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Endobronchial migration of endotracheal tube- Caution in edentulous patients!

Surendra Kumar[1], Amit Kumar[2], Zuhaib Ahmad Wani[3], Nikhil Jain[4], Vinita Kumar Jaggi[5],

Introduction

Endotracheal intubation is the safest method to secure a patent airway of an anaesthetised patient. Endotracheal tube (ETT) is secured externally to patient's facial skin overlying mandible and maxilla using adhesive tape or other commercially available devices. However, position of ETT tip can change either due to movement of tissue or due to movement of the ETT itself, or both. We report a case wherein ETT tip moved to right main bronchus due to both these factors and detection was delayed due to different reasons, a Swiss-cheese model of mishaps, resulting in atelectasis of left lung, which was managed successfully.

Care Report

A 59 Years old female patient, ASA physical status II, was scheduled for Robot assisted radial hysterectomy. Preoperatively she had history of pulmonary tuberculosis 7 years back which resulted in left apical fibrosis, she had prominent upper incisors and absent premolars and molars in both upper and lower jaws. Routine monitoring including ECG, NIBP, plethysmography, capnography, temperature was instituted. Lower thoracic epidural catheter was placed and general anaesthesia was induced, airway was secured using ETT as per norms. The ETT was placed under vision, distal depth marker on the ETT was seen to pass beyond the vocal cords, ETT was secured at 20 cm mark at the angle of mouth using adhesive tapes. Lungs were ventilated using pressure controlled mode of positive pressure ventilation. Forced air warmer was applied on upper body. Surgical drapes were applied after part preparation.

Pneumoperitoneum was created using CO2, about 20 minutes after creation of pneumoperitoneum haemoglobin saturation fell from 98-99% to 90% which rose to 93-94% on increasing FiO2 to 1.0. Trendenlenburg position was applied which soon resulted in fall in SpO2 to around 90% on FiO2 1.0, and increased insignificantly on increasing inspiratory pressure, the haemoglobin saturation continued to fall and stabilised at 84-85%. PetCO2 decreased from 36-38mmHg to 30-32mmHg. Peak airway pressure increased from 18-20mmHg to 26-30mmHg. Endobronchial intubation was suspected but chest auscultation revealing bilateral air entry with no apparent further reduction in breath sounds on left side which already had reduced breath sounds preoperatively, ruled it out. ETT was noted to be secured at 20cm mark at the angle of mouth;

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however it was seen to be pushed inside the oral cavity dragging along, the angle of mouth between the edentulous parts of maxilla and mandible, which was retracted to its normal anatomical position. Pneumothorax was ruled out by presence of breath sounds bilaterally and absence of air escape on needle thoracostomy. Desufflation of peritoneal cavity resulted in marginal reduction in peak airway pressure to 25-27mmHg. Chest x-ray revealed atelectasis of left lung and ETT tip placed in right main bronchus. The ETT was immediately retracted 3cm and repositioned in trachea. Soon, SpO2 increased to above 96%, peak airway pressures dropped to 22-25mmHg, PetCO2 values were within normal limits all through, fluctuating between 30-38mmHg. The surgery was resumed and completed uneventfully about 4 hours after the incidence. Post-operatively chest x-ray was repeated which revealed incomplete re-expansion of atelectatic left lung, positive pressure ventilation was continued overnight and repeat chest x-ray next morning showed expanded left lung, prompting extubation of trachea (Figure 1). Patient continued deep breathing exercises including incentive spirometry and was discharged on 5th post-operative day in stable general condition and without any dyspnoea.

Discussion

Endotracheal intubation is the safest and commonly employed method to secure airway intraoperatively, this however, is not fail safe and ETT can displace from its initial position. Its tip can either displace distally into bronchii or can move proximally and come out of trachea. The distal displacement into bronchus is often the result of pressure exerted on the diaphragm due to increased intra-abdominal pressure (IAP), which causes basal atelectasis and also pushes the lungs upwards resulting in tip of ETT relocating into bronchus, thus it can be said that tissues from below over the tip of ETT. The other reason can be movement of ETT from above itself into the tissue, the tip of ETT can also move into the bronchus due to loosening of its securing device or due to pressure exerted on the proximal end of ETT. In our case both these factors contributed to migration of the ETT tip.

