65-85	Away	. . .	27-55	. . .
Basilar artery	Transforaminal	90-120	Away	. . .	30-57	. . .

Note.—Anterior and posterior communicating arteries are detectable only with transcranial Doppler sonography if they act as collateral routes of circulation (ie, exhibiting increased blood flow). ACA = anterior cerebral artery, CS = carotid siphon, MCA = middle cerebral artery, PCA = posterior cerebral artery, r = reversal of flow, TICA = terminal internal carotid artery, ↓ = decreased flow, ↑ = increased flow.

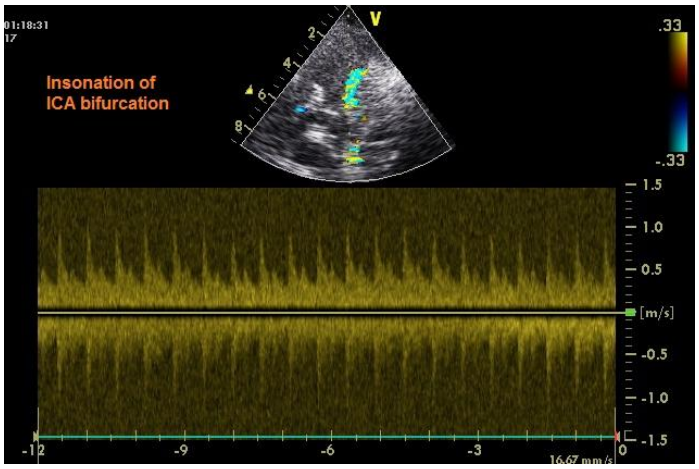


Figure 5: TCCDI - ICA bifurcation flow velocity recordings

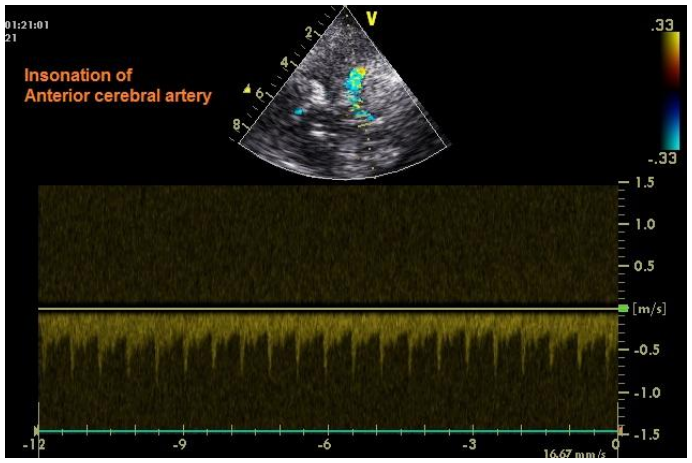


Figure 6: TCCDI - ACA flow velocity recordings

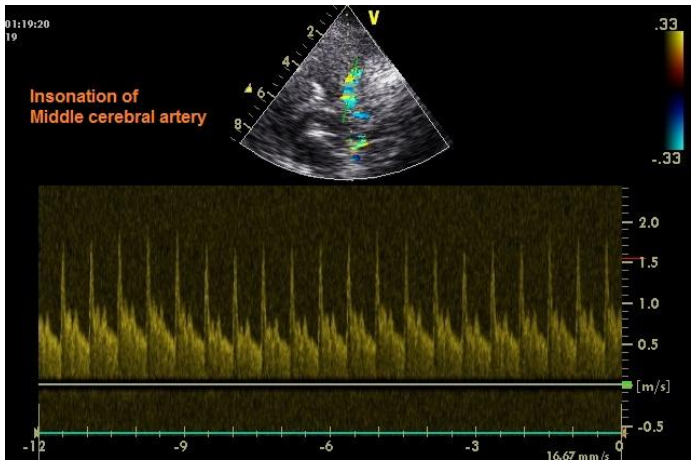


Figure 7: TCCDI - MCA flow velocity recordings

CLINICAL APPLICATIONS OF TCD

Clinical utility of TCD is established in detection of cerebral vasospasm following aneurismal subarachnoid hemorrhage and screening of sickle cell disease patients for stroke risk(Class-I). Valuable information can be obtained from TCD in intracranial steno-occlusive disease and cerebral circulatory arrest (Class-II). TCD examination is helpful in embolism detection during carotid endarterectomy and cardiac surgeries using bypass (Class II-III).[159]

TCD examination is also useful in monitoring of cerebral thrombolysis, assessment of cerebral autoregulation, assessment of vasomotor reactivity and detection of traumatic subarachnoid hemorrhage induced vasospasm (Class II-III). TCD can also provide information about intracardiac shunts and extracranial carodid stenosis, but other investigatory modalities are preferable (Class II -IV).[159]

The advantages of TCD are non-invasiveness and bed side assessment without any ionizing radiation. It is repeatable, less expensive and has good temporal resolution. However, TCD examination is operator dependent, skill and expertise needed to analyse and interpret findings. TCD will be difficult in uncooperative patients and patients with poor bony windows. TCD also has poor spatial resolution compared to other imaging modalities.

VALIDITY OF TCD IMAGING

TCD measures the velocity of red blood cell moving within a vessel. Provided the cross-sectional area of the insonated blood vessel remains constant, the CBF and FV vary directly with one another. The MCA diameter appears to be relatively constant under changing conditions of BP and carbon dioxide tension in the normal brain, as demonstrated in healthy volunteers.[160] Good correlations between relative changes in FV and CBF have been reported experimentally and in clinically stable patients. Ringelstein *et al* reported an overall 87.5% sensitivity and specificity for TCD ultrasonography based blood flow assessment.[161] Validation study by Bishop *et al* demonstrated a good correlation between changes in MCA flow velocities and changes in CBF measured by intravenous ^{133}Xenon, both at rest and in response to hypercapnoea.[162]

FACTORS AFFECTING TCD VELOCITIES

$PaCO_2$: Arterial pCO_2 is a potent modulator of cerebral blood flow. Ringelstein *et al* demonstrated 5% flow velocity change per mmHg change in PCO_2.[161] In a study by Kirkham *et al* in normal volunteers, a linear relationship demonstrated between maximal Doppler frequency and end expiratory pCO2 in the range of 20 – 60 mmHg with a change of 2.9% in MCA flow velocity per mmHg change in pCO_2.[163]

Hematocrit : According to Hagen-Poiseuille law if all other factors are constant, blood flow is indirectly proportional to viscosity. Brass *et al* has

correlated inverse relationship with hematocrit values and TCD flow velocities.[164]

Age and gender : The flow velocities, systolic / diastolic velocity ratio and resistant index, all are age dependent.[165,166] In the first few days of life end diastolic velocity may drop below the lowest velocity measurable by most TCD instruments (6cm/Sec). Velocities continue to increase slowly after second month; by 6th year of age levels are approximately 4 times the value measured at birth. Then they decrease linearly to 70% of the maximum velocity by the age of 16 to 18. Numerous TCD studies have also shown corresponding age associated decline in blood flow velocities. In a study of 120 normal individuals Vriens *et al* demonstrated 20% decline in blood flow velocity from 20 to 70 years of age.[166] Girls who were 10 years of age or older showed a tendency toward higher MV than did boys of same age.

CEREBRAL HEMODYNAMIC INDICES DERIVED FROM TCD

Pulsatility index and Resistant index

Gosling Pulsatility index (PI) and Poucelet Resistant index (RI) are TCD flow velocity derived formulas indirectly indicating distal cerebral vascular resistance.[167]

$$\mathbf{PI} = \frac{\mathbf{sys\ FV - dia\ FV}}{\mathbf{mean\ FV}} \qquad \mathbf{RI} = \frac{\mathbf{sys\ FV - dia\ FV}}{\mathbf{sys\ FV}}$$

The normal value of Pulsatility index is around 06 to 1.1. Increase in distal vascular resistance decreases the diastolic flow velocity and thus increases PI. Various studies have showed that clinical conditions like increased ICP and vasospasm after aneurismal subarachnoid hemorrhage, where the distal resistance to blood flow is high the PI was increased and decreasing trend shows resolution of the clinical scenario. Resistant index is less studied among these indices. Resistant index approaching towards the value of 1 indicates decreasing diastolic flow and thus increasing distal vascular resistance.

PI may be influenced by different factors, like hemodynamic, respiratory, and hematologic parameters. For this reason, the trend of change in PI is considered than absolute values. The main advantage of PI is that, being a ratio it is not affected by the angle of insonation.

eCPP and ZFP

Cerebral perfusion pressure is the difference between effective upstream pressure and the downstream pressure. The effective upstream pressure is usually mean arterial pressure. But the effective downstream pressure is determined by ICP, CVP or cerebral vascular resistance. Thus a more general concept of zero flow pressure is proposed (ZFP), where it is defined as the pressure at which flow in the vessel will cease.

eCPP and ZFP are calculated using the method described by Belfort.[168]

The estimated Cerebral perfusion pressure (eCPP) is calculated as :

$$\mathbf{eCPP = MFV \times \frac{(MAP\text{-}DAP)}{MFV\text{-}DFV}}$$

where MAP and DAP are Mean and Diastolic arterial pressures and MFV and DFV are Mean and Diastolic flow velocitites.

The zere flow pressure (ZFP) is the calculated as :[168,169]

$$\mathbf{ZFP = MAP - eCPP}$$

Decrease in ZFP indicates increase in downstream pressure, can be due to increase in ICP, increase in vascular resistance or increase in central venous pressure.

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

1. To assess the effects of loading dose of intravenous Dexmedetomidine on cerebral blood flow and dynamic cerebral autoregulation in patients with intra cranial tumors.

2. To assess the effects of intravenous Dexmedetomidine on cerebral vascular hemodynamics in patients with intra cranial tumours.

3. To compare the effects of intravenous Dexmedetomidine on the dynamic cerebral vascular autoregulation and cerebral hemodynamics in patients with and without intracranial pathology.

METHODOLOGY

METHODOLOGY

The study was approved by Institute ethics committee. Patients posted for neurosurgical intervention were enrolled in this study. They were divided into two groups:

Group S : (Study group) Patients who had intra cranial tumour posted for tumour decompression

Group C : (Control group) Patients who had lumbar disc disease posted for discectomy

The following were the inclusion criteria for Group S:

1. Patients who had unilateral intra axial tumour confined to the territory of Middle cerebral arterial supply.
2. American society of Anesthesiology (ASA) class 1 and 2.
3. Age 18-40 years.
4. Preoperative Glasgow coma scale (GCS) 15.

The following were the inclusion criteria for Group C:

1. Patients who were posted for Lumbar disc surgeries.
2. Screening MRI brain showed no intra cranial pathology.
3. ASA class 1 and 2.

4. Age 18 to 40 years.
5. Preoperative GCS 15

Exclusion criteria in both groups were:

1. Patient refusal for participation in study
2. ASA class 3 and above
3. Age less than 18 years and more than 40 years
4. Preoperative GCS <15
5. Emergency surgery
6. Intracranial vascular abnormalities like aneurysm and arterio-venous malformations.
7. Posterior fossa tumours
8. Preoperative heart rate <50/min, presence of heart block
9. Systemic hypertension, Diabetes mellitus
10. Known allergy to Dexmedetomidine or other α_2 agonists
11. Patients on beta blockers, having coronary artery disease, Left ventricular dysfunction
12. Pregnant or Nursing woman
13. Documented cases of carotid stenosis and atherosclerosis
14. Screening ultrasound (Grey-scale and Doppler) examination revealed carotid artery plaque or stenosis in preoperative period the day before surgery.

Patients who met the inclusion criteria were explained about the study drug and study protocol. Informed written consent was obtained from patients who were willing to participate in this study.

Data pooled from previous studies, indicate that the mean±SD value for the Transient hyperaemic response ratio (THRR) is 1.36±0.09, and that for the Strength of autoregulation (SA) is 0.98±0.09 under normal physiological conditions. A change of more than 2 SD is considered statistically significant. We calculated that 15 subjects would be required to reject the null hypothesis for a more than 2 SD change in the value of SA or THRR at a significance level of 90% power and α=0.05 (NCSS-PASS, USA). As there is possibility of poor temporal window and difficult MCA insonation in approximately 10 to 20% of general population, recruitment of participants was done till 15 subjects completed the whole study protocol in each group.[264,278]

Patients were kept fasting for 8 hours before the proposed study time. No premedication was used in patients who were enrolled in this study.

Patients were shifted to the operating room. Patients were kept comfortably in supine position with head resting on a head pillow. Electro cardiogram and pulse oxymetry monitors were attached (PHILIPS intellivue MX700, India).

After local anaesthesia (0.5 to 1 cc of 2% Lignocaine) infiltration, intravenous access with 18G cannula was obtained and Lactated ringers solution was started at the flow rate of approximately 100ml/hour. For blood pressure measurements invasive BP was used. Under local anaesthesia infiltration radial artery was cannulated with 20G cannula. For end tidal CO_2 estimation ($EtCO_2$) sample was obtained from mouth piece and analysed in side stream monitor (S/5 monitor, GE healthcare, UK). Continuous monitoring of Heart rate, SpO2, EtCO2 and invasive blood pressure were monitored and recorded.

TCD examination

For TCD examination 2MHz transducer probe (Vivid-i, GE health care, UK) was place in the temporal window and M_1 segment of MCA was identified according to anatomical location, colour scale imaging, depth of insonation and direction of flow. After a steady state of flow velocity (FV) recording, angle correction was applied so that the angle between linear segment of M_1 and angle of insonation was less than 15°. Base line FV was recorded for 10 seconds. After informing the patient, gentle compression of common carotid artery was done with continuouly monitoring FV. Compression was maintained for 10 seconds and then abruptly released. FV were monitored continuously for 10 seconds following release of compression. Throughout the procedure the obtained FV data were stored in the hardware. For analysis time-averaged mean of the outer envelope of the flow velocity profile preceding the compression

(F_1), immediately after compression (F_2) and immediately after the release of compression (F_3) were selected.

The Transient hyperaemic response test (THR test) was accepted when it fulfilled the following criteria:

- Onset of compression resulted in sudden decrease in FV
- Heart rate and Blood pressure remained stable during the procedure
- Flow transits after the compression were absent
- The power of the reflected Doppler signal was constant (as it indicates that the MCA diameter remains constant)

Transient hyperaemic response testing was done on right side MCA followed by left side MCA. After 90 seconds THR testing was repeated on both sides. The average value from two samples was recorded as baseline values.

Injection Dexmedetomidine (available as 100mcg/ml in 2ml ampoule) was diluted in 50 ml of 0.9% saline to get a concentration of 4mcg/ml. Dexmedetomidine infusion was started with help of infusion pump with the dose of 1mcg/Kg over 10 minutes. During infusion of Dexmedetomidine heart rate and blood pressure were maintained with Inj. Atropine, infusion of Lactated Ringer solution or Inj. Mephentermine. $EtCO_2$ and SpO_2 values were continuously monitored and recorded. In case of fall in SpO_2 oxygen was supplemented through nasal prongs.

Transient hyperaemic response test was repeated on both sides after the infusion of Dexmedetomidine. Angle of insonation corrected to that of baseline THR testing. Flow velocity data and vital parameters data were stored in hardware for further analysis. Autoregulatory indices and cerebral hemodynamic indices were calculated offline.

Patients were excluded when there was poor temporal window, difficulty in insonation of MCA, standard test criteria for THR test were not met and change of $EtCO_2$ was more than ± 1mmHg of the baseline.

Once the study protocol was completed, infusion of Dexmedetomidine was stopped. Anaesthesia was induced with Propofol (2 to 4 mg/Kg), Fentanyl (2mcgKg) and Vecuroneum (0.9mg/Kg). After intubation surgical procedure was commenced.

Intraoperative and postoperative complications were documented.

STATISTICS

DATA ANALYSIS

Demographic data including age, gender and weight of the two groups of patients were collected and tabulated. Data of vital parameters [Heart rate, Invasive Blood pressure (systoloic, Diastolic, Mean), SpO_2 and $EtCO_2$] were recorded in 2 minute intervals. Data regarding type of surgery, duration of surgery, intraoperative complications and postoperative complications were collected.

TCCDI Flow velocity data recorded during autoregulatory assessment were collected from the TCD machine hardware. For analysis, time-averaged mean of the outer envelope of the flow velocity profile preceding the compression (F_1), immediately after compression (F_2), and immediately after the release of compression (F_3) are selected. Average flow velocity data from the baseline recording (i.e. 10 seconds recording before compression) was used to calculate the hemodynamic indices.

As autoregulation and hemodynamic indices were assessed from both hemispheres, the study group were sub-divided as follows :

Group S (Patients with intracranial tumour)

- **Group S_T** - data from hemisphere that had tumour
- **Group S_N** - data from contralateral hemisphere that did not have tumour

Group C (patient without any intracranial tumour - lumbar disc disease)

- **Group C_R** - data from Right MCA
- **Group C_L** - data from Left MCA

In all the four subgroups, from the collected flow velocity data the following autoregulatory and cerebral hemodynamic parameters were calculated before and after infusion of loading dose of inj. Dexmedetomidine (1mcg/Kg over 10 min).

The cerebral autoregulatory indices calculated were :

- Transient hyperaemic response ratio (THRR)

$$\mathbf{THRR} = \frac{\mathbf{F_3}}{\mathbf{F_1}}$$

- Strength of autoregulation (SA)

$$\mathbf{SA} = \frac{\mathbf{F_3 \times P_2}}{\mathbf{MAP \times F_1}}$$

- Compression ratio (%) (CR)

$$\mathbf{CR} = \frac{(\mathbf{F_1 - F_2}) \times \mathbf{100}}{\mathbf{F_1}}$$

Where F_1 represents'time averaged mean flow velocity' from the spectral envelope before compression, F_2 flow velocity immediately after compression, F_3 represents velocity immediately after release of compression.
MAP –is average mean arterial pressure during the study period, and P_2 estimated perfusion pressure in MCA at the onset of compression calculated as $P_2 = MAP*(F_2/F_1)$

Cerebral hemodynamic indices calculated were :

- Mean flow velocity in MCA - **mFV (cm / second)** - recorded from velocity waveform before compression during each part of study
- Pulsatility index (PI)

$$\mathbf{PI} = \frac{\mathbf{sys\ FV - dia\ FV}}{\mathbf{mean\ FV}}$$

- Resistant index (RI)

$$\mathbf{RI} = \frac{\mathbf{sys\ FV - dia\ FV}}{\mathbf{sys\ FV}}$$

- Effective cerebral perfusion pressure (eCPP) mmHg

$$\mathbf{eCPP = mean\ FV\ x\ \frac{mean\ BP - dia\ BP}{mean\ FV - dia\ FV}}$$

- Zero flow pressure (ZFP) mmHg

$$\mathbf{ZFP = mean\ BP - eCPP}$$

Where 'meanBP' and 'dia BP' represents Mean blood pressure and Diastolic blood pressure; 'sysFV', 'diaFV' and meanFV represents Systolic, Diastolic and Mean flow velocities respectively.

STATISTICS

SPSS version 16 (SPSS inc, Chicago 2007) was used for statistical analysis.

Student t-test was used to find difference between demographic parameters like age and weight between two groups. Chi-square test was used to assess the difference between gender distributions among two groups. One way ANOVA was used to find difference in vital parameters throughout the study period.

In all four subgroup (Group S_T, S_N, C_R and C_L) Paired t-test was used to assess the statistical difference of autoregulatory parameters (THR Ratio, Strength of autoregulation) between baseline and after administration of loading dose of Dexmedetomidine (1mcg/Kg/10min). Similarly paired t-test was used to assess the difference of cerebral hemodynamic parameters (mean FV, PI, RI, eCPP and ZFP) before and after administration of Dexmedetomidine.

'p' value less than 0.05 was considered statistically significant.

RESULTS

RESULTS

Twenty four patients were recruited for 'Group S' to achieve the target of 15 satisfactory THRR test protocol, as 4 patients were excluded because of poor bone window, 1 patient excluded because of difficulty in localising straight segment of MCA in tumour side and 4 patients excluded because standard criterias of THRR testing were not met. Twenty patients were recruited for 'Group C', because in 3 patients poor bone window was present and in 2 patients standard criterias of THRR testing were not fulfilled.

The observations and analysis of autoregulatory and cerebral hemodynamic parameters are as follows.

TABLE - 1 DEMOGRAPHIC FACTORS

	Group S (n-15)	**Group C (n-15)**	**p**
AGE (years) mean±SD	33.1 ± 5.04	34.1 ± 3.4	0.365
GENDER Male:Female	6:9	10:5	0.272
WEIGHT (kg) mean±SD	64.27 ± 7.5	63.73 ± 5.8	0.831

Mean age in Group-S was 33.1 with SD of 5.04 years. The mean age in Group-C group was 34.1 with SD of 3.4 years. The difference between two groups was not statistically significant (p-0.365).

Gender distribution (Male : Female) were 6:9 and 10:5 among Group-S and Group-C respectively. The difference of gender distribution was not statistically significant (p-0.272).

Mean weight of patients were 64.2±7.5 Kg in Group-S and 63.73±5.8 Kg in Group-C and the difference was not statistically significant (p-0.831).

TABLE - 2 : DIAGNOSIS AND SURGICAL INTERVENTION

Group	Diagnosis	n	Surgical intervention	Duration*
Group S	Right temporal glioma	9	Pterional craniotomy and decompression	251 ± 64
	Left temporal glioma	6		
Group C	L_3 - L_4 PIVD	12	Laminectomy and discectomy	133 ± 36
	L_4 - L_5 PIVD	3		

*Note : * Duration of surgery in minutes mean±Sd*

Group S patients were having Glioma as diagnosed by MR imaging. Among the 15 patients 9 had right sided tumour and 6 had left sided tumour. For all patients pterional craniotomy and tumour decompression was done. Among Group C patients 12 had posterior disc protrusion at L_3 - L_4 level and 3 had at L_4 - L_5 level. Laminectomy and discectomy was done in all patients. Mean duration of surgery in Group S was 251±64 minutes and in Group C was 133± 36 minutes.

VITAL PARAMETERS

Table - 3 : Vital parameters - Group S

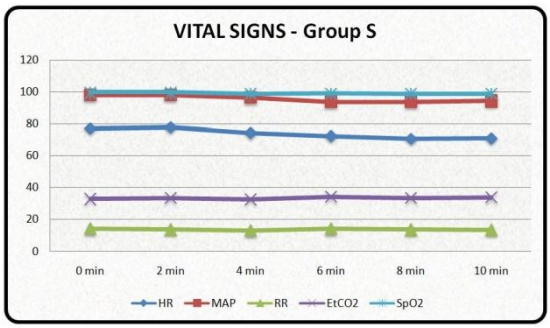
(n=15)	0 min	2 min	4 min	6 min	8 min	10 min	p
HR *(per min)*	77.2± 7.7	77.9±6.9	74.3±7.1	72.3±6.0	70.6±4.3	70.9±4.6	0.223
MAP *(mmHg)*	98.0±5.4	98.0±6.7	96.3±5.3	93.7±6.6	93.7±3.2	94.3±5.4	0.922
RR (*per min)*	14.3±1.4	14.1±1.0	13.2±0.7	14.2±1.9	13.9±1.2	13.7±2.1	0.345
$EtCO_2$ *(mmHg)*	33.1±1.5	33.4±1.3	32.6±1.1	34.2±1.0	33.5±1.1	33.7±1.4	0.333
SpO_2 *(%)*	99.7±0.5	99.8±0.9	98.9±0.4	99.1±0.6	98.9±1.0	98.9±1.2	0.121

Table - 4 : Vital parameters - Group C

(n=15)	0 min	2 min	4 min	6 min	8 min	10 min	p
HR *(per min)*	77.0 ±5.8	76.4±7.1	75.3±7.2	73.4±3.1	73.7±5.4	73.2±6.0	0.122
MAP *(mmHg)*	97.2±3.6	99.4±5.3	95.3±5.1	96.2±4.4	95.4±4.1	93.7±4.3	0.124
RR (*per min)*	14.7±1.4	14.5±1.2	13.2±1.0	14.3±1.1	14.4±0.9	14.1±1.7	0.332
$EtCO_2$ *(mmHg)*	32.8±1.2	33.4±1.1	35.1±1.2	33.4±1.1	33.5±0.8	33.4±1.1	0.219
SpO_2 *(%)*	99.9±0.3	99.8±0.4	98.4±0.3	99.6±0.3	99.5±0.4	99.2±1.0	0.887

Note :

- *Values shown as mean±SD*
- *Autoregulatory and cerebral hemodynamics were assessed with TCD during baseline (0min) and after infusion of Dexmedetomidine (10 min).*
- ***HR** - Heart rate, **MAP** - Mean arterial pressure, **RR** - Respiratory rate, **$EtCO_2$** - End tidal CO_2, **SpO_2** - Oxygen saturation measured in pulseoximetry.*



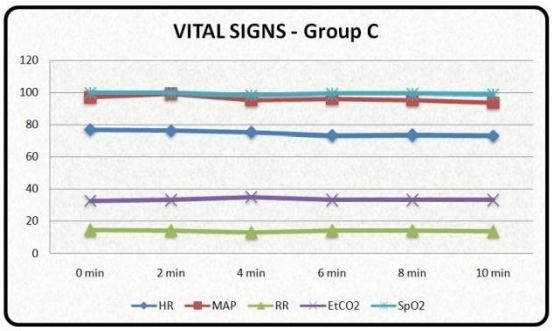


Table 3 and 4 shows that in both groups, during and after administration of loading dose of Dexmedetomidine, vital parameters were maintained comparable to baseline.

AUTOREGULATORY INDICES

Table - 5 : Autoregulatory indices - Group S

(n=15)	S_T			S_N		
	Baseline	After Dex	p	Baseline	After Dex	p
CR	43.5 ± 2.4	43.2 ± 2.1	**-**	41.7 ± 1.1	43.1 ± 1.7	**-**
THRR	1.58 ± 0.92	1.52 ± 0.11	***0.914***	1.44 ± 0.05	1.16 ± 0.06	***0.000****
SA	0.89 ± 0.05	0.86 ± 0.08	***0.217***	0.84 ± 0.03	0.66 ± 0.04	***0.000****

Table - 6 : Autoregulatory indices - Group C

(n=15)	C_R			C_L		
	Baseline	After Dex	p	Baseline	After Dex	p
CR	40.9 ± 1.0	42.1 ± 1.0	**-**	40.5 ± 1.0)	41.3 ± 0.9	**-**
THRR	1.43 ± 0.04	1.13 ± 0.06	***0.000****	1.44 ± 0.03	1.12 ± 0.01	***0.000****
SA	0.85 ± 0.02	0.65 ± 0.04	***0.000****	0.86 ± 0.02	0.66 ± 0.03	***0.000****

Note :

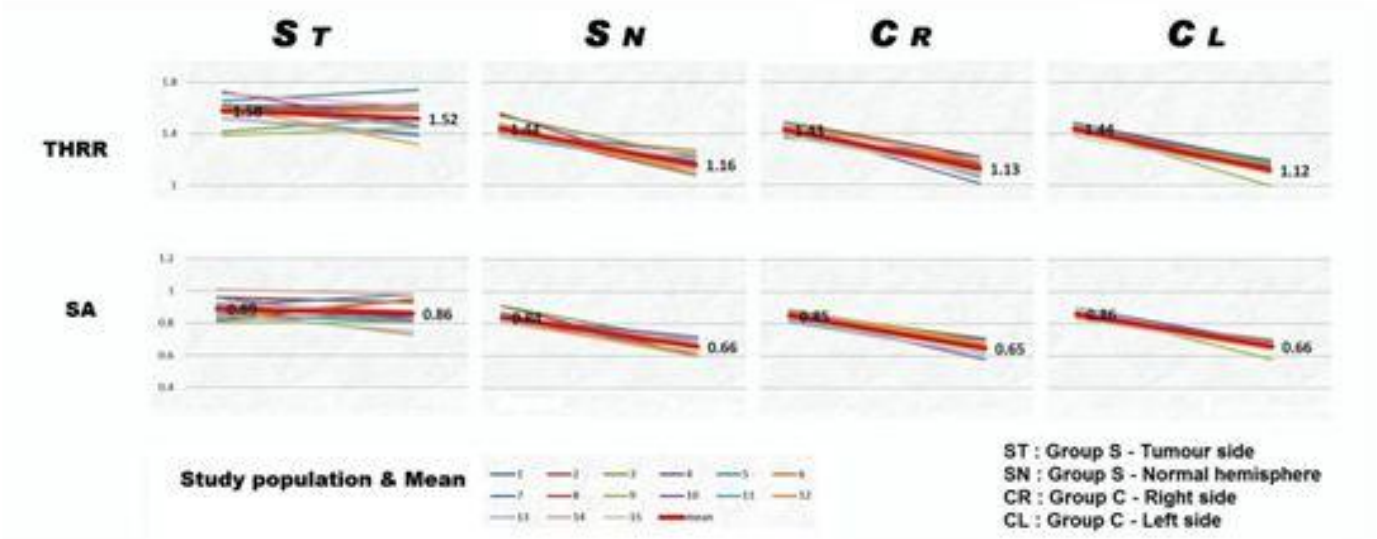
- *Values shown as mean±SD*
- ***After Dex** - after loading dose of Dexmedetomidine, **CR** - Compression ratio, **THRR** - Transient hyperaemic response ratio, **SA** - Strength of autoregulation*
- ** statistically significant (p<0.05).*

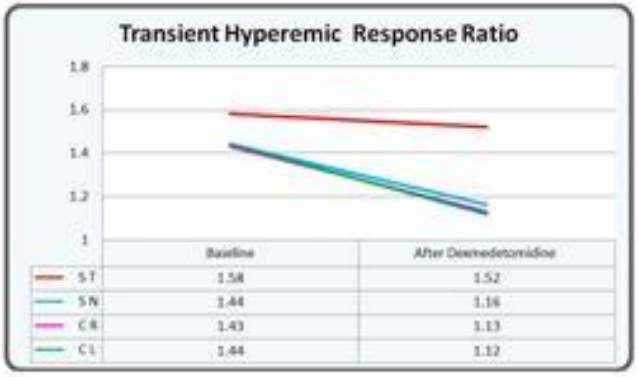
Compression ratio was around 40% in all study subsets.

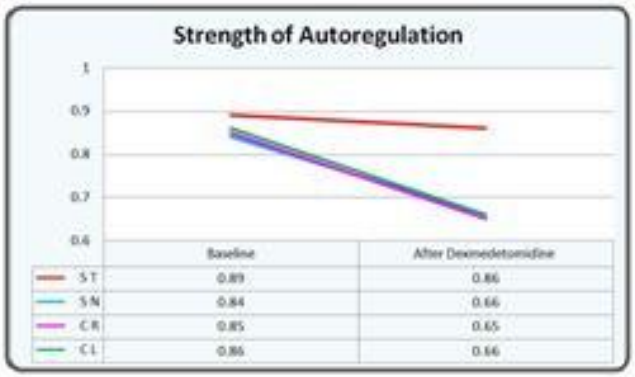
Transient hyperaemic response ratio (THRR) in S_T subset was 1.58±0.92. After administration of Dexmedetomidine the value was 1.52±0.11 and the difference was not statistically significant (p-0.914). THRR values in S_N, C_R and C_L were 1.44±0.05, 1.43±0.04 and 1.44±0.03 respectively. However, after administration of Dexmedetomidine the values were significantly reduced to 1.16±0.06, 1.13±0.06 and 1.12±0.01 respectively (p-0.00*).

Strength of autoregulation (SA) in S_T subset was 0.89±0.05. After administration of Dexmedetomidine the value was 0.86±0.08 and the difference was not statistically significant (p-0.217). SA values in S_N, C_R and C_L were 0.84±0.03, 0.85±0.02 and 0.86±0.02 respectively. After administration of Dexmedetomidine the values were 0.66±0.04, 0.65±0.04 and 0.66±0.03. Statistically significant reduction in SA values were observed in all the three subset of studies (p-0.00*)

AUTOREGULATORY INDICES







CEREBRAL HEMODYNAMIC INDICES

Table - 7 : Mean flow velocity (mmHg) - Group S

Patient No.	S_T		S_N	
	Baseline	After Dex	Baseline	After Dex
1	65.3	54.7	60.7	45.7
2	58.0	51.3	58.0	39.0
3	58.7	49.3	59.3	45.7
4	65.3	55.7	64.7	47.7
5	65.3	58.7	64.0	46.0
6	54.0	48.3	59.3	48.7
7	52.0	45.7	57.0	43.3
8	49.3	49.7	57.7	43.3
9	58.7	49.7	59.0	41.3
10	55.0	48.7	58.3	45.3
11	53.3	47.3	58.3	41.7
12	59.3	52.3	63.7	44.0
13	58.3	53.0	64.3	40.7
14	49.7	50.7	53.3	42.0
15	54.7	49.3	60.0	44.0
Mean±SD	**57.13 ± 5.2**	**50.95 ± 3.4**	**59.84 ± 3.1**	**43.89 ± 2.6**
p	**0.000***		**0.000***	

Table - 8 : Mean flow velocity (mmHg) - Group C

Patient No.	C_R		C_L	
	Baseline	After Dex	Baseline	After Dex
1	67.3	44.0	61.7	45.7
2	61.3	42.7	59.3	39.0
3	56.0	40.7	54.3	45.7
4	62.0	49.7	60.0	47.7
5	62.7	51.0	62.0	46.0
6	57.3	46.0	56.0	48.7
7	58.3	41.7	54.7	43.3
8	53.0	42.3	54.7	43.3
9	57.0	43.7	57.7	41.3
10	57.7	44.3	57.0	45.3
11	54.3	40.7	52.7	41.7
12	57.3	44.0	55.0	44.0
13	58.0	45.3	56.7	40.7
14	51.7	45.0	53.0	42.0
15	58.7	49.3	58.0	44.0
Mean	**58.18 ± 3.9**	**44.69 ± 3.2**	**56.8 ± 2.9**	**43.89 ± 2.6**
p	***0.000****		***0.000****	

***** *Statistically significant (p<0.05)*

In all subset of groups, mean flow velocity showed statistically significant decrease from base line (p-0.00*) after administration of loading dose of Dexmedetomidine.