Pneumoperitoneum and trendelenburg position are recognised factors causing ETT misplacement,1 The additional factor in our case, acting on the proximal end of the ETT, was that the upper and lower jaws of the patient were edentulous in their large part creating a very compliant space for the ETT to be pushed into it along with the adhesive tape. The tape kept the ETT still secured to the skin but the skin not being a rigid and fixed structure was pushed inside the oral cavity along with the ETT and tape due to inadvertent pressure by surgical drapes or hands of the personnel. This downward movement of ETT could be prevented by securing the ETT with other means. In our case the ETT secured to skin at angle of mouth with adhesive tape could be moved up and down upto 1.9cm (Figure 2). There is no established best practice to secure the ETT,2 we routinely use adhesive tapes to secure ETT. Anaesthesiologists and surgeons have fixed the tube with wires in patients with facial burns; and suturing the tube to gums and used intermaxillary fixation screws in edentulous patients.3 Commercial devices for fixing the tube with integral bite block, such as Haider tube guard and Thomas tube holder do not allow any movement of tube after fixation and may be better suited than tapes[4-5].

Endobronchial intubation is the commonest cause of intraoperative desaturation of haemoglobin,6 pneumothorax, pleural effusion, bronchospasm are other important causes. Chest auscultation, increasing airway pressure, direct visualisation with a flexible bronchoscope and radiography are different tools which help in detection of this event. We suspected endobronchial intubation but normal auscultation and history of reduced breath sounds on left side of chest preoperatively misled

us in believing that the ETT was properly placed. The air blowing from forced air warmer created noise which misled us in 'listening the breath sounds', noisy environment and thoracic transmission of sounds during mechanical ventilation are known to reduce sensitivity of auscultation in detecting endobronchial intubation.[7]

Chest auscultation has sensitivity of only 80% detecting endobronchial intubation.8 Sugiyama et al demonstrated that the breath sounds could be auscultated equally over two lungs until the tip of a murphy type ETT was inside the right main bronchus, upto 2cm beyond the carina, because air egressing from murphy eye escaped between the tube cuff and tracheal wall to ventilate the other lung, breath sounds over the left lung disappeared only when the ETT tip was 3.2cm or more inside the right main bronchus, beyond the carina,9 the ETT we used also had a murphy eye.
In case of endobronchial intubation the peak airway pressure is expected to rise, but because of pneumoperitoneum the rise was camouflaged, moreover the pressure control mode of ventilation, by altering respiratory mechanics, did not allow the pressure to rise to the extent it would have risen to otherwise.

Flexible bronchoscope could have clinched the diagnosis earlier but we did not have access to it due to logistical limitations. A chest x-ray finally showed the ETT tip in right bronchus and the atelectatic left lung.

Different respiratory manoeuvres, based on employing positive airway pressure to open up the alveoli, have been described to help re-expansion of atelectatic lung.10 In our case the lung re-expanded partially by the end of surgery and we decided to ventilate with positive pressure to allow complete expansion which was done by next morning. Thereafter, deep breathing exercise including incentive spirometry helped in keeping the alveoli open, as has been shown to be effective previously also.[10]

Significance of the case

This case highlights the significance of strong clinical suspicion of endobronchial intubation, more than one factor may contribute to displacement in the same patient, some of which are avoidable. And that more than one safety/ detection methods may fail (cf. Swiss cheese model of mishaps; tube fixation, auscultation, airway pressure and unavailability of flexible bronchoscope in this case). It being an edentulous patient, use of a commercial tube fixation device would have eliminated one factor for ETT displacement.

Acknowledgements

Submitted with written consent of the concerned patient.

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COMPARISON OF CLINICAL PERFORMANCE OF LARYNGEAL SUCTION II WITH I-GEL UNDER CONTROLLED VENTILATION.

Seema Kalra[1], Nitin Hayaran[2]

ABSTRACT

The Laryngeal Tube Suction II (LTS II) ,a newer supraglottic airway device is a further development of the Laryngeal Tube Suction (LTS), allows separation of the respiratory and alimentary tracts. We aimed to compare the clinical performance of LTS II with that of the I-gel and haemodynamic changes.