Table - 9 : cerebral hemodynamic indices - Group S

(n=15)	S_T			S_N		
	Baseline	After Dex	p	Baseline	After Dex	p
PI	0.80 ± 0.11	0.73 ± 0.54	**0.022***	0.92 ± 0.16	1.27 ± 0.19	**0.000***
RI	0.52 ± 0.46	0.49 ± 0.02	**0.022***	0.56 ± 0.06	0.68 ± 0.05	**0.000***
eCPP	53.82 ± 13.5	53.69 ± 12.6	**0.973**	48.12 ±13.9	31.43 ± 8.8	**0.000***
ZFP	44.18 ± 15.9	40.64 ± 15.6	**0.394**	49.9 ± 16.2	62.9 ± 11.0	**0.005***

Table - 10 : cerebral hemodynamic indices - Group C

(n=15)	C_R			C_L		
	Baseline	After Dex	p	Baseline	After Dex	p
PI	0.89 ± 0.11	1.03 ± 0.13	**0.010***	0.82 ± 0.06	1.27 ± 0.18	**0.000***
RI	0.56 ± 0.04	0.61 ± 0.44	**0.009***	0.53 ± 0.03	0.68 ± 0.05	**0.000***
eCPP	46.32 ± 6.4	34.89 ± 7.6	**0.000***	49.37 ± 5.7	28.95 ± 8.0	**0.000***
ZFP	50.87 ± 7.6	58.85 ± 8.5	**0.007***	47.83 ± 7.2	64.78 ± 8.6	**0.000***

*Note : **PI** - Pulsatility index, **RI** - Resistant index, **eCPP** - Effective cerebral perfusion pressure, **ZFP** - Zero flow pressure, **After Dex** - After administration of loading dose of Dexmedetomidine.*

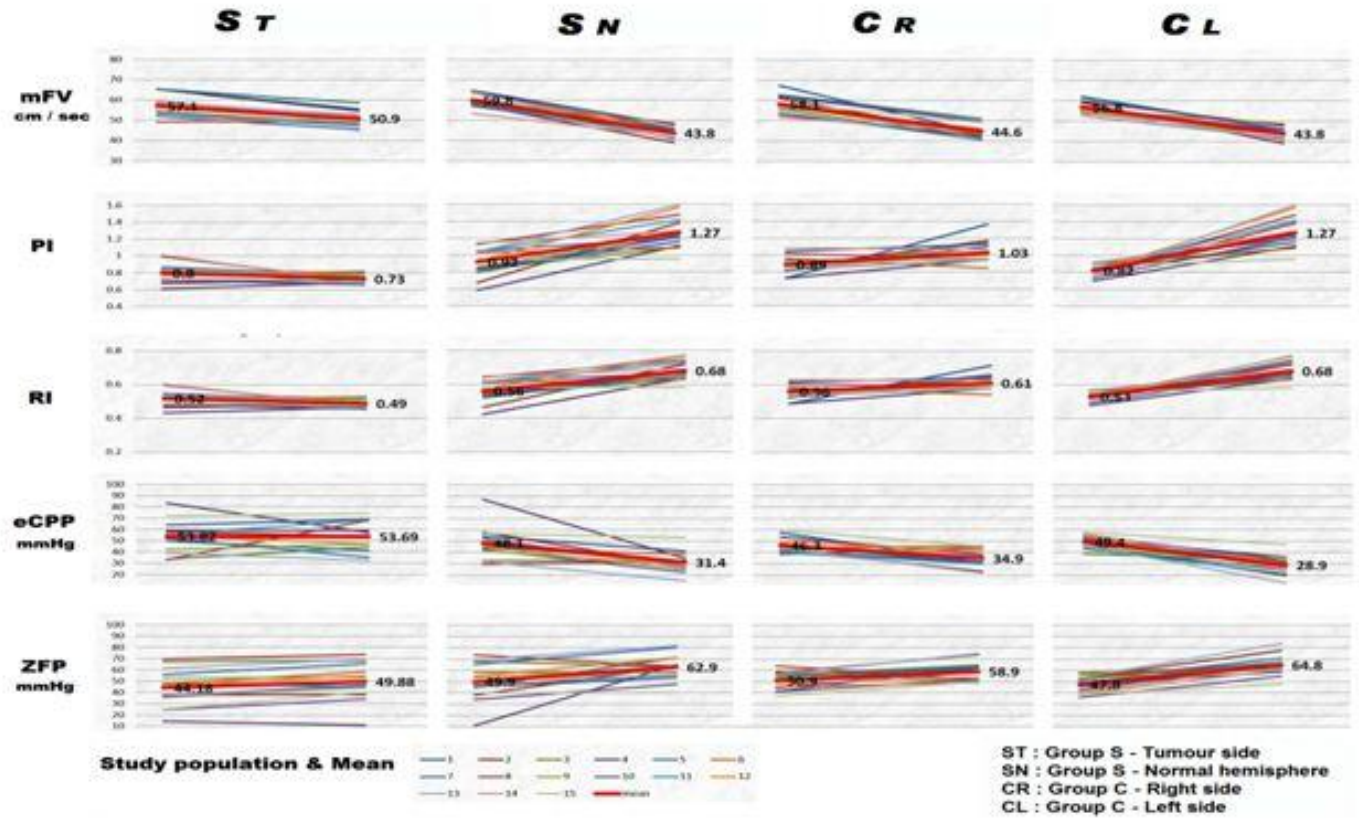
***** *Statistically significant (p<0.05)*

In S_T subset, PI and RI were decreased from baseline (0.8±0.11 to 0.73±0.54 and 0.52±0.46 to 0.49±0.02) and this decrease was statistically significant (p-0.022 and 0.022).

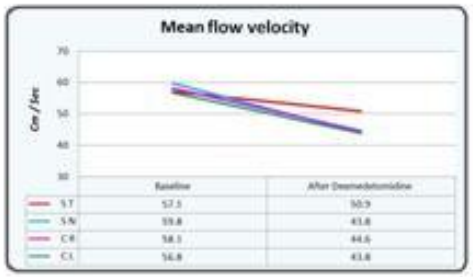
In S_N, C_R and C_L subsets, significant increase in PI and RI values observed after administration of Dexmedetomidine ($p<0.05$).

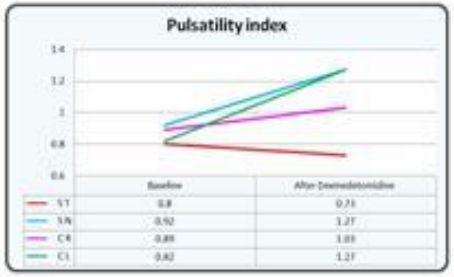
Analysis of eCPP and ZFP in S_T subset showed no significant difference after administration of Dexmedetomidine (p-0.973 and 0.394). in S_N, C_R and C_L subsets statistically significant difference observed between eCPP and ZFP values after administration of Dexmedetomidine ($p<0.05$).

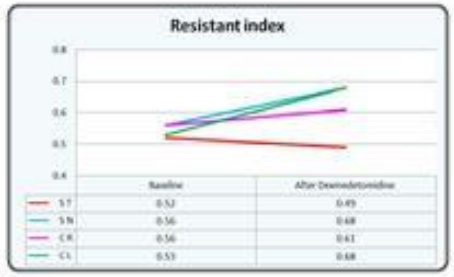
CEREBRAL HEMODYNAMIC INDICES

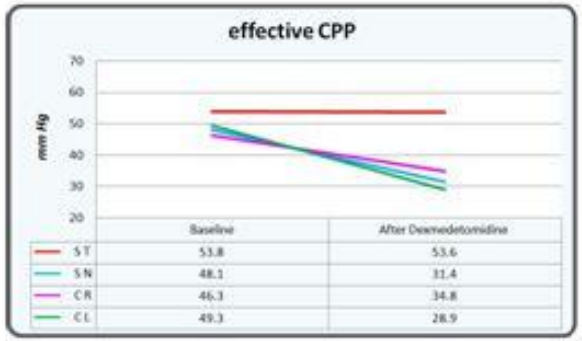


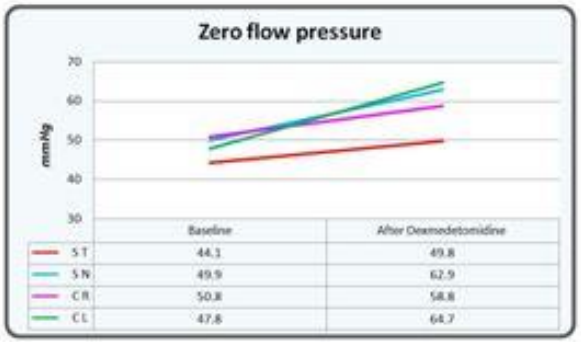
CEREBRAL HEMODYNAMIC INDICES











ST : Group S - Tumour side
SN : Group S - Normal hemisphere
CR : Group C - Right side
CL : Group C - Left side

Table - 11 : Comprehensive table showing comparison of various Autoregulatory and Cerebral hemodynamic indices between groups.

INDEX		Group S		Group C	
		ST	**SN**	**CR**	**CL**
THRR	Baseline	1.58 ± 0.92	1.44 ± 0.05	1.43 ± 0.04	1.44 ± 0.03
	After Dex	1.52 ± 0.11	1.16 ± 0.06	1.13 ± 0.06	1.12 ± 0.01
	p	***0.914***	***0.000****	***0.000****	***0.000****
SA	Baseline	0.89 ± 0.05	0.84 ± 0.03	0.85 ± 0.02	0.86 ± 0.02
	After Dex	0.86 ± 0.08	0.66 ± 0.04	0.65 ± 0.04	0.66 ± 0.03
	p	***0.217***	***0.000****	***0.000****	***0.000****
FV	Baseline	57.13 ± 5.2	59.84 ± 3.1	58.18 ± 3.9	56.8 ± 2.9
	After Dex	50.95 ± 3.4	43.89 ± 2.6	44.69 ± 3.2	43.89 ± 2.6
	p	***0.000****	***0.000****	***0.000****	***0.000****
PI	Baseline	0.80 ± 0.11	0.92 ± 0.16	0.89 ± 0.11	0.82 ± 0.06
	After Dex	0.73 ± 0.54	1.27 ± 0.19	1.03 ± 0.13	1.27 ± 0.18
	p	***0.022****	***0.000****	***0.010****	***0.000****
RI	Baseline	0.52 ± 0.46	0.56 ± 0.06	0.56 ± 0.04	0.53 ± 0.03
	After Dex	0.49 ± 0.02	0.68 ± 0.05	0.61 ± 0.44	0.68 ± 0.05
	p	***0.022****	***0.000****	***0.009****	***0.000****
eCPP	Baseline	53.82 ± 13.5	48.12 ± 13.9	46.32 ± 6.4	49.37 ± 5.7
	After Dex	53.69 ± 12.6	31.43 ± 8.8	34.89 ± 7.6	28.95 ± 8.0
	p	***0.973***	***0.000****	***0.000****	***0.000****
ZFP	Baseline	44.18 ± 15.9	49.9 ± 16.2	50.87 ± 7.6	47.83 ± 7.2
	After Dex	40.64 ± 15.6	62.9 ± 11.0	58.85 ± 8.5	64.78 ± 8.6
	p	***0.394***	***0.005****	***0.007****	***0.000****

- *Values shown as mean±SD*
- ***After Dex** - after loading dose of Dexmedetomidine, **CR** - Compression ratio, **THRR** - Transient hyperaemic response ratio, **SA** - Strength of autoregulation ,**FV** - Peak flow velocity, **PI** - Pulsatility index, **RI** - Resistant index, **eCPP** - Effective cerebral perfusion pressure, **ZFP** - Zero flow pressure.*
- ***** *statistically significant ($p<0.05$).*

Table - 12 : Intraoperative and postoperative complications

	Complications	**Group S (n/15)**	**Group C (n/15)**
Study period	Hypotension	1	2
	Bradycardia	2	2
	SpO2 < 95%	0	0
	Allergic reaction	0	0
	Nausea / Vomiting	0	0
	Respiratory depression	0	0
Intra operative period	Hypotension	0	0
	Bradycardia	0	0
Post operative period	Hypotension	0	0
	Bradycardia	0	0
	Nausea / Vomiting	0	0

Note :

- *Study period Hypotension, Bradycardia defined as 10% decrease from baseline. Respiratory depression defined as decrease in respiratory rate or increase in $EtCO_2$ more than 2mmHg from baseline.*
- *Intraoperative and postoperative period Hypotension and Bradycardia defined as 20% decrease from baseline, not explained by surgical and anaesthetic events at that point of time.*

DISCUSSION

DISCUSSION

Our study has shown that in tumour hemisphere, following the loading dose (1mcg/Kg over 10min) of Dexmedetomidine the dynamic autoregulation was maintained. In non-tumour hemisphere of study group and in both hemispheres of control group the loading dose of Dexmedetomidine caused impairment of dynamic autoregulation.

Dexmedetomidine is an α_2 agonist, now widely used as an anesthetic adjuvant and in critical care settings because of sedative, analgesic and sympatholytic properties. Dexmedetomidine is also used as sole agent for procedural sedation and in sedation for ventilated patients.[62]

Clinical side effects of Dexmedetomidine usually described in literature are mainly concerned about the cardiovascular effects like hypotension and bradycardia.[62,63] Very few studies focus on the cerebral hemodynamic effects of Dexmedetomidine. Various studies have shown that Dexmedetomidine decrease the mean flow velocity in cerebral blood vessels disproportionate to the decrease in metabolism, constricts the pial vessels, decrease CBFV response to CO_2 and weakens the dynamic autoregulation. Most of the studies on

Dexmedetomidine and cerebral hemodynamics were conducted upon animals or healthy human volunteers without any intracranial pathology.

The use of Dexmedetomidine is in increasing trend particularly in patients with intracranial pathology, because of its property of maintaining stable hemodynamics and inducing conscious sedation.

Theoretically, the combination of systemic hemodynamic effects of Dexmedetomidine like hypotension and bradycardia, and cerebral hemodynamic effects like decreased mean flow velocity and weakening of cerebral autoregulation may cause an imbalance in the demand - supply ratio of the central nervous system. Though there are concerns that this effect can be exaggerated when Dexmedetomidine is used for patients with intracranial pathology where the regional hemodynamics might be altered previously by the primary disease process itself, there are no studies till date addressing this issue.

This study is thus planned to assess the cerebral autoregulatory and cerebral hemodynamic effects with Dexmedetomidine in patients with intracranial tumours.

In our study, pre-procedure USG screening was done to rule out any vascular pathology in common carotid arteries like plaque and stenosis, that might cause abnormal intracranial flow velocities. It was also ensured that the patient has no risk of atheroma embolisation during carotid compression.

Transcranial colour Doppler imaging was used with angle correction option to ensure that same segment of artery was insonated in the same angle before and after Dexmedetomidine administration thus increasing the sensitivity of test results.

Patients diagnosed with MR spectroscopy, as having glioma which were well defined and confined to the territory of MCA were included, as gliomas are intra axial tumours with no supply from external carotid arteries. Patients with lumbar disc disease posted for discectomy, were selected as control groups. Screening MR images were checked to rule out intracranial pathology in this control group. Age, gender and body weight distribution was comparable between two groups (Table-1).

During the study, the systemic factors that can possibly affect cerebral blood flow velocity were maintained within the acceptable range after administration of Inj. Dexmedetomidine (Table 3,4). Thus, we can postulate that the autoregulatory and cerebral hemodynamic parameters obtained were mainly due to the drug's effect on cerebral circulation and not due to the alteration in systemic hemodynamics.

AUTOREGULATORY INDICES

Autoregulatory assessment was carried out with Transient hyperaemic response induced by carotid compression. THR ratio is widely used in evaluation of anaesthetic agents and their effect on cerebral autoregulation, because of simplicity, reproducibility and without any major complications.[47] This has been validated against standard dynamic autoregulatory assessment technique like 'Thigh cuff method' and static autoregulatory assessment technique using Phenylephrine infusion.[48,49] These indices also correlate with CO_2 induced vasodilatory changes.[170]

From various clinical studies and validation studies the normal value of Transient hyperaemic response ratio (THRR) was estimated to be around 1.36± 0.09 and more than 2 standard deviations was accepted as significant change from the base line.[48,49,171] The results of our study show that THR ratio in tumour hemisphere showed no statistical difference from the baseline (p-0.914) after administration of initial loading dose of Dexmedetomidine (Table-11). In non tumour hemisphere and in control group administration of Dexmedetomidine resulted in significant decrease in THR ratios ($p<0.05$)(Table-11). The strength of autoregulation (SA) is calculated by normalizing the THRR for changes in MAP of the MCA at the onset of compression. Normal value for SA is around 0.8 – 1.1.[48,49,171] Decrease in SA index denotes impaired autoregulation.

In our study the SA values were maintained in tumour hemisphere (p-0.217) and significant decrease observed in non tumour hemisphere and in control group ($p<0.05$) (Table-11). These results collectively show that with administration of loading dose of Dexmedetomidine (1mcg/Kg/10min) autoregulation was maintained in hemisphere with tumour and altered in non pathological hemispheres.