Prospective randomized study, conducted in sixty patients of ASA grades I/II undergoing surgery under general anaesthesia, after Institutional Ethics committee approval. Patients assigned into two groups GLT and GIG , to receive supraglottic airways LTS II or I-gel . Primary outcome was airway leak pressure. Secondary outcome was success rate of insertion, number of attempts taken to insert, time and ease of insertion, fibreoptic assessment of supraglottic device (SGD) and postoperative airway morbidity. Hemodynamic changes were measured . Demographic profile and haemodynamic changes were comparable in both groups. Median airway leak pressures of GIG and GLT were 23.7±6.12 and 30.16±6.83cm H2O, respectively . (P≤0.01).I-gel was easy to insert in 80% patients versus 73% for LTS II. First attempt success rate for insertion was 87% versus 80% in GIG compared with GLT . .Fibreoptic view through I-gel was Grade I in 80% vs. 0 in LTS,Grade II (10% GIG - versus 47 % in GLT)

Statistical analysis used: Repeated measure ANOVA was done using Fischer's exact test

To conclude, I-gel and LTS II were comparable in terms of clinical performance .However the airway leak pressure was significantly more with Laryngeal tube suction II.

Key-words: Airway management, controlled ventilation, general anesthesia, laryngeal tube suction II

INTRODUCTION

Since the introduction of the classic laryngeal mask airway the field of supraglottic airway devices (SGD) has experienced a remarkable evolution . The I-gel (Intersurgical Inc., Berkshire,UK),is a single use noninflatable SGD with a gastric tube is being used in anaesthesia practice and provides higher airway leak pressure than the classic LMA (cLMA).1I-gel can be used for spontaneous as well as positive pressure ventilation (PPV).2The Laryngeal Tube Suction II (LTS II) (VBM Medizintechnik Gmbh, Sultz, Germany) is a further development of the Laryngeal Tube Suction (LTS),which separates the respiratory and alimentary tracts.LTS II has a

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longer shaft ,a more pointed tip, and an oval distal cuff which fits the oesophageal inlet. The two types of LTS-II are disposable and reusable type .Disposable type (LTS-D) constitutes of latex free PVC material, whereas the reusable type (LTS-II) is of latex free silicone material for repeated use. 3

Till date, there are few studies comparing the I-gel to the LTS. Cook et al and Gaitini et al have shown that both devices were safe and effective in mechanically ventilated anaesthetized adult patients.4,5

We hypothesized that the LTS II and the I-gel perform similarly as measured by oropharyngeal leak pressure in paralyzed patients. Secondary outcome measures were: success rate and ease of insertion, time to successful insertion, number of attempts of insertion, manoeuvres needed at time of insertion, ease of gastric tube insertion and postoperative airway morbidity.

Methods

Approval of the study protocol was obtained from the Institutional ethical committee of IGESI Hospital, Jhilmil, Delhi, before commencing the trial. Written informed consent was obtained from each patient . ASA physical status I-II patients scheduled for elective minor surgeries like fibroadenoma, short orthopaedic procedures like open reduction and internal fixation of fractures were randomly assigned into one of two groups GLT and GIG. GLT comprised of patients intubated with Laryngeal tube II and I-Gel respectively.

Exclusion criteria were:

1. Predicted difficult airway (based on a history of difficult airway, inter-incisor distance < 20 mm, cervical spine pathology, modified Mallampati class 4, or thyromental distance < 65 mm)
2. Presence of disease of upper respiratory tract
3. Increased risk of aspiration
4. Preoperative sore throat

Patients were premedicated with oral tablet ranitidine 150 mg and alprazolam 0.25mg on the night before and in the morning of surgery. In the operation theatre all patients received glycopyrrolate 0.2mg and midazolam 1mg intravenously. Standard monitoring was started before induction of anaesthesia.

They were preoxygenated with oxygen for 3 min; anaesthesia was induced with fentanyl 2 μg.kg−1, propofol 2 mg.kg−1, and after confirmation of facemask ventilation, atracurium 0.5 mg.kg−1 was given for muscle relaxation. Both the supraglottic devices were inserted 3 minutes after administration of neuromuscular relaxants by an experienced anaesthetist.Size of LTS II chosen and its insertion were as per manufacturer's instructions. The size selected was based on the height of the patient. Size 3 was selected for patients shorter than 155 cm, size 4 for those between 155 and 180 cm, and size 5 for those taller than 180 cm. The position of the device was reconfirmed and anesthesia was maintained with oxygen / nitrous oxide /sevoflurane and atracurium. Cuff pressure was measured with an aneroid barometer (VBM, Sulz, Germany). The time interval Ti was from the time of insertion of LTS II/I-Gel after removal of facemask, till confirmation of correct placement by square wave capnography .The baseline pulse rate, mean arterial blood pressure, arterial saturation (SpO2) and end tidal CO2 (ETCO2) were recorded automatically using Criticare Poet monitor just after insertion of LTS II/ I-Gel at 2, 5, 10, 15 min following insertion. Airway leak pressure was determined by closing the expiratory valve of the bains circuit at a fixed gas flow of 3 l/min and noting the airway pressure at which equilibrium was obtained.Airway pressure was not allowed to exceed 40 cm H2O. At this time gas leakage was detected at the mouth by an audible leak .Any ECG changes which occurred during the procedure were also noted .Number of attempts taken to insert LTS II/I-Gel was also noted. The procedure was abandoned if more than two

attempts were taken to insert LTS II/I-gel .Ease of insertion of the supraglottic devices was classified as four grades:

Grade 0 - being easy,
1 –being slightly difficult,
2 being moderately difficult and
3 being extremely difficult.

If it was not possible to ventilate the lungs, the following adjustments were allowed and a number of airway manipulations to establish the airway were given a Manoeuver score as follows:

Score 1- neck extension or flexion,
Score 2 jaw thrust,
Score 3 chin liftpushing, or pulling of the device.

Fibreoptic (FO) assessment of the SGD's position was performed after successful insertion. Fibreoptic assessment of anatomical position was done by the following grading system [6]
Grade 1- perfect view of the vocal cords;
Grade 2- partial view of the vocal cords or a view of the arytenoids only;
Grade 3 - view of the epiglottis only;
Grade 4 - view of the cuff of the device or the pharynx or esophageal sphincter.

Critical incidents which were anticipated: accidental extubation laryngospasm / bronchospasm and minor complications– sore throat, hoarseness, trauma to lips, tongue, dentition. Gastric tube insertion was attempted in all the patients. The supraglottic devices were removed after adequate recovery of neuromuscular blockade. Upper airway trauma was assessed following surgery by observing the presence of blood on the airway device used.

Results

Results were expressed as mean±S.D. The demographic profile of patients in two groups i.e. age , weight, height, ASA physical status were comparable(Table 1) . Median oropharyngeal leak pressures of GIG and GLT were 23.7±6.12 and 30.16±6.83cm H2O, respectively (P ≤0.01) (Table 2). I-gel insertion time Ti was significantly less compared with LTS II -24.37 ±10.213 vs. 34.36±17.096 sec, (P≤0.01).I-gel was easy to insert in 80% patients versus 73% for LTS II. First attempt success rate for insertion of I-gel was 87% versus 80% with the LTS II. Manoeuver scores – 33% patients needed no manoeuvre and 63%- one manoeuvre in GIG compared with the GLT where 80% patients needed one manoeuvre. Fibreoptic view through I-gel was Grade I in 80% vs. 0 in LTS, Grade II (10% -I-Gel vs. 47 % in LTS) It was noted that 7cases in GLT had blood smeared on the device after removal. These same patients complained of sore throat 24 hours later. There was no case of regurgitation or aspiration.
Repeated measure ANOVA was done using Fischer's exact test . Multiple comparisons were done using students paired t- test .p ≤ 0.01 was significant.

value ≤ 0.01

Table 1: Demographic Profile of the patients

Particulars	Group I-gel	Group LTS II	p
Age(years)	34(7.5)	32(8.8)	≥0.05
Weight(kg)	58.7(9.90)	59.4(9.27)	≥0.05
Height (cms)	158.6(9.07)	153.57(7.14)	≥0.05
Male:Female	17:13	16:14	≥0.05