In vivo experiments conducted by Ishiyama *et al* in dogs showed that topical administration of Dexmedetomidine in the concentration of 10^{-3} did not produce large and small artery and small veins constriction even after increasing the MAP to 15 -25%. [172] This result was obtained as the part of the study, which was originally designed to assess the mechanisms of cerebral vascular effects with Dexmedetomidine. This study was not designed to assess the autoregulation and other varying concentrations of Dexmedetomidine did not showed the same result. However, the authors suggested that Dexmedetomidine could impair cerebral autoregulation.

Ogawa *et al* analysed effect of Dexmedetomidine on dynamic cerebral autoregulation in a randomized, double blinded cross over study including 14 healthy volunteers.[39] The dynamic regulation was estimated by transfer function analysis between CBF velocity variability and arterial pressure variability, which was induced by thigh cuff method. Low dose Dexmedetomidine regimen consisted of 3mcg/Kg/hour for 10 minutes followed by maintenance of

0.2mcg/Kg/Hour for 60 minutes. In high dose regimen 6mcg/Kg/hour for 10 minutes followed by 0.4mcg/Kg/hour for 60 minutes infusion was used. The autoregulation was assessed in the maintenance phase. The study showed that transfer function gain significantly increased and phase decreased in the very-low frequency range, suggesting alterations in dynamic cerebral autoregulation. The dynamic rate of regulation and percentage restoration in CBF velocity were also significantly decreased when a temporal decrease in arterial pressure was induced by thigh cuff release.

Our study was designed to assess the autoregulation after the initial bolus dose (1 mcg/Kg over 10 min) with the use of Transient hyperaemic response testing, which is one of the widely used and validated method of autoregulatory assessment, but it does not differentiate phase, limits or gain of autoregulation like thigh cuff method. In our study, significantly decreased autoregulatory indices were observed in Non pathological hemispheres, similar to results obtained from human volunteers by Ogawa *et al*.[39]

The THR ratio and SA indices were maintained in tumour hemisphere, which is the primary area of interest in this study. Sharma *et al* assessed cerebral autoregulation in 35 patients with supratentorial tumours using THR technique.[19] Overall cohort analysis showed that cerebral autoregulation was maintained before and after tumour resection. However, autoregulation was impaired preoperatively in patients with large tumour size and 24 hours

postoperatively when there was midline shift of more than 5 mm. Schmieder *et al* assessed cerebral autoregulation in patients with intracranial tumour with thigh cuff method.[20] Fifty patients were included and autoregulatory indices were correlated with size, location, histology of the tumour and presence of accompanying disease. The authors concluded that cerebral autoregulation is preserved in patients with intracranial tumours regardless of the tumour size, if the clinical status of the patient prior to the surgery was good. The authors also suggested that the accompanying diseases like diabetes and hypertension could alter autoregulation. The maximum size of tumour in our study was 6 cm and no patient had midline shift. Patients having diabetes and hypertension were also excluded from the study.

In our study the base line THR ratio and SA values in tumour hemisphere showed that autoregulatory phenomenon was intact. After administration of loading dose of Dexmedetomidine (1mcg/Kg/10min) no significant difference observed in THRR and SA values in tumour hemisphere in contrary to non tumour hemisphere and control group, where the indices showed impairment of autoregulation (Table-11). This can be due to the effect of vascular pattern of glioma tumour.

Study conducted by Hardebo *et al* showed that blood vessels in malignant gliomas exhibit regressive changes in all layers of the vascular wall.[173] Those

blood vessels were not innervated by vasoactive nerves and totally lose vascular reactivity to vasoactive agents just outside the visible tumour font. In this study blood vessels were taken from normal brain tissue and tumour site and contraction tested with depolarising dose of potassium, nor adrenaline, serotonin, neuropeptide Y, prostaglandin F_2 and UTP. Dilatation of blood vessels tested with VIP, Substance P and Acetylcholine. Vessels obtained from normal brain tissue reacted to all agents and those from glioma showed no reaction to any agent. Apart from lack of neural control, alteration of the collagen content and smooth muscle arrangement were also described in blood vessels innervating glial tumours.[174,175]

Alpha-2 adrenergic receptors are widely distributed in cerebral vasculature and innervated by extrinsic sympathetic outflow from cervical sympathetic ganglion.[7] Alpha-2 stimulation causes vasoconstriction in isolated cerebral vessels and in various animal models. Study by Ishiyama *et al* in canine model showed that topical administration of clonidine constricts both pial arterial and venous vessels where as intravenous clonidine constricts only pial vessels.[176] These effects were concentration dependent and were reversed by administration of α_2 antagonist Yohimbine. Study by the same author with Dexmedetomidine showed similar results in canine model.[172] The authors concluded that the vasoconstrictor effect of Dexmedetomidine appears to be mediated by activation of α_2 adrenoceptors. Vasoconstrictive property was also

demonstrated in studies where the administration of Dexmedetomidine prevented inhalational anaesthetics and CO_2 induced vasodilatation.[70,74]

THR ratio was used in our study for assessment of autoregulation. The physiological basis of THRR analysis is that, in response to sudden decrease in perfusion pressure the distal vasculature should dilate to compensate for the decrease in blood supply. THR ratio in non tumour hemisphere and in control group showed statistically significant decrease after administration of Dexmedetomidine. As discussed previously, Dexmedetomidine as an α_2 agonist causes vasoconstriction of cerebral blood vessels and this phenomenon may antagonise the normal dilatation response to temporary vascular occlusion resulting in decreased autoregulatory indices (THRR and SA) in transient hyperaemic response testing.

In peri-tumour region, as there is possibility of lack of adrenergic receptors and altered smooth muscle architecture, the action of Dexmedetomidine may be less pronounced. Therefore, the obtained autoregulatory indices, which show no significant difference from the baseline, might be due to lack of action of Dexmedetomidine in tumour vasculature.

The other end of autoregulatory spectrum, where there is an increase in perfusion pressure, there should be distal vasoconstriction to prevent hyperaemia. As a vasoconstrictor, the effect of Dexmedetomidine during increased perfusion pressure may be different. This phenomenon can be

assessed by static autoregulatory assessment using vasoconstrictors like Phenylephrine.

Lam *et al* assessed the influence of Dexmedetomidine on CO_2 reactivity and Cerebral autoregulation in healthy volunteers.[177] In first phase of this study, 50ml saline was given over 50 minutes to 7 healthy volunteers. Bilateral MCA flow velocity assessed using TCD during normoventilation, hyperventilation and breath holding. CO_2 reactivity was analysed as % change in flow velocity per mmHg change in $PaCO_2$ using linear regression analysis. After return to normoventilation MAP was raised by 20 mmHg from baseline with infusion of 0.01% Phenylephrine and MCA velocity was continuously recorded. Cerebral autoregulation was quantified with autoregulatory index (ARI = % change in estimated cerebrovascular resistance/% change in MAP). Same protocol used after inj. Dexmedetomidine 1mcg/Kg/20 min followed by 0.6mcg/kg/hr dose for 30 minutes duration. The CO_2 reactivity was reduced, but the authors contributed it to reduced MCA flow velocity. Although not statistically significant, the autoregulatory index was increased with Dexmedetomidine from 0.73±0.14 to 0.82±0.05.

In our study and in the study by Ogawa *et al*[39] autoregulation was assessed by decreasing the perfusion pressure (temporary carotid occlusion and sudden release of thigh cuff) and observing the compensatory dilatation in cerebral vascular bed. These studies showed impaired autoregulation probably

because of vasoconstrictory nature of Dexmedetomidine. However, volunteer study by Lam *et al*[177] where the vasoconstrictive response of cerebral vasculature to increase in perfusion pressure was assessed, increase in ARI was observed with Dexmedetomidine. As Dexmedetomidine itself is a vasoconstrictor, the physiological process of vasoconstriction could be exaggerated or maintained with this static autoregulation assessment technique. This shows that effect of Dexmedetomidine on cerebral autoregulation may vary with the change in perfusion pressure.

Decrease in perfusion pressure is common in anaesthesia and critical care scenario. Decrease in the MAP is one of the proven side effects of Dexmedetomidine itself. As Dexmedetomidine is shown to alter autoregulation in the scenario of decreased perfusion pressure, the drug can cause serious effect on cerebral vascular homeostasis. This effect can be exaggerated in neurosurgical and neurotrauma patients where baseline abnormalities of autoregulation can be present.

There are few controlled studies in human addressing the influence of anaesthetics on cerebral autoregulation. Very few studies specifically address the issue of anaesthetic agents induced alteration in cerebral blood flow autoregulation. Conti *et al* assessed the effects of Propofol-Remifentanil based TIVA and Sevoflurane on two varying depth of anaesthesia (BIS value of 50

and 35) with THRR based autoregulation assessment.[38] This study showed that Propofol-Remifentanyl based TIVA maintains autoregulation in both anaesthetic levels, where as with Sevoflurane autoregulation was preserved at lower concentrations and impaired with higher concentrations. The authors proposed that vasodilatation and luxury perfusion by Sevoflurane impaired the autoregulatory response and because of increase in CVR the autoregulation was maintained in TIVA group. Tibble *et al* compared THRR testing with Static autoregulation testing to assess the graded impairment of cerebral autoregulation.[48] Although this study was not designed to assess the autoregulatory effects of Desflurane, the increasing concentration of Desflurane was associated with gradual decrease in THRR values.

Strebel *et al* with 'Thigh cuff' method assessed the effects of Isoflurane, Desflurane and Propofol on cerebral autoregulation.[34] Low dose (0.5 MAC) Isoflurane delayed but did not reduce the autoregulatory response. Low dose Desflurane decreased both speed and magnitude of autoregulatory response. On high dose (1.5 MAC) both agents ablated autoregulation. No significant alterations were noted in autoregulatory parameters with low and high dose of Propofol (100 and 200mcg/Kg/min). Similar results were obtained in a study by Bedforth *et al* where 1.5 MAC concentration of Desflurane abolished autoregulatory response.[178] In another Study by same author showed that, Sevoflurane concentrations up to 1.2 MAC preserved the autoregulation.[179]

However, addition of Nitrous oxide impaired the autoregulation. The authors proposed that vasodilatory property of Nitrous oxide lead to ablation of autoregulation.

In most of the studies, vasodilatory property of inhalational anaesthetic agents was proposed as reason for decreased autoregulatory response. Our study is contradictory to this findings, as Dexmedetomidine shown to be cerebral vasoconstrictor caused alteration in autoregulatory response (Non pathological hemispheres). The vasoactive drugs has been shown to affect the limits of autoregulation as well as gradient of autoregulation in varying magnitude depending upon the primary mechanism of action and secondary effects like reduction of $CMRO_2$.[41,42,180] THRR testing assess both the gradient as well as the limits of autoregulatory plateau without differentiating between the two. Therefore, there is possibility that volatile agents and Dexmedetomidine can alter the different components of autoregulation thus presenting as different study results.

CEREBRAL HEMODYNAMIC INDICES

Mean flow velocity

Dexmedetomidine caused statistically significant decrease in mean flow velocity in all subsets of patients in our study in spite of maintaining mean arterial pressure comparable to baseline values (Table 7,8 and 11).

Lee *et al* measured middle cerebral artery blood flow velocity by use of TCD in healthy volunteers after administration of clonidine and showed a significant decrease in flow velocity.[64]

In a study by Zornow *et al* six healthy volunteers were infused with four different doses of Dexmedetomidine and MCA flow velocity were assessed using TCD.[65] There was statistically non-significant increase in CO_2 tension with increasing dosage of Dexmedetomidine. This study showed that hypnotic dose of Dexmedetomidine results in modest decrease in flow velocity even with maintained mean arterial pressure and increasing CO_2 levels. The decrease in flow velocity was also corresponding to the increase in Dexmedetomidine dosage. The authors have also shown that the change in flow velocity occurs within minutes of change in Dexmedetomidine infusion rates.

Drummond *et al* conducted a study in six healthy volunteers to assess the cerebral blood flow velocity, cerebral metabolic rate and response to carbon di-oxide with Dexmedetomidine infusion.[181] Parameters were obtained at six time intervals after baseline pre-sedation assessment – baseline with hyperventilation, Dexmedetomidine concentration of 0.6ng/ml, 1.2ng/ml, 1.2ng/ml with arousal, 1.2ng/ml with hyperventilation and 30 minutes after discontinuation of Dexmedetomidine. This study showed that with increasing concentration of Dexmedetomidine there was decrease in flow velocity and this decrease in flow velocity was aggravated by hyperventilation. Flow velocity values increased during arousal and in recovery period.

In a study by Lam *et al*, Dexmedetomidine was given as 1mcg/Kg/20 min bolus dose, followed by 0.6mcg/kg/hr for 30 minutes duration.[177] The MCA flow velocity reduced from 70±6 to 53±3 cm/sec after administration of Dexmedetomidine.

Results of our study are also consistent with findings reported in literature that Dexmedetomidine causes decrease in cerebral blood flow velocity.

In a study by Dong *et al*, induction of anaesthesia with Thiopentone was associated with decrease in flow velocity.[182] This decrease was consistently seen

in patients with and without intracranial tumours. Similarly the other commonly used induction agent, Propofol is also associated with decrease in cerebral blood flow velocities. [183,184]

In contrast to intravenous induction agents, inhalational agents are associated with increase in cerebral blood flow velocities (CBFV). Nitrous oxide alone and with combination of other inhalational agents have been shown to increase the CBFV.[185] Other inhalational agents like Isoflurane, Enflurane, Sevoflurane and Desflurane also shows dose dependent increase in CBFV.[186,187] These results collectively show that cerebral vasoconstrictive effect of intravenous agents leads to decrease in CBFV and dose dependent vasodilatory effects of inhalational agents results in increase in CBFV.

Dexmedetomidine as a vasoconstrictor decreases the CBFV similar to intravenous induction agents. However the mechanism of intra venous agents induced vasoconstriction is due to decrease in $CMRO_2$ (flow metabolism coupling) and Dexmedetomidine induced vasoconstriction is primarily due to direct effect on α_2 receptors of cerebral blood vessels.

Pulsatility index and Resistant index

Gosling Pulsatility index is a useful indicator of CPP and hemodynamic symmetry. However, the validity of PI to describe CVR, ICP and lower limit of autoregulation is questioned.

Studies have shown that PI may or may not be a reliable indicator of intracranial pressure.[188,189] Study by Richards *et al* in rabbits showed that PI could not be used as an indicator for marking the lower limit of autoregulation.[190] In a study by Czosnyka *et al* in rabbits, the PI was compared with laser Doppler flowmetry derived cerebral perfusion pressure in different scenarios.[191] The correlation between CVR and PI was seen in hypercapnic challenge. Hemorrhagic hypotension, ganglion blockade induced hypotension and intracranial hypertension scenarios did not produced a correlation between PI and CVR. The authors concluded that PI could not be interpreted simply as an index of CVR in all circumstances. However, sudies have shown that PI can be reliable monitor of cererbral hemodynamic asymmetry and decreasing cerebral perfusion pressure.[192]

The correlation of PI and CVR in patients with intracranial space occupying lesion is not known. As per the formula, the increasing trend of PI indicates the decrease in diastolic flow velocity, which can be due to increase in ICP, increase in CVR or decrease in CPP. Although the ICP is not measured in our study, as Dexmedetomidine has shown to have minimal

effect on ICP and acts as cerebral vasoconstrictor, theoretically the raising trends of PI in our study can be due to increased cerebral vascular resistance or decrease in cerebral perfusion pressure and not due to increase in ICP.

The normal value for PI is quoted between 0.6 to 0.9.[167] In our study, administration of Dexmedetomidine the PI values in tumour hemisphere showed significant decrease (p-0.022) from baseline. However, in non tumour hemisphere and in control group significant increase from baseline ($p<0.05$) was observed (Table 11). This result shows that cerebral perfusion is maintained in hemisphere with tumour and decreased in non pathological hemispheres.

Similar result of increasing trend in PI was obtained in a study done by Zornow *et al* in healthy volunteers, where four different concentration of Dexmedetomidine was given and the pulsatility index was obtained for each plasma concentration of Dexmedetomidine.[65] There was gradual increase in PI from baseline correlating with increasing plasma concentration of Dexmedetomidine. Pulsatility Index values decreased towards baseline after stopping Dexmedetomidine infusion.

Resistant index is less commonly used index in assessment of cerebral vascular physiology. Increasing trend of Resistant index (RI) towards 1

indicates decrease in diastolic flow due to increase in cerebral vascular resistance or increase in ICP. In our study tumour hemisphere showed significant reduction in RI (p-0.022) and non-tumour hemisphere and control group showed significant increase in RI ($p<0.05$) (Table 11). As discussed previously for PI, the increasing RI may be due to vasoconstrictory action of Dexmedetomidine and not due to increase in ICP.

The PI and RI values observed in tumour hemisphere indicate that there is no significant decrease in cerebral perfusion pressure after administration of Dexmedetomidine. This phenomenon can be due to non-reactivity of blood vessels around the tumour. The increasing trend of PI and RI values in non pathological hemispheres show the possibility of decrease in cerebral perfusion with the use of initial bolus dose of Dexmedetomidine (1mcg/Kg/10min) which was used in this study.