ASA Physical status I/ II/ III	18/9/3	17/10/3	≥0.05

Table 2: Clinical performance of Supraglottic devices

Device performance	**G_{IG}**	**G_{LT}**
Median airway leak pressure(cmH_2O)	23.7±6.12	30.16±6.83*
Success rate n (%)	30(100)	28(93)
Insertion attempts n(%) First attempt/Second attempt	24(80)/ 6(20)	22(73) / 6(20)
Ease of insertion n (%) Easy/Slightly difficult /moderately Difficult	24(80) /5(17)/1(3)	22(73)/ 6(20)/2(7)
Manoeuver score 0/1/2/3	10/19/1/0*	4/20/6/0
Insertion time T_i (sec)	24.37 ±10.213*	34.36±17.096
Fibreoptic assessment 1/2/3/4	25/4/1/0	0/14/5/11
Blood on ETT /Sore throat n (%)	2(7) /2(7)	4(14)/5(17)

Discussion:

Higher airway leak pressure is a marker of efficacy and safety when using supraglottic devices. Laryngeal Suction II (LTS II) provided better airway seal as determined by higher airway leak pressures, without significant increase in postop airway morbidity .The oropharyngeal leak pressure quantifies the glottic seal when using supraglottic airway devices. The leak pressure is also a measure of providing the feasibility of positive pressure ventilation and the degree of airway protection. [7]

The airway leak pressures we obtained for the I-gel and LTS II were considerably lower than previously reported. However some studies with Asian subjects have demonstrated lower pressures, similar to our results . 3 Cavus et al found airway leak pressure of LTS II more than Proseal (20-40cm H2O versus 22-30 cmH2O. 8 Thee et al found airway leak pressure of LTS II more than ILMA (20-40cmH2O versus 12-30 cmH2O).[9]

In a study by Russo et al (comparing I-gel and LTS-D lower leak pressures were found with LTS –D (24 versus 26 cm H20 at cuff pressures of 60 cm H20).10 Genzwuerker et al got comparable results for LTS II and LMA-Proseal especially

airway leak pressures: 33.1 (15–40) and 32.0 cmH2O (18– 40 cmH2O) and clinical performance. [11]

The lower seal with I-gel could be because it is cuff less, has lower surface area compared with LTS II .Mihai et al, 8 assessed the LTS II and found 73% first attempt success rate of insertion which is similar to our study and they got 95% second attempt success rate of insertion However Amini et al got 93% % first attempt success rate of insertion of LTS II, as only one anesthetist performed the insertions and allowed manipulation of the head ie.jaw thrust manoeuvre. 12 We probably got lower success rate of insertion, because no manipulation of the head was allowed while inserting SGD, and the anaesthetists were more experienced with I-gel insertion.

Kikuchi et al showed that the overall success rate of LTS-II insertion was 74% which is similar to our study.[3] This was probably because no manoeuvre was applied before insertion of the device and many anaesthetists inserted the SGD.

We were only able to visualize the glottis fibreoptically in 47% of patients without any manipulation. This and the small airway orifices of the device make the LTS II a less likely choice for use during difficult airway management .Russo et al10 found that the fibreoptically assessed position was more frequently suboptimal with the LTS-D however they were able to visualize laryngeal structures in72% of the patients. Kim et al. demonstrated that the view of the laryngeal structures during the fibreoptic assessments of the LTS-II depended significantly on the position of the head. 13 Mihai et al. were able to visualize the glottis only in 51% of the cases with the LTS-II.14 While assessing the anatomical position of the LTS-D and LTS-II the vocal cords were visible (grade I to II) in 25% and 33.3% in the LTS-D and LTS-II groups respectively in a study by Amini et al. 12 LTS II has additional advantage of access to the gastrointestinal tract via the drain tube hence giving protection against regurgitation, and pulmonary aspiration .There was no difference in the haemodynamic parameters obtained after insertion of the supraglottic devices. All gastric tubes were successfully inserted on the first attempt. On removal of the LTS II blood was seen in 13% of cases and 14% of patients complained of sore throat in the recovery room or at 24 hours.