In a study by Schregal *et al*, cerebral vascular effects of Halothane, Alfentanil and Propofol were compared.[184] The pulsatility index showed a short-term increase after Alfentanil and a decrease after Halothane. Infusion of Propofol resulted in strong increase of PI after initial 3 minutes and gradual decline to base line was observed towards 20 minutes. The change in PI values were consistent with vasodilatory effect of Halothane and vasoconstrictory effect of Propofol and Alfentanil.

Vajramuni *et al* evaluated regional differences in the cerebral blood flow effects of inhalational anesthetics (Nitrous oxide-Halothane) between normal and tumour areas.[193] Eight patients having fronto-temporal gliomas were included. TCD assessment of flow velocities were done before induction of anaesthesia and after achieving steady state with Nitrous oxide : Oxygen (60:40) and Halothane 0.5%. PI and RI were decreased compared to baseline after administration of Nitrous oxide and Halothane. The percentage decrease in PI and RI values in both hemispheres were comparable. The authors proposed that vasodilatory action of Nitrous oxide-Halothane caused decrease in PI and RI values.

In our study, PI and RI index were increased in non-pathological hemispheres supporting the fact that Dexmedetomidine acts as cerebral vasoconstrictor and there is possibility of decreased perfusion pressure with the initial loading dose.

eCPP and ZFP

Cerebral perfusion pressure (CPP) is the net pressure gradient causing blood flow to the brain.[192] It must be maintained within narrow limits because decreased perfusion pressure could cause brain tissue to become ischemic or increase in perfusion pressure can lead to increase in intra cranial pressure, both detrimental for survival of neurons. Theoretically, the pressure gradient that drives the blood calculated as the difference between effective upstream

pressure and downstream pressure. The upstream pressure is usually the mean arterial pressure. As the cranium is a closed cavity the effective downstream pressure can be central venous pressure (CVP) or intra cranial pressure (ICP) whichever is higher depending upon the clinical scenario.

CPP = MAP – (CVP or ICP)

However, it has been shown that in subjects with normal intracranial pressure, cerebrovascular tone can be the major determinant of the downstream component of cerebral perfusion pressure.[194] Thus, a more general concept of ZFP has been introduced, where ZFP is defined as the pressure at which flow in a vessel would cease. Thus, in the cerebral circulation, the ZFP can be a function of intracranial pressure, central venous pressure or vascular tone.

As ZFP is the pressure at which the flow ceases, the cerebral perfusion pressure can be estimated from the difference between MAP and ZFP.

CPP = MAP – ZFP

Transcranial doppler assisted estimation of Cerebral perfusion pressure (eCPP) was initially described by Aaslid.[195] Although numerous investigators have described various formulae for calculating eCPP, the commonly used one is based on the method described by Belfort *et al*.[168,195]

As ZFP cannot be measured directly, indirect methods of calculating ZFP from the instantaneous relationship between middle cerebral artery blood-flow

velocity and MAP during a cardiac cycle have been described. Because these measurements can be reliably obtained noninvasively in routine clinical practice, the method has potential for wider clinical and research applications.

Formula for calculating eCPP and ZFP (Belfort *et al*)[168] :

$$\text{eCPP} = \text{mean FV} \times \frac{\text{mean BP - dia BP}}{\text{mean FV - dia FV}}$$

$$\text{ZFP} = \text{mean BP - eCPP}$$

In a study by Marval *et al,* the effects of Propofol and Sevoflurane on eCPP and ZFP were assessed with and without hyperventilation.[196] Administration of Propofol resulted in decrease in eCPP and increase in ZFP, and no change was observed after induction of hypocapnoea. In patients who received Sevoflurane eCPP was maintained and ZFP was decreased. Induction of hypocapnoea resulted in decreased eCPP and increased ZFP. As Propofol is a vasoconstrictor it decreased eCPP and increased ZFP, and because of pre-existing vasoconstriction induction of hypocapnoea had no effect. On the other hand, Sevoflurane as a vasodilator, showed maintenance of eCPP and decrease in ZFP which was reversed by hypocapnoea mediated vasoconstriction.

In a study by Moppett *et al*, administration of Norepinephrine despite increasing MAP no significant change was observed in eCPP. However, ZFP showed an increase from baseline.[41] In the same study administration of Glycerol tri-nitrate resulted in increase in eCPP and decrease in ZFP. The authors postulated that increase in MAP by Norepinephrine could have resulted in cerebral vasoconstriction because of autoregulatory response, thus increasing ZFP and because of increased vascular resistance eCPP was not increased. As GTN is a vasodilator the eCPP was increased and ZFP was decreased.

These studies show that vascular tone of cerebral blood vessels plays important role in control of cerebral perfusion pressure.

In our study there was no significant change in eCPP and ZFP in Tumour hemisphere (p-0.973 and 0.394). However, in Non tumour hemisphere and in control group there were statistically significant decrease in eCPP and increase in ZFP after administration of loading dose of Dexmedetomidine ($p<0.05$) (Table-10).

It is shown that, in conditions of normal intracranial pressure and central venous pressure, vascular tone may be the dominant component of ZFP.[194] Assuming that the ICP and central venous pressure were normal in the control group of this study the decrease in eCPP and increase in ZFP can be attributed to increase in CVR. Dexmedetomidine is shown to act as vasoconstrictor in cerebral circulation in various studies. Dexmedetomidine is also shown to

increase the cerebral venous tone.[81] Studies have shown that Clonidine and Dexmedetomidine have minimal effect on intra cranial pressure.[83,84]

Thus, it can be explained that the decrease in eCPP and increase in ZFP in our study could be due to Dexmedetomidine induced vasoconstriction and increase in CVR and not due to direct effect on ICP. In our study, the obtained values of increasing PI and RI in non pathological hemispheres also supports the vasoconstrictory nature of Dexmedetomidine.

In patients with intracranial tumour, there is possibility of increased intra cranial pressure and that may influence the eCPP and ZFP values. In our study, the the values obtained from non tumour hemisphere, showed decrease in eCPP and increase in ZFP. This result was similar to results obtained from the control group, thus indicating minimal effect of ICP in perfusion pressure values in contralateral side of tumour hemisphere.

In Tumour side of study group, the presence of space occupying lesion can contribute to the increased downstream pressure and can cause decrease in eCPP and increase in ZFP. However, surprisingly the baseline eCPP and ZFP values were grossly similar to non-pathological hemispheres (Table -11). After administration of Dexmedetomidine, the eCPP was maintained and there was non-significant decrease in ZFP. This shows that in tumour hemisphere the cerebral perfusion was maintained. Similar to autoregulatory indices and PI, RI

values this phenomenon can be due to non-reactivity of vascular bed to Dexmedetomidine in and around the tumour region.

As the **CPP = MAP – ZFP**, any drug or manoeuvre that decreases the MAP or increases the ZFP, can seriously affect the cerebral perfusion pressure. As the 'Hypotension' is proven cardiovascular side effect of Dexmedetomidine and in our study the 'increase in ZFP' is also demonstrated there is possibility of decreased cerebral perfusion pressure when given in the initial loading dose of 1 mcg/Kg/10min.

LIMITATIONS

In this study the initial bolus dose of Dexmedetomidine (1mcg/Kg over 10 min) was used. Many studies have suggested that the systemic hemodynamic effects like hypotension and bradycardia can be prevented by increasing the duration of bolus dose administration or by omitting the bolus dose. Like the systemic effects, the cerebral vascular effects of maintenance dose of Dexmedetomidine may be different. Low dose Dexmedetomidine has shown to activate central sympatholytic mechanism and may not have direct vascular effect in cerebral vasculature. Studies have shown dose dependent increase in PI and decrease in flow velocities with Dexmedetomidine. Clinically maintenance dose is used as 0.1 to 1 mcg/Kg/hour and the effect of maintenance dose of Dexmedetomidine on cerebral vascular autoregulation can be different from the bolus dose that was used in our study. Thus, further studies are warranted to

assess the effect of Dexmedetomidine on cerebral hemodynamics with varying maintenance doses.

Baseline THRR values in tumour side were in the higher range compared to normal values published in literature. This may suggest relative baseline hyperaemic status around tumour region even before administration of study drug. This baseline hyperaemia could have affected the test results.

In contrary to non pathological hemispheres tumour hemisphere shows maintained autoregulatory and hemodynamic indices. The possible explanation to this phenomenon is the abnormal vascular pattern and it's non reactivity to Dexmedetomidine. Tumours with maximum diameter of 4 to 6 cm were included in this study. In this study the flow velocity of MCA was used to assess autoregulation and hemodynamic indices which supplies both normal and tumour zone of the particular hemisphere. The contribution of tumour region and it's vasculature to affect the whole MCA flow velocity is not known. Although tumours from MCA territory were included, supply from other arterial zone could not be ruled out.

CONCLUSION

CONCLUSION

In our study the dynamic autoregulatory indices were maintained in tumour hemisphere after administration of initial bolus dose of Dexmedetomidine (1mcg/Kg over 10min). In non tumour hemisphere and in control group the dynamic autoregulation was abolished after administration of initial bolus dose of Dexmedetomidine.

Mean flow velocity was decreased in all study subsets with the use of initial bolus dose of Dexmedetomidine. Decreased PI and RI values and maintained eCPP and ZFP values show that Dexmedetomidine has minimal effect on vascular resistance and perfusion pressure in tumour hemisphere. In non pathological side increasing PI and RI values along with decreased eCPP and increased ZFP shows that Dexmedetomidine causes increase in vascular resistance and decreases perfusion pressure.

Findings of our study in non pathological hemispheres are in concordance with results obtained from healthy volunteer studies.

The autoregulatory indices and hemodynamics which were maintained in tumour hemisphere can be due to non reactivity of the tumour vasculature to Dexmedetomidine, but the exact mechanism for this phenomenon is unclear. Mechanism of action of Dexmedetomidine on tumour vessels and clinical implications of these effects needs to be evaluated.

As data from non pathological sides show that Dexmedetomidine abolishes the dynamic autoregulatory response, decreases cerebral blood flow velocity, increases distal vascular resistance and decreases the perfusion pressure, this drug should be used with caution in neuro anaesthesia and critical care setting where there is possibility of baseline cerebral hemodynamic abnormality because of primary disease process itself.

Future studies involving modalities like NIRS, SjvO2 or cerebral microdialysis needs to be conducted to understand complete action of Dexmedetomidine on pathological side to elucidate the mechanism of action and clinical implications.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Wahl M, Schilling L. Regulation of cerebral blood flow--a brief review. Acta Neurochir Suppl (Wien). 1993; 59:3-10.
2. Busija DW, Heistad DD. Factors involved in the physiological regulation of the cerebral circulation. Rev Physiol Biochem Pharamacol. 1984; 101:161–211
3. Johnston AJ, Steiner LA, Gupta AK, Menon DK. Cerebral oxygen vasoreactivity and cerebral tissue oxygen reactivity. Br J Anaesth. 2003; 90(6):774-86.
4. Reivich M. Arterial pCO_2 and cerebral hemodynamics. Am J Physiol. 1964; 206:25-35.
5. Fortune JB, Feustel PJ, deLuna C, Graca L, Hasselbarth J, Kupinski AM. Cerebral blood flow and blood volume in response to O2 and CO2 changes in normal humans. J Trauma. 1995; 39(3):463-71.
6. Lanier WL. Cerebral metabolic rate and hypothermia: their relationship with ischemic neurologic injury. J Neurosurg Anesthesiol. 1995; 7(3):216-21.
7. Ter Laan M, van Dijk JM, Elting JW, Staal MJ, Absalom AR. Sympathetic regulation of cerebral blood flow in humans: a review. Br J Anaesth. 2013;111(3):361-7.
8. Harrison MJ. Influence of haematocrit in the cerebral circulation. Cerebrovasc Brain Metab Rev. 1989; 1(1):55-67.
9. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev. 1990; 2(2):161-92.
10. Wahl M. Local chemical, neural, and humoral regulation of cerebrovascular resistance vessels. J Cardiovasc Pharmacol. 1985;7 Suppl 3:36-46.
11. Baumbach GL, Heistad DD. Regional, segmental, and temporal heterogeneity of cerebral vascular autoregulation. Ann Biomed Eng. 1985; 13:303-10.
12. Verma PK, Panerai RB, Rennie JM, Evans DH. Grading of cerebral autoregulation in preterm and term neonates. Pediatr Neurol. 2000; 23(3):236-42.
13. Van Beek AH, Claassen JA, Rikkert MG, Jansen RW. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. J Cereb Blood Flow Metab. 2008; 28(6):1071-85
14. Cipolla MJ. Cerebrovascular function in pregnancy and eclampsia. Hypertension. 2007; 50(1):14-24
15. Czosnyka M, Smielewski P, Piechnik S, Steiner LA, Pickard JD. Cerebral autoregulation following head injury. J Neurosurg. 2001; 95(5):756-63.
16. Muizelaar JP, Ward JD, Marmarou A, Newlon PG, Wachi A. Cerebral blood flow and metabolism in severely head-injured children. Part 2: Autoregulation. J Neurosurg. 1989; 71(1):72-6.
17. Jünger EC, Newell DW, Grant GA, Avellino AM, Ghatan S, Douville CM, Lam AM, Aaslid R, Winn HR. Cerebral autoregulation following minor head injury. J Neurosurg. 1997; 86(3):425-32.
18. Dernbach PD, Little JR, Jones SC, Ebrahim ZY. Altered cerebral autoregulation and CO2 reactivity after aneurysmal subarachnoid hemorrhage. Neurosurgery. 1988; 22(5):822-6.
19. Sharma D, Bithal PK, Dash HH, Chouhan RS, Sookplung P, Vavilala MS. Cerebral autoregulation and CO_2 reactivity before and after elective supratentorial tumor resection. J Neurosurg Anesthesiol. 2010; 22(2):132-7.
20. Schmieder K, Schregel W, Harders A, Cunitz G. Dynamic cerebral autoregulation in patients undergoing surgery for intracranial tumors. Eur J Ultrasound. 2000; 12(1):1-7.
21. Kader A, Young WL. The effects of intracranial arteriovenous malformations on cerebral hemodynamics. Neurosurg Clin N Am. 1996; 7(4):767-81.
22. Reinhard M, Roth M, Müller T, Czosnyka M, Timmer J, Hetzel A. Cerebral autoregulation in carotid artery occlusive disease assessed from spontaneous blood pressure fluctuations by the correlation coefficient index. Stroke. 2003; 34(9):2138-44.
23. Molina C, Sabín JA , Montaner J, Rovira A, Abilleira S, Codina A. Impaired cerebrovascular reactivity as a risk marker for first-ever lacunar infarction: A case-control study. Stroke. 1999; 30(11):2296-301.

24. Nakase H, Nagata K, Otsuka H, Sakaki T, Kempski O. Local cerebral blood flow autoregulation following "asymptomatic" cerebral venous occlusion in the rat. J Neurosurg. 1998; 89(1):118-24.
25. Pedersen M, Brandt CT, Knudsen GM, Ostergaard C, Skinhøj P, Frimodt-Møller N, Møller K. Cerebral blood flow autoregulation in early experimental S. Pneumonia meningitis. J Appl Physiol. 2007; 102(1):72-8.
26. Müller M, Marziniak M. The linear behavior of the system middle cerebral artery flow velocity and blood pressure in patients with migraine: lack of autonomic control? Stroke. 2005; 36(9):1886-90.
27. Kim YS, Immink RV, Stok WJ, Karemaker JM, Secher NH, van Lieshout JJ. Dynamic cerebral autoregulatory capacity is affected early in Type 2 diabetes. Clin Sci (Lond). 2008; 115(8):255-62.
28. Strauss GI, Hansen BA, Herzog T, Larsen FS. Cerebral autoregulation in patients with end-stage liver disease. Eur J Gastroenterol Hepatol. 2000; 12(7):767-71.
29. Skinner H, Mackaness C, Bedforth N, Mahajan R. Cerebral haemodynamics in patients with chronic renal failure: effects of haemodialysis. Br J Anaesth. 2005; 94(2):203-5.
30. Terborg C, Schummer W, Albrecht M, Reinhart K, Weiller C, Röther J. Dysfunction of vasomotor reactivity in severe sepsis and septic shock. Intensive Care Med. 2001; 27(7):1231-4.
31. Urbano F, Roux F, Schindler J, Mohsenin V. Impaired cerebral autoregulation in obstructive sleep apnea. J Appl Physiol. 2008; 105(6):1852-7.
32. Dagal A, Lam AM. Cerebral autoregulation and anesthesia. Curr Opin Anaesthesiol. 2009; 22(5):547-52.
33. LVavilala MS, Lee LA, Lam AM. The lower limit of cerebral autoregulation in children during sevoflurane anesthesia. J Neurosurg Anesthesiol. 2003; 15(4):307-12.
34. Strebel S, Lam AM, Matta B, Mayberg TS, Aaslid R, Newell DW. Dynamic and static cerebral autoregulation during isoflurane, desflurane, and propofol anesthesia. Anesthesiology. 1995; 83(1):66-76.
35. Iacopino DG, Conti A, Battaglia C, Siliotti C, Lucanto T, Santamaria LB, Tomasello F. Transcranial Doppler ultrasound study of the effects of nitrous oxide on cerebral autoregulation during neurosurgical anesthesia: a randomized controlled trial. J Neurosurg. 2003; 99(1):58-64.
36. Harrison JM, Girling KJ, Mahajan RP. Effects of target-controlled infusion of propofol on the transient hyperaemic response and carbon dioxide reactivity in the middle cerebral artery. Br J Anaesth. 1999; 83(6):839-44.
37. Steiner LA, Johnston AJ, Chatfield DA, Czosnyka M, Coleman MR, Coles JP, Gupta AK, Pickard JD, Menon DK. The effects of large-dose propofol on cerebrovascular pressure autoregulation in head-injured patients. Anesth Analg. 2003; 97(2):572-6.
38. Conti A, Iacopino DG, Fodale V, Micalizzi S, Penna O, Santamaria LB. Cerebral haemodynamic changes during propofol-remifentanil or sevoflurane anaesthesia: transcranial Doppler study under bispectral index monitoring. Br J Anaesth. 2006; 97(3):333-9.
39. Ogawa Y, Iwasaki K, Aoki K, Kojima W, Kato J, Ogawa S. Dexmedetomidine weakens dynamic cerebral autoregulation as assessed by transfer function analysis and the thigh cuff method. Anesthesiology. 2008;109(4):642-50.
40. Endoh H, Honda T, Ohashi S, Hida S, Shibue C, Komura N. The influence of nicardipine-, nitroglycerin-, and prostaglandin E(1)-induced hypotension on cerebral pressure autoregulation in adult patients during propofol-fentanyl anesthesia. Anesth Analg. 2002; 94(1):169-73.
41. Moppett IK, Sherman RW, Wild MJ, Latter JA, Mahajan RP. Effects of norepinephrine and glyceryl trinitrate on cerebral haemodynamics: transcranial Doppler study in healthy volunteers. Br J Anaesth. 2008; 100(2):240-4
42. Moppett IK, Wild MJ, Sherman RW, Latter JA, Miller K, Mahajan RP. Effects of ephedrine, dobutamine and dopexamine on cerebral haemodynamics: transcranial Doppler studies in healthy volunteers. Br J Anaesth. 2004; 92(1):39-44.
43. Bouma GJ, Muizelaar JP. Relationship between cardiac output and cerebral blood flow in patients with intact and with impaired autoregulation. J Neurosurg. 1990; 73(3):368-74.

44. Panerai RB. Assessment of cerebral pressure autoregulation in humans--a review of measurement methods. Physiol Meas. 1998; 19(3):305-38.
45. Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA. Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. Neurocrit Care. 2009; 10(3):373-86.
46. Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke. 1989; 20(1):45-52.
47. Giller CA. A bedside test for cerebral autoregulation using transcranial Doppler ultrasound. Acta Neurochir (Wien). 1991; 108(1-2):7-14.
48. Tibble RK, Girling KJ, Mahajan RP. A comparison of the transient hyperaemic response test and the static autoregulation test to assess graded impairment in cerebral autoregulation during propofol, desflurane, and nitrous oxide anesthesia. Anesth Analg. 2001; 93(1):171-6.
49. Smielewski P, Czosnyka M, Kirkpatrick P, McEroy H, Rutkowska H, Pickard JD. Assessment of cerebral autoregulation using carotid artery compression. Stroke. 1996; 27(12):2197-203.
50. Zhang R, Zuckerman JH, Giller CA, Levine BD. Transfer function analysis of dynamic cerebral autoregulation in humans. Am J Physiol. 1998; 274:233-41.
51. Zweifel C, Czosnyka M, Lavinio A, Castellani G, Kim DJ, Carrera E, Pickard JD, Kirkpatrick PJ, Smielewski P. A comparison study of cerebral autoregulation assessed with transcranial Doppler and cortical laser Doppler flowmetry. Neurol Res. 2010; 32(4):425-8.
52. Caicedo A, De Smet D, Vanderhaegen J, Naulaers G, Wolf M, Lemmers P et al. Impaired cerebral autoregulation using near- infrared spectroscopy and its relation to clinical outcomes in premature infants. Adv Exp Med Biol. 2011;701:233-9.
53. Czosnyka M, Smielewski P, Kirkpatrick P, Piechnik S, Laing R, Pickard JD. Continuous monitoring of cerebrovascular pressure-reactivity in head injury. Acta Neurochir Suppl. 1998; 71:74-7.
54. Lang EW, Lagopoulos J, Griffith J, Yip K, Yam A, Mudaliar Y, Mehdorn HM, Dorsch NW. Cerebral vasomotor reactivity testing in head injury: the link between pressure and flow. J Neurol Neurosurg Psychiatry. 2003; 74(8):1053-9.
55. Cavill G, Simpson EJ, Mahajan RP. Factors affecting assessment of cerebral autoregulation using the transient hyperaemic response test. Br J Anaesth. 1998; 81(3):317-21.
56. Bhana N, Goa KL, McClellan KJ. Dexmedetomidine. Drugs. 2000; 59(2):263-8.
57. Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular Dexmedetomidine hydrochloride in adult human volunteers. Anesthesiology. 1993; 78(5):813-20.
58. Gyires K, Zádori ZS, Török T, Mátyus P. Alpha(2)-Adrenoceptor subtypes-mediated physiological, pharmacological actions. Neurochem Int. 2009; 55(7):447-53.
59. Nelson LE, Lu J, Guo T, Saper CB, Franks NP, Maze M. The alpha2-adrenoceptor agonist dexmedetomidine converges on an endogenous sleep-promoting pathway to exert its sedative effects. Anesthesiology. 2003; 98(2):428-36.
60. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev. 2003; 42(1):33-84.
61. Jaakola ML, Salonen M, Lehtinen R, Scheinin H. The analgesic action of dexmedetomidine--a novel alpha 2-adrenoceptor agonist--in healthy volunteers. Pain. 1991; 46(3):281-5.
62. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent). 2001; 14(1):13-21.
63. Gerlach AT, Dasta JF. Dexmedetomidine: An updated review. Ann Pharmacother 2007; 41: 245-52.
64. Lee HW, Caldwell JE, Dodson B, Talke P, Howley J. The effect of clonidine on cerebral blood flow velocity, carbon dioxide cerebral vasoreactivity, and response to increased arterial pressure in human volunteers. Anesthesiology. 1997; 87(3):553-8.
65. Zornow MH, Maze M, Dyck JB, Shafer SL. Dexmedetomidine decreases cerebral blood flow velocity in humans. J Cereb Blood Flow Metab. 1993; 13(2):350-3.

66. Prielipp RC, Wall MH, Tobin JR, Groban L, Cannon MA, Fahey FH, Gage HD, Stump DA, James RL, Bennett J, Butterworth J. Dexmedetomidine-induced sedation in volunteers decreases regional and global cerebral blood flow. Anesth Analg. 2002; 95(4):1052-9.
67. Ganjoo P, Farber NE, Hudetz A, Smith JJ, Samso E, Kampine JP, Schmeling WT. In vivo effects of dexmedetomidine on laser-Doppler flow and pial arteriolar diameter. Anesthesiology. 1998; 88(2):429-39.
68. Asano Y, Koehler RC, Kawaguchi T, McPherson RW. Pial arteriolar constriction to alpha 2-adrenergic agonist dexmedetomidine in the rat. Am J Physiol. 1997; 272;2547-56.
69. Karlsson BR, Forsman M, Roald OK, Heier MS, Steen PA. Effect of dexmedetomidine, a selective and potent alpha 2-agonist, on cerebral blood flow and oxygen consumption during halothane anesthesia in dogs. Anesth Analg. 1990; 71(2):125-9.
70. Zornow MH, Fleischer JE, Scheller MS, Nakakimura K, Drummond JC. Dexmedetomidine an alpha 2-adrenergic agonist, decreases cerebral blood flow in the isoflurane-anesthetized dog. Anesth Analg. 1990; 70(6):624-30.
71. McPherson RW, Koehler RC, Kirsch JR, Traystman RJ. Intraventricular dexmedetomidine decreases cerebral blood flow during normoxia and hypoxia in dogs. Anesth Analg. 1997; 84(1):139-47.
72. Drummond JC, Sturaitis MK. Brain tissue oxygenation during Dexmedetomidine administration in surgical patients with neurovascular injuries. J Neurosurg Anesthesiol. 2010; 22(4):336-41.
73. Sturaitis MK, Lopez D, Munoz L, Toleikis SC, Tuman KJ. Effect of dexmedetomidine on brain tissue oxygenation (PtiO2) in patients undergoing cerebrovascular surgery. Anesth Anal**g.** 2004; 98: S139.
74. Fale A, Kirsch JR, McPherson RW. Alpha 2-adrenergic agonist effects on normocapnic and hypercapnic cerebral blood flow in the dog are anesthetic dependent. Anesth Analg. 1994; 79(5):892-8.
75. Globus MY, Busto R, Dietrich WD, Martinez E, Valdés I, Ginsberg MD. Direct evidence for acute and massive norepinephrine release in the hippocampus during transient ischemia. J Cereb Blood Flow Metab. 1989; 9(6):892-6.
76. Kuhmonen J, Haapalinna A, Sivenius J. Effects of dexmedetomidine after transient and permanent occlusion of the middle cerebral artery in the rat. J Neural Transm. 2001; 108(3):261-71.
77. Maier C, Steinberg GK, Sun GH, Zhi GT, Maze M. Neuroprotection by the alpha 2-adrenoreceptor agonist dexmedetomidine in a focal model of cerebral ischemia. Anesthesiology. 1993; 79(2):306-12.
78. Talke P, Bickler PE. Effects of dexmedetomidine on hypoxia-evoked glutamate release and glutamate receptor activity in hippocampal slices. Anesthesiology. 1996; 85(3):551-7.
79. Huang R, Chen Y, Yu AC, Hertz L. Dexmedetomidine-induced stimulation of glutamine oxidation in astrocytes: a possible mechanism for its neuroprotective activity. J Cereb Blood Flow Metab. 2000; 20(6):895-8.
80. Degos V, Charpentier TL, Chhor V, Brissaud O, Lebon S, Schwendimann L, Bednareck N, Passemard S, Mantz J, Gressens P. Neuroprotective effects of Dexmedetomidine against glutamate agonist-induced neuronal cell death are related to increased astrocyte brain-derived neurotrophic factor expression. Anesthesiology. 2013; 118(5):1123-32.
81. McCormick JM, McCormick PW, Zabramski JM, Spetzler RF. Intracranial pressure reduction by a central alpha-2 adrenoreceptor agonist after subarachnoid hemorrhage. Neurosurgery. 1993; 32(6):974-9.
82. Zornow MH, Scheller MS, Sheehan PB, Strnat MA, Matsumoto M. Intracranial pressure effects of dexmedetomidine in rabbits. Anesth Analg. 1992; 75(2):232-7.
83. Favre JB, Gardaz JP, Ravussin P. Effect of clonidine on ICP and on the hemodynamic responses to nociceptive stimuli in patients with brain tumors. J Neurosurg Anesthesiol. 1995; 7(3):159-67.

84. Talke P, Tong C, Lee HW, Caldwell J, Eisenach JC, Richardson CA. Effect of dexmedetomidine on lumbar cerebrospinal fluid pressure in humans. Anesth Analg. 1997; 85(2):358-64.
85. Mirski MA, Rossell LA, McPherson RW, Traystman RJ. Dexmedetomidine decreases seizure threshold in a rat model of experimental generalized epilepsy. Anesthesiology. 1994; 81(6):1422-8.
86. Ard J, Doyle W, Bekker A. Awake craniotomy with dexmedetomidine in pediatric patients. J Neurosurg Anesthesiol. 2003; 15(3):263-6.
87. Bekker AY, Kaufman B, Samir H, Doyle W. The use of dexmedetomidine infusion for awake craniotomy. Anesth Analg. 2001; 92(5):1251-3.
88. Bischoff P, Mahlstedt D, Blanc I, Schulte am Esch J. Quantitative topographical electroencephalographic analysis after intravenous clonidine in healthy male volunteers. Anesth Analg. 1998; 86(1):202-7.
89. Farber N, Poterack K, Schmelling W. Dexmedetomidine and halothane produce similar alterations in electroencephalographic and electromyographic activity in cats. Brain Res. 1997; 774:131–141.
90. Maksimow A, Snapir A, Särkelä M, Kentala E, Koskenvuo J, Posti J, Jääskeläinen SK, Hinkka-Yli-Salomäki S, Scheinin M, Scheinin H. Assessing the depth of dexmedetomidine-induced sedation with electroencephalogram (EEG)-based spectral entropy. Acta Anaesthesiol Scand. 2007; 51(1):22-30.
91. Sturaitis MK, Ford EW, Palac SM, Smith MC, Tuman KJ. Effect of dexmedetomidine on operative conditions and electrocorticographic responses during asleep craniotomy for seizure focus resection. Epilepsia. 2003; 44:A331.
92. Li BH, Lohmann JS, Schuler HG, Cronin AJ. Preservation of the cortical somatosensory-evoked potential during dexmedetomidine infusion in rats. Anesth Analg. 2003; 96(4):1155-60.
93. Thornton C, Lucas MA, Newton DE, Doré CJ, Jones RM. Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 2: Auditory and somatosensory evoked responses. Br J Anaesth. 1999; 83(3):381-6.
94. Bala E, Sessler DI, Nair DR, McLain R, Dalton JE, Farag E. Motor and somatosensory evoked potentials are well maintained in patients given dexmedetomidine during spine surgery. Anesthesiology. 2008; 109(3):417-25.
95. Bloom M, Beric A, Bekker A. Dexmedetomidine infusion and somatosensory evoked potentials. J Neurosurg Anesthesiol. 2001; 13(4):320-2.
96. Sturaitis MK, Ford EW, Toleikis SC, Toleikis JR, Braverman B, Tuman KJ. Neurophysiologic monitoring of ophthalmic artery aneurysm surgery: Facilitating the use of flash electroretinograms (F-ERG) and visual evoked potentials (VEP). Anesthesiology. 2004; 101:A313.
97. Bloor BC, Ward DS, Belleville JP, Maze M. Effects of intravenous Dexmedetomidine in humans. II. Hemodynamic changes. Anesthesiology. 1992; 77(6):1134-42.
98. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical applications. Curr Opin Anaesthesiol. 2008; 21(4):457-61.
99. Bekker A, Gold M, Basile J. Hemodynamic and respiratory changes related to the use of dexmedetomidine in patients undergoing awake carotid endarterectomy. Anesthesiology. 2003; 100:A136.
100. Roekaerts PM, Prinzen FW, De Lange S. Beneficial effects of dexmedetomidine on ischaemic myocardium of anaesthetized dogs. Br J Anaesth. 1996; 77(3):427-9.
101. Talke P, Li J, Jain U, Leung J, Drasner K, Hollenberg M, Mangano DT. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. Anesthesiology. 1995; 82(3):620-33.
102. Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P, Heard S, Cheung A, Son SL, Kallio A. The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. Anesth Analg. 2000; 90(4):834-9.
103. Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous Dexmedetomidine in humans. I. Sedation, ventilation, and metabolic rate. Anesthesiology. 1992; 77(6):1125-33.

104. Ramsay MA, Luterman DL. Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology. 2004; 101(3):787-90.
105. Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. Crit Care. 2000; 4(5):302-8.
106. Groeben H, Mitzner W, Brown RH. Effects of the alpha2-adrenoceptor agonist dexmedetomidine on bronchoconstriction in dogs. Anesthesiology. 2004; 100(2):359-63.
107. Weinger MB, Partridge BL, Henry AF. Dexmedetomidine does not modify the neuromuscular blocking action of vecuronium in the anaesthetized rat. Br J Anaesth. 1995; 74(4):455-7.
108. Talke PO, Caldwell JE, Richardson CA, Kirkegaard-Nielsen H, Stafford M. The effects of dexmedetomidine on neuromuscular blockade in human volunteers. Anesth Analg. 1999; 88(3):633-9.
109. Weinger MB, Segal IS, Maze M. Dexmedetomidine, acting through central alpha-2 adrenoceptors, prevents opiate-induced muscle rigidity in the rat.Anesthesiology. 1989; 71(2):242-9.
110. Asai T, Mapleson WW, Power I. Differential effects of clonidine and dexmedetomidine on gastric emptying and gastrointestinal transit in the rat. Br J Anaesth. 1997; 78(3):301-7.
111. Maze M, Virtanen R, Daunt D, Banks SJ, Stover EP, Feldman D. Effects of dexmedetomidine, a novel imidazole sedative-anesthetic agent, on adrenal steroidogenesis: in vivo and in vitro studies. Anesth Analg. 1991; 73(2):204-8.
112. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth. 2001; 86(5):650-6.
113. Gellai M, Edwards RM. Mechanism of alpha 2-adrenoceptor agonist-induced diuresis. Am J Physiol. 1988; 255:317-23.
114. Menegaz RG, Kapusta DR, Mauad H, de Melo Cabral A. Activation of alpha(2)-receptors in the rostral ventrolateral medulla evokes natriuresis by a renal nerve mechanism. Am J Physiol Regul Integr Comp Physiol. 2001; 281(1):98-107.
115. Nishina K, Akamatsu H, Mikawa K, Shiga M, Maekawa N, Obara H, Niwa Y. The effects of clonidine and dexmedetomidine on human neutrophil functions. Anesth Analg. 1999; 88(2):452-8.
116. Tasdogan M, Memis D, Sut N, Yuksel M. Results of a pilot study on the effects of propofol and dexmedetomidine on inflammatory responses and intraabdominal pressure in severe sepsis. J Clin Anesth. 2009; 21(6):394-400.
117. Can M, Gul S, Bektas S, Hanci V, Acikgoz S. Effects of dexmedetomidine or methylprednisolone on inflammatory responses in spinal cord injury. Acta Anaesthesiol Scand. 2009; 53(8):1068-72.
118. Venn RM, Grounds RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit: patient and clinician perceptions. Br J Anaesth. 2001; 87(5):684-90.
119. Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. Anesth Analg. 2004; 98(1):153-8.
120. Hsu YW, Cortinez LI, Robertson KM, Keifer JC, Sum-Ping ST, Moretti EW, Young CC, Wright DR, Macleod DB, Somma J. Dexmedetomidine pharmacodynamics: part I:crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology. 2004; 101(5):1066-76.
121. Dasta JF, Kane-Gill SL, Durtschi AJ. Comparing dexmedetomidine prescribing patterns and safety in the naturalistic setting versus published data. Ann Pharmacother. 2004; 38:1130-5.
122. Guinter JR, Kristeller JL. Prolonged infusions of dexmedetomidine in critically ill patients. Am J Health Syst Pharm. 2010; 67:1246–53
123. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA. 2007; 298(22):2644-53.

124. Xia ZQ, Chen SQ, Yao X, Xie CB, Wen SH, Liu KX. Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. J Surg Res. 2013; 24;685-9
125. DeMuro JP, Botros DG, Wirkowski E, Hanna AF. Use of dexmedetomidine for the treatment of alcohol withdrawal syndrome in critically ill patients: a retrospective case series. J Anesth. 2012; 26(4):601-5.
126. Oschman A, McCabe T, Kuhn RJ. Dexmedetomidine for opioid and benzodiazepine withdrawal in pediatric patients. Am J Health Syst Pharm. 2011; 68(13):1233-8.
127. Short J. Use of dexmedetomidine for primary sedation in a general. intensive care unit. Crit Care Nurse. 2010; 30(1):29-38.
128. James ML, Olson DM, Graffagnino C. A pilot study of cerebral and haemodynamic physiological changes during sedation with dexmedetomidine or propofol in patients with acute brain injury. Anaesth Intensive Care. 2012; 40(6):949-57.
129. Arcangeli A, D'Alò C, Gaspari R. Dexmedetomidine use in general anaesthesia. Curr Drug Targets. 2009; 10(8):687-95.
130. Yildiz M, Tavlan A, Tuncer S, Reisli R, Yosunkaya A, Otelcioglu S. Effect of dexmedetomidine on haemodynamic responses to laryngoscopy and intubation : perioperative haemodynamics and anaesthetic requirements. Drugs R D. 2006; 7(1):43-52.
131. Sakurai Y, Obata T, Odaka A, Terui K, Tamura M, Miyao H. Buccal administration of dexmedetomidine as a preanesthetic in children. J Anesth. 2010; 24(1):49-53.
132. Yuen VM, Hui TW, Irwin MG, Yuen MK. A comparison of intranasal dexmedetomidine and oral midazolam for premedication in pediatric anesthesia: a double-blinded randomized controlled trial. Anesth Analg. 2008; 106(6):1715-21.
133. Santos LC, Ludders JW, Erb HN, Martin-Flores M, Basher KL, Kirch P. A randomized, blinded, controlled trial of the antiemetic effect of ondansetron on dexmedetomidine-induced emesis in cats. Vet Anaesth Analg. 2011; 38(4):320-7.
134. Massad IM, Mohsen WA, Basha AS, Al-Zaben KR, Al-Mustafa MM, Alghanem SM. A balanced anesthesia with dexmedetomidine decreases postoperative nausea and vomiting after laparoscopic surgery. Saudi Med J. 2009; 30(12):1537-41.
135. Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, Skrivanek G, Macaluso A, Shah M, Provost DA. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. Anesth Analg. 2008; 106(6):1741-8.
136. Grant SA, Breslin DS, MacLeod DB, Gleason D, Martin G. Dexmedetomidine infusion for sedation during fiberoptic intubation: a report of three cases. J Clin Anesth. 2004; 16(2):124-6.
137. Bergese SD, Candiotti KA, Bokesch PM, Zura A, Wisemandle W, Bekker AY; AWAKE Study Group. A Phase IIIb, randomized, double-blind, placebo-controlled, multicenter study evaluating the safety and efficacy of dexmedetomidine for sedation during awake fiberoptic intubation. Am J Ther. 2010; 17(6):586-95.
138. Kamibayashi T, Maze M. Clinical uses of alpha2 –adrenergic agonists. Anesthesiology. 2000; 93(5):1345-9.
139. Uyar AS, Yagmurdur H, Fidan Y, Topkaya C, Basar H. Dexmedetomidine attenuates the hemodynamic and neuroendocrinal responses to skull-pin head-holder application during craniotomy. J Neurosurg Anesthesiol. 2008; 20(3):174-9.
140. Tanskanen PE, Kyttä JV, Randell TT, Aantaa RE. Dexmedetomidine as an anaesthetic adjuvant in patients undergoing intracranial tumour surgery: a double-blind, randomized and placebo-controlled study. Br J Anaesth. 2006; 97(5):658-65.
141. Gunes Y, Mediha T, Tahsin E, Hayri O. Anesthesia for craniotomy comparison of sevoflurane, desflurane, or isoflurane anesthesia supplemented with an infusion of dexmedetomidine during supratentorial craniotomy. Neurosurg Q. 2009; 19:110–5.
142. Drown MB. Integrative review utilizing dexmedetomidine as an anesthetic for monitored anesthesia care and regional anesthesia. Nurs Forum. 2011; 46(3):186-94.

143. Mason KP, Zgleszewski SE, Dearden JL, Dumont RS, Pirich MA, Stark CD, D'Angelo P, Macpherson S, Fontaine PJ, Connor L, Zurakowski D. Dexmedetomidine for pediatric sedation for computed tomography imaging studies. Anesth Analg. 2006; 103(1):57-62.
144. Rozet I, Muangman S, Vavilala MS, Lee LA, Souter MJ, Domino KJ, Slimp JC, Goodkin R, Lam AM. Clinical experience with dexmedetomidine for implantation of deep brain stimulators in Parkinson's disease. Anesth Analg. 2006; 103(5):1224-8.

145. Bekker AY, Basile J, Gold M, Riles T, Adelman M, Cuff G, Mathew JP, Goldberg JD. Dexmedetomidine for awake carotid endarterectomy: efficacy, hemodynamic profile, and side effects. J Neurosurg Anesthesiol. 2004; 16(2):126-35.
146. Cooper L, Candiotti K, Gallagher C, Grenier E, Arheart KL, Barron ME. A randomized, controlled trial on dexmedetomidine for providing adequate sedation and hemodynamic control for awake, diagnostic transesophageal echocardiography. J Cardiothorac Vasc Anesth. 2011; 25(2):233-7.
147. Mack PF, Perrine K, Kobylarz E, Schwartz TH, Lien CA. Dexmedetomidine and neurocognitive testing in awake craniotomy. J Neurosurg Anesthesiol. 2004; 16(1):20-5.
148. Ard JL Jr, Bekker AY, Doyle WK. Dexmedetomidine in awake craniotomy: a technical note. Surg Neurol. 2005; 63(2):114-6.
149. Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Comparison of Dexmedetomidine and midazolam sedation and antagonism of dexmedetomidine with atipamezole. J Clin Anesth. 1993; 5(3):194-203.
150. Grosu I, Lavand'homme P. Use of dexmedetomidine for pain control. F1000 Med Rep. 2010; 2:90.
151. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B. Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth. 2006; 53(7):646-52.
152. Abu-Halaweh SA, Al Oweidi AK, Abu-Malooh H, Zabalawi M, Alkazaleh F, Abu-Ali H, Ramsay MA. Intravenous dexmedetomidine infusion for labour analgesia in patient with preeclampsia. Eur J Anaesthesiol. 2009; 26(1):86-7.
153. Roberts SB, Wozencraft CP, Coyne PJ, Smith TJ. Dexmedetomidine as an adjuvant analgesic for intractable cancer pain. J Palliat Med. 2011; 14(3):371-3.
154. White H, Venkatesh B. Applications of transcranial Doppler in the ICU: a review. Intensive Care Med. 2006; 32(7):981-94.
155. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg. 1982 ; 57(6):769-74
156. Krejza J, Rudziński W, Mariak Z. Transcranial color-coded Doppler sonography: getting started. Neurol Neurochir Pol. 2001; 35:101-9.
157. Ringelstein EB, Kahlscheuer B, Niggemeyer E, Otis SM. Transcranial Doppler sonography: anatomical landmarks and normal velocity values. Ultrasound Med Biol. 1990; 16(8):745-61.
158. Lupetin AR, Davis DA, Beckman I, Dash N. Transcranial Doppler sonography. Part 1. Principles, technique, and normal appearances. Radiographics. 1995; 15(1):179-91.
159. Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E. et al. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2004;62(9):1468-81.
160. Huber P, Handa J. Effect of contrast material, hypercapnia, hyperventilation, hypertonic glucose and papaverine on the diameter of the cerebral arteries. Angiographic determination in man. Invest Radiol. 1967; 2(1):17-32.
161. Ringelstein EB, Sievers C, Ecker S, Schneider PA, Otis SM. Noninvasive assessment of CO2-induced cerebral vasomotor response in normal individuals and patients with internal carotid artery occlusions. Stroke. 1988; 19(8):963-9.

162. Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke. 1986; 17(5):913-5.
163. Kirkham FJ, Padayachee TS, Parsons S, Seargeant LS, House FR, Gosling RG. Transcranial measurement of blood velocities in the basal cerebral arteries using pulsed Doppler ultrasound: velocity as an index of flow. Ultrasound Med Biol. 1986; 12(1):15-21.
164. Brass LM, Pavlakis SG, DeVivo D, Piomelli S, Mohr JP. Transcranial Doppler measurements of the middle cerebral artery. Effect of hematocrit. Stroke. 1988; 19(12):1466-9.
165. Schöning M, Niemann G, Hartig B. Transcranial color duplex sonography of basal cerebral arteries: reference data of flow velocities from childhood to adulthood. Neuropediatrics. 1996; 27(5):249-55.
166. Vriens EM, Kraaier V, Musbach M, Wieneke GH, van Huffelen AC. Transcranial pulsed Doppler measurements of blood velocity in the middle cerebral artery: reference values at rest and during hyperventilation in healthy volunteers in relation to age and sex. Ultrasound Med Biol. 1989; 15(1):1-8.
167. Arnolds BJ, von Reutern GM. Transcranial Doppler sonography. Examination technique and normal reference values. Ultrasound Med Biol. 1986 Feb;12(2):115-23.
168. Belfort MA, Saade GR, Yared M, Grunewald C, Herd JA, Varner MA, Nisell H. Change in estimated cerebral perfusion pressure after treatment with nimodipine or magnesium sulfate in patients with preeclampsia. Am J Obstet Gynecol. 1999; 181(2):402-7.
169. Hancock SM, Mahajan RP, Athanassiou L. Noninvasive estimation of cerebral perfusion pressure and zero flow pressure in healthy volunteers: the effects of changes in end-tidal carbon dioxide. Anesth Analg. 2003; 96(3):847-51
170. Mahajan RP, Cavill G, Simpson EJ. Reliability of the transient hyperemic response test in detecting changes in cerebral autoregulation induced by the graded variations in end-tidal carbon dioxide. Anesth Analg. 1998; 87(4): 843-9.
171. Bellapart J, Fraser JF. Transcranial Doppler assessment of cerebral autoregulation. Ultrasound Med Biol. 2009 Jun;35(6):883-93.
172. Ishiyama T, Dohi S, Iida H, Watanabe Y, Shimonaka H. Mechanisms of dexmedetomidine-induced cerebrovascular effects in canine in vivo experiments. Anesth Analg. 1995; 81(6):1208-15.
173. Hardebo JE, Kåhrström J, Salford LG. Lack of neural control and reactivity to vasoactive agents in malignant glioma arteries. J Neurosurg. 1991; 74(4):633-5.
174. Challa VR, Moody DM, Brown WR, Zagzag D. A morphologic study of the vasculature of malignant gliomas using thick celloidin sections and alkaline phosphatise stain. Clin Neuropathol. 2004; 23(4):167-72.
175. Vajkoczy P, Menger MD. Vascular microenvironment in gliomas. Cancer Treat Res. 2004; 117:249-62.
176. Ishiyama T, Dohi S, Iida H. The vascular effects of topical and intravenous alpha2-adrenoceptor agonist clonidine on canine pial microcirculation. Anesth Analg. 1998; 86(4):766-72.
177. Lam AM, Bhatia S, Lee LA, Visco E, Vavilala MS. Influence of dexmedetomidine on CO2 reactivity and cerebral autoregulation in healthy volunteers. Anesthesiology 2001; 95:A341.
178. Bedforth NM, Girling KJ, Skinner HJ, Mahajan RP. Effects of desflurane on cerebral autoregulation. Br J Anaesth. 2001; 87(2):193-7.
179. Bedforth NM, Girling KJ, Harrison JM, Mahajan RP. The effects of sevoflurane and nitrous oxide on middle cerebral artery blood flow velocity and transient hyperemic response. Anesth Analg. 1999; 89(1):170-4.
180. Schroeder T, Schierbeck J, Howardy P, Knudsen L, Skafte-Holm P, et al. Effect of labetalol on cerebral blood flow and middle cerebral arterial flow velocity in healthy volunteers. Neurol Res. 1991; 13(1):10-2.

181. Drummond JC, Dao AV, Roth DM, Cheng CR, Atwater BI, Minokadeh A, Pasco LC, Patel PM. Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. Anesthesiology. 2008; 108(2):225-32.
182. Dong ML, Kofke WA, Policare RS, Wang AS, Acuff J, Sekhar LN, et al. Transcranial Doppler ultrasonography in neurosurgery: effects of intracranial tumour on right middle cerebral artery flow velocity during induction of anaesthesia. Ultrasound Med Biol. 1996; 22(9):1163-8.
183. Ederberg S, Westerlind A, Houltz E, Svensson SE, Elam M, Ricksten SE. The effects of propofol on cerebral blood flow velocity and cerebral oxygen extraction during cardiopulmonary bypass. Anesth Analg. 1998; 86(6):1201-6.
184. Schregel W, Bredenkötter U, Sihle-Wissel M, Cunitz G. Transcranial Doppler ultrasound: effects of intravenous anesthetics in neurosurgical patients. Ultraschall Med. 1995; 16(2):60-4.
185. Kolbitsch C, Hörmann C, Benzer A. Nitrous oxide and cerebral haemodynamics. Acta Anaesthesiol Scand. 1996; 40(3):392.
186. Berkowitz RA, Hoffman WE, Cunningham F, McDonald T. Changes in cerebral blood flow velocity in children during sevoflurane and halothane anesthesia. J Neurosurg Anesthesiol. 1996; 8(3):194-8.
187. Thiel A, Schindler E, Dyckmans D, Hempelmann G. Transcranial doppler sonography. Effect of sevoflurane in comparison to isoflurane. Anaesthesist. 1997 Jan;46(1):29-33.
188. Bellner J, Romner B, Reinstrup P, Kristiansson KA, Ryding E, Brandt L. Transcranial Doppler sonography pulsatility index (PI) reflects intracranial pressure (ICP). Surg Neurol. 2004; 62(1):45-51.
189. Behrens A, Lenfeldt N, Ambarki K, Malm J, Eklund A, Koskinen LO. Transcranial Doppler pulsatility index: not an accurate method to assess intracranial pressure. Neurosurgery. 2010; 66(6):1050-7.
190. Richards HK, Czosnyka M, Whitehouse H, Pickard JD. Increase in transcranial Doppler pulsatility index does not indicate the lower limit of cerebral autoregulation. Acta Neurochir Suppl. 1998; 71:229-32.
191. Czosnyka M, Richards HK, Whitehouse HE, Pickard JD. Relationship between transcranial Doppler-determined pulsatility index and cerebrovascular resistance: an experimental study. J Neurosurg. 1996; 84(1):79-84.
192. White H, Venkatesh B. Cerebral perfusion pressure in neurotrauma: a review. Anesth Analg. 2008; 107(3):979-88.
193. Vajramuni GV, Umamaheswara Rao GS, Pillai SV. Cerebral blood flow velocity changes under nitrous oxide halothane anesthesia in patients with frontotemporal gliomas: a comparison of the normal and abnormal cerebral hemispheres. Neurol India. 2004; 52(1):79-81.
194. Weyland A, Buhre W, Grund S, Ludwig H, Kazmaier S, Weyland W, Sonntag H. Cerebrovascular tone rather than intracranial pressure determines the effective downstream pressure of the cerebral circulation in the absence of intracranial hypertension. J Neurosurg Anesthesiol. 2000; 12(3):210-6.
195. Steiner LA, Czosnyka M. Estimation of critical closing pressure and cerebral perfusion pressure using transcranial Doppler. Br J Anaesth. 2003; 90(3):396-7.
196. Marval PD, Perrin ME, Hancock SM, Mahajan RP. The effects of propofol or sevoflurane on the estimated cerebral perfusion pressure and zero flow pressure. Anesth Analg. 2005; 100(3):835-40.

APPENDIX

Effects of Dexmedetomidine on cerebral blood flow autoregulation and cerebral hemodynamics in patients with intracranial tumours

PROFORMA

study group : Group S / Group C **Serial number :**

Name : Diagnosis : For Group S
Age : Proposed surgery : Tumour site :
Gender: Date of surgery : Tumour size :
I.P number :
Patient weight : Kg

Vital parameters	Baseline	2 min	4 min	6 min	8 min	10 min
Heart Rate						
Mean BP						
Respiratory rate						

		MCA-TAM fv			Autoreegulatory indices				Hemodynamic indices				
Rt. MCA	Test	F_1	F_2	F_3	THRR	P2	SA	CR	mFV	PI	RI	eCPP	ZFP
Baseline	1												
	2												
	Mean												
After Dex	1												
	2												
	Mean												
Lt. MCA	Test	F_1	F_2	F_3	THRR	P2	SA	CR	mFV	PI	RI	eCPP	ZFP
Baseline	1												
	2												
	Mean												
After Dex	1												
	2												
	Mean												

$EtCO_2$							
SpO_2							

***TAM-fv** -Time averaged mean flow velocity from outer envelope; **P2** – estimated blood pressure at the onset of Carotid compression; **F1** –flow velocity before compression; **F2** –flow velocity during compression; **F3**- flow velocity after release of compression; **SA** – strength of autoregulation; **CR** – compression ratio; **mFV**-mean flow velocity, **PI**-Pulsatility index, **RI**-Resistant index; **eCPP**- estimated cerebral perfusion pressure; **ZFP** - Zeroflow pressure*

Duration of surgery (min): _____

	Adverse events	Intervention
Study period	Hypotension	
	Bradycardia	
	SpO_2 < 95%	
	Nausea / Vomiting	
	Respiratory depression	
	Allergic reaction	
Intra operative period	Hypotension	
	Bradycardia	
Post operative period	Hypotension	
	Bradycardia	
	Nausea / Vomiting	
Other complications		

MASTER CHART – GROUP S

Pt. No	AGE	SEX	WT	TUMOR SIDE	TUMOR SIZE	B-HR	D-HR	B-MAP	D-MAP	B-RR	D-RR	B-CO2	D-CO2	B-SO2	D-SO2
1	32	F	56	R	3X4X6	72	68	100	95	12	15	32	35	100	98
2	35	F	66	R	4X5X5	80	76	96	92	14	12	33	34	100	100
3	31	M	70	R	5X5X5	74	65	101	96	15	12	31	35	98	98
4	36	F	72	L	6X6X5	76	69	98	100	14	16	35	32	100	98
5	29	M	58	R	6X4X5	74	68	98	98	14	12	34	35	99	100
6	32	F	68	R	4X5X6	82	76	102	97	16	11	36	37	100	96
7	32	F	60	R	5X5X5	89	74	108	103	14	11	33	33	100	100
8	32	F	69	R	5X5X4	90	76	103	96	16	18	35	35	100	98
9	34	M	65	L	5X4X4	64	62	95	92	15	14	34	33	100	99
10	36	F	58	R	6X4X6	68	64	84	80	16	14	33	32	100	100
11	35	M	54	R	4X5X5	81	71	93	88	15	12	33	34	100	100
12	33	M	80	L	5X5X5	77	68	100	96	12	16	31	33	100	100
13	37	M	72	R	6X6X5	88	66	101	97	12	14	32	33	100	98
14	33	F	61	R	6X6X6	74	65	94	91	14	12	32	33	99	98
15	29	F	55	R	4X5X5	70	66	97	94	16	16	33	32	100	100

GROUP S – TUMOUR SIDE (S_T) – CEREBRAL AUTOREGULATORY AND HEMODYNAMIC INDICES

Pt. No	B-CR	D-CR	B-THRR	D-THRR	B-SA	D-SA	B-mFV	D-mFV	B-PI	D-PI	B-RI	D-RI	B-eCPP	D-eCPP	B-ZFP	D-ZFP
1	41.7	40.0	1.52	1.40	0.89	0.84	65.3	54.7	0.70	0.70	0.48	0.48	63.9	69.1	36.1	45.4
2	40.5	42.1	1.62	1.61	0.96	0.93	58.0	51.3	0.67	0.72	0.46	0.49	58.0	54.1	38.0	38.0
3	42.2	43.4	1.42	1.53	0.82	0.86	58.7	49.3	0.80	0.81	0.52	0.53	33.7	44.4	67.3	68.3
4	47.8	42.0	1.58	1.63	0.82	0.95	65.3	55.7	0.61	0.68	0.43	0.47	83.3	57.1	14.7	11.2
5	47.1	46.7	1.63	1.51	0.86	0.81	65.3	58.7	0.84	0.80	0.54	0.52	49.9	41.2	48.1	45.3
6	46.4	41.1	1.57	1.62	0.84	0.95	54.0	48.3	0.83	0.77	0.54	0.51	54.0	54.9	48.0	58.2
7	45.1	43.5	1.66	1.74	0.91	0.98	52.0	45.7	0.87	0.77	0.55	0.51	52.0	35.2	56.0	65.3
8	41.5	45.2	1.57	1.59	0.92	0.87	49.3	49.7	0.99	0.70	0.60	0.48	33.2	68.1	69.8	73.7
9	42.4	44.0	1.39	1.45	0.80	0.81	58.7	49.7	0.85	0.77	0.54	0.51	42.2	47.1	52.8	53.4
10	44.4	44.3	1.73	1.47	0.96	0.82	55.0	48.7	0.71	0.66	0.48	0.46	59.2	59.3	24.8	34.0
11	42.9	44.1	1.61	1.46	0.92	0.81	53.3	47.3	0.86	0.65	0.55	0.46	55.7	68.7	37.3	47.1
12	45.6	44.4	1.61	1.32	0.88	0.73	59.3	52.3	0.78	0.82	0.51	0.53	54.2	47.5	45.8	54.7
13	44.0	45.6	1.52	1.38	0.85	0.75	58.3	53.0	0.84	0.74	0.54	0.49	39.3	32.6	61.7	69.3
14	41.0	39.2	1.71	1.61	1.01	0.98	49.7	50.7	1.01	0.69	0.60	0.47	56.6	52.1	37.4	44.2
15	40.2	45.8	1.55	1.57	0.93	0.85	54.7	49.3	0.75	0.69	0.50	0.47	72.0	74.0	25.0	40.2

GROUP S– NON TUMOUR SIDE (S_N)– CEREBRAL AUTOREGULATORY AND HEMODYNAMIC INDICES

Pt. No	B-CR	D-CR	B-THRR	D-THRR	B-SA	D-SA	B-mFV	D-mFV	B-PI	D-PI	B-RI	D-RI	B-eCPP	D-eCPP	B-ZFP	D-ZFP
1	40.4	44.4	1.47	1.09	0.87	0.60	60.7	45.7	0.82	1.16	0.53	0.65	54.6	41.4	45.4	53.6
2	41.7	44.0	1.56	1.08	0.91	0.60	58.0	39.0	0.67	1.38	0.46	0.72	58.0	28.2	38.0	63.8
3	41.3	44.3	1.54	1.22	0.91	0.68	59.3	45.7	0.83	1.09	0.53	0.63	32.7	32.9	68.3	63.1
4	42.2	43.4	1.43	1.18	0.83	0.67	64.7	47.7	0.59	1.11	0.42	0.64	86.8	35.1	11.2	64.9
5	42.6	42.9	1.43	1.19	0.82	0.68	64.0	46.0	0.80	1.24	0.52	0.68	52.7	26.6	45.3	71.4
6	41.0	44.0	1.41	1.27	0.83	0.71	59.3	48.7	1.03	1.09	0.61	0.63	43.8	38.6	58.2	58.4
7	42.3	43.6	1.43	1.24	0.83	0.70	57.0	43.3	1.05	1.20	0.62	0.67	42.8	22.5	65.3	80.5
8	41.6	40.7	1.43	1.08	0.83	0.64	57.7	43.3	1.13	1.48	0.64	0.74	29.3	32.5	73.7	63.5
9	44.1	44.7	1.46	1.09	0.82	0.60	59.0	41.3	0.86	1.26	0.55	0.68	41.6	28.6	53.4	63.4
10	40.7	39.0	1.42	1.18	0.84	0.72	58.3	45.3	0.84	1.21	0.54	0.67	50.0	32.1	34.0	47.9
11	40.4	42.0	1.38	1.15	0.82	0.67	58.3	41.7	1.05	1.42	0.62	0.73	45.9	31.8	47.1	56.2
12	42.7	44.4	1.42	1.12	0.81	0.62	63.7	44.0	0.93	1.57	0.57	0.77	45.3	24.9	54.7	71.1
13	41.3	41.7	1.39	1.21	0.81	0.71	64.3	40.7	1.04	1.60	0.61	0.77	31.7	15.0	69.3	82.0
14	43.6	42.3	1.48	1.13	0.83	0.65	53.3	42.0	1.14	1.29	0.65	0.69	49.8	28.0	44.2	63.0
15	40.8	45.8	1.38	1.25	0.82	0.68	60.0	44.0	0.95	0.95	0.58	0.58	56.8	53.4	40.2	40.6

MASTER CHART – GROUP C

Pt. No	AGE	SEX	WT	B-HR	D-HR	B-MAP	D-MAP	B-RR	D-RR	B-CO2	D-CO2	B-SO2	D-SO2
1	34	M	64	75	70	99	95	14	12	33	35	100	98
2	37	M	70	79	76	100	97	16	14	34	34	100	100
3	29	M	59	80	73	97	96	14	12	32	32	100	99
4	36	F	66	68	66	98	100	15	16	32	32	100	98
5	37	M	71	74	78	96	95	18	14	35	35	100	100
6	35	M	65	80	76	103	97	16	13	31	32	99	98
7	32	F	78	84	83	98	94	14	17	33	33	100	100
8	30	M	59	90	86	102	96	15	16	35	35	99	97
9	39	M	61	70	65	97	92	15	12	31	34	100	100
10	35	M	64	70	68	89	82	16	14	33	32	100	100
11	31	M	60	82	72	92	89	14	12	33	34	100	100
12	37	F	59	76	77	95	90	13	16	32	33	100	100
13	28	F	57	75	69	100	97	12	14	32	34	100	99
14	33	F	66	78	70	95	91	14	13	33	33	100	100
15	38	M	57	74	69	97	95	15	16	34	33	100	100

GROUP C – Right side (C_R) – CEREBRAL AUTOREGULATORY AND HEMODYNAMIC INDICES

Pt. No	B-CR	D-CR	B-THRR	D-THRR	B-SA	D-SA	B-mFV	D-mFV	B-PI	D-PI	B-RI	D-RI	B-eCPP	D-eCPP	B-ZFP	D-ZFP
1	42.0	42.9	1.46	1.12	0.85	0.64	67.3	44.0	0.73	1.36	0.49	0.71	57.7	30.8	41.3	64.2
2	41.7	42.1	1.49	1.22	0.87	0.71	61.3	42.7	0.85	1.17	0.54	0.66	42.5	23.0	57.5	74.0
3	40.7	40.3	1.49	1.17	0.88	0.70	56.0	40.7	0.80	1.16	0.52	0.65	41.1	31.1	55.9	64.9
4	41.3	42.0	1.43	1.09	0.84	0.63	62.0	49.7	0.73	0.95	0.49	0.58	53.7	38.0	44.3	62.0
5	42.2	42.2	1.41	1.11	0.82	0.64	62.7	51.0	0.94	0.94	0.58	0.58	41.4	31.9	54.6	63.1
6	39.4	43.1	1.40	1.19	0.85	0.68	57.3	46.0	0.96	0.85	0.59	0.54	43.8	46.0	59.2	51.0
7	40.4	42.5	1.37	1.22	0.82	0.70	58.3	41.7	1.05	1.13	0.62	0.64	45.9	31.9	52.1	62.1
8	40.4	42.0	1.42	1.16	0.84	0.67	53.0	42.3	1.02	0.94	0.61	0.58	38.3	44.5	63.7	51.6
9	39.3	40.8	1.45	1.13	0.88	0.67	57.0	43.7	0.84	0.94	0.54	0.58	42.8	41.5	54.3	50.5
10	41.6	42.9	1.45	1.01	0.85	0.58	57.7	44.3	0.82	1.11	0.53	0.64	47.9	29.9	41.1	52.1
11	41.4	39.7	1.49	1.06	0.88	0.64	54.3	40.7	0.90	1.01	0.56	0.60	39.9	29.8	52.1	59.2
12	39.1	43.1	1.47	1.19	0.89	0.68	57.3	44.0	0.91	0.95	0.57	0.58	49.6	40.9	45.4	49.1
13	42.4	43.2	1.41	1.08	0.81	0.61	58.0	45.3	0.83	0.95	0.53	0.58	43.5	22.1	56.5	74.9
14	41.6	41.6	1.46	1.09	0.85	0.64	51.7	45.0	1.08	1.07	0.63	0.62	47.1	36.6	47.9	54.4
15	40.2	42.7	1.38	1.10	0.83	0.63	58.7	49.3	0.85	0.99	0.54	0.60	59.8	45.3	37.2	49.7

GROUP C – Left side (C_L) – CEREBRAL AUTOREGULATORY AND HEMODYNAMIC INDICES

Pt. No	B-CR	D-CR	B-THRR	D-THRR	B-SA	D-SA	B-mFV	D-mFV	B-PI	D-PI	B-RI	D-RI	B-eCPP	D-eCPP	B-ZFP	D-ZFP
1	40.0	40.7	1.49	1.15	0.90	0.68	61.7	45.7	0.81	1.16	0.53	0.65	51.8	36.2	47.2	58.8
2	41.1	42.5	1.48	1.19	0.87	0.68	59.3	39.0	0.78	1.38	0.51	0.72	46.4	19.5	53.6	77.5
3	41.2	40.5	1.44	1.18	0.84	0.70	54.3	45.7	0.85	1.09	0.54	0.63	39.0	32.9	58.0	63.1
4	39.8	40.5	1.41	1.14	0.85	0.68	60.0	47.7	0.70	1.11	0.48	0.64	55.7	32.4	42.3	67.6
5	40.8	42.7	1.45	1.20	0.86	0.69	62.0	46.0	0.87	1.24	0.55	0.68	44.8	24.2	51.2	70.8
6	41.1	41.7	1.43	1.13	0.84	0.66	56.0	48.7	0.91	1.09	0.57	0.63	46.1	35.8	56.9	61.2
7	40.9	39.7	1.43	1.14	0.85	0.69	54.7	43.3	0.91	1.20	0.57	0.67	52.5	30.0	45.5	64.0
8	40.5	41.2	1.42	1.10	0.84	0.65	54.7	43.3	0.80	1.48	0.52	0.74	48.5	28.4	53.5	67.6
9	39.3	42.5	1.45	1.00	0.88	0.58	57.7	41.3	0.82	1.26	0.53	0.68	44.2	31.0	52.8	61.0
10	41.2	39.7	1.46	1.10	0.86	0.66	57.0	45.3	0.74	1.21	0.49	0.67	52.9	27.2	36.1	54.8
11	42.7	41.2	1.49	1.10	0.85	0.65	52.7	41.7	0.84	1.42	0.54	0.73	43.1	21.2	48.9	67.8
12	40.0	41.7	1.41	1.17	0.85	0.68	55.0	44.0	0.82	1.57	0.53	0.77	55.0	24.9	40.0	65.1
13	38.4	41.9	1.47	1.09	0.90	0.64	56.7	40.7	0.78	1.60	0.51	0.77	46.4	13.1	53.6	83.9
14	41.2	42.5	1.45	1.11	0.85	0.64	53.0	42.0	0.91	1.29	0.56	0.69	56.3	30.3	38.7	60.7
15	40.2	41.5	1.38	1.10	0.83	0.64	58.0	44.0	0.88	0.95	0.55	0.58	58.0	47.1	39.0	47.9

***Pt No** – PATIENT NUMBER* ***B-** BASELINE* ***D-** AFTER ADMINISTRATION OF DEXMEDETOMIDINE*

***HR** – HEART RATE* ***MAP** – MEAN BLOOD PRESSURE* ***RR** – RESPIRATORY RATE* ***SO2** – SpO2* ***CO2**-EtCO2*

CR- *COMPRESSION RATIO* ***THRR –*** *TRANSIENT HYPERREMIC RESPONSE RATIO* ***SA –*** *STRENGTH OF AUTOREGULATION*

mFV - *MEAN FLOW VELOCITY* ***PI –*** *PULSATILITY INDEX* ***RI –*** *RESISTANT INDEX*

eCPP- *ESTIMATED CEREBRAL PERFUSION PRESSURE* ***`ZFP –*** *ZERO FLOW PRESSURE*