There were some limitations of our study. First of all, we limited the number of insertion attempts to two. Another factor might be that the two anaesthetists had less experience inserting the LTS-II than they had with I-gel .Potentially, the LTS II adds on some of the positive features of laryngeal masks (effortless handling), and the Proseal LMA (PLMA) i.e. adequate airway seal and access to the gastrointestinal tract . Due to these advantages and higher airway leak pressure, it may find a place in anaesthesia, after failed intubation and perhaps for dealing with the airway during cardiopulmonary resuscitation.[14]

In conclusion, the Laryngeal tube suction II has a higher airway leak pressure and a similar clinical performance, as compared to I-gel, in patients who are mechanically ventilated. Hence it may offer an advantage over I-gel in providing a good airtight seal and more studies need to be done to see if it can be used in full stomach patients.

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CONTINUOUS RENAL REPLACEMENT THERAPY- AN OVERVIEW

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ABSTRACT
Renal replacement therapy is one such technological advance that is now routinely used in intensive care as a renal support. Over the years, use of renal replacement therapy (RRT) has been extended further in various clinical settings. CRRT has been extremely useful in haemodynamically unstable patients. It has an added advantage of precise volume control which leads to precision in fluid removal especially in patients of cerebral and pulmonary edema. Patients of sepsis where after initial adequate fluid resuscitation, a late conservative pattern of fluid removal is advocated, where CRRT comes to its rescue.Here, we send a detailed description about CRRT and its latest updates.

Key words: CRRT, Intensive Care Unit, Indications and Usage

INTRODUCTION
Critical care medicine is one of the most rapidly developing medical specialties in recent times. Over the last few decades, there has been a tremendous advance in technology, diagnostics and treatment of critically ill patients. Renal replacement therapy is one such technological advance that is now routinely used in intensive care as a renal support. Over the years, use of renal replacement therapy (RRT) has been extended further in various clinical settings.

TYPES
Renal replacement therapy, broadly can be divide into two types, intermittent and continuous therapies. The intermittent therapies are Intermittent hemodialysis (IHD), sustained low efficiency daily dialysis (SLEDD) and peritoneal dialysis (PD). The continuous therapies are continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemofiltration (CVVHF) and continuous veno-venous hemodiafiltration (CVVHDF) and slow continuous Ultrafiltration (SCUF).

MECHANISM OF ACTION
Principles
Diffusion: Movement of solute against concentration gradient is known as diffusion. Whether in solution or in an extracorporeal membrane, the diffusivity of a solute is inversely proportional to its molecular weight. Consequently, as solute molecular weight increases, diffusion becomes a relatively inefficient solute removal mechanism and the relative importance of convection increases.

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Diffusion occurs whenever a concentration gradient (dc) exists for solutes not restricted by the porosity of the membrane. The diffusion flux is influenced by the characteristics of the membrane including surface area, thickness and temperature of the solution and the diffusion coefficient of the solute (D).

Convection: Movement of solute against pressure gradient is called convection. In the process of convection, a lot of solvent is also dragged along with the solute (solvent drag). Convection-based replacement techniques (Hemofiltration and hemodiafiltration) using high-flux membrane-filters are aimed at maximizing the removal of so-called medium and high-molecular weight solutes (higher than 1000 kDa up to several thousand kDa), as opposed to the so-called low-molecular weight toxins.
Hemofiltration: A predominantly convective technique, it removes larger quantities of hydrophilic large molecular-weight compounds than diffusion-based hemodialysis. In the ICU setting, hemofiltration leads to greater cytokine removal by a combination of membrane adsorption and convection.

Adsorption: Adsorption is the clinging of solutes to the membrane filter surface that leads to its removal from blood. Adsorption of solutes occurs to varying degrees in all CRRT circuits and can be a contributor for large-molecule removal, depending on membrane characteristics. This may be limited by saturation of the membrane binding sites that can occur within a few hours.

CRRT MODALITIES (Based on principles)

1. SLOW CONTINUOUS ULTRAFILTRATION (SCUF)

Primary therapeutic goal: Safe management of fluid removal
Primary indications: Fluid overload without significant electrolyte imbalance
Principle used: Ultrafiltration
Therapy characteristics: No dialysate or substitution solutions, Fluid removal only
SCUF is a very useful modality in patients of diuretic resistant and hemodynamically unstable pulmonary oedema. It is also helpful in removing fluid in cases of cerebral oedema especially in patient of acute liver failure and subsequent hepatic encephalopathy (1). Figure 1 demonstrates SCUF technique.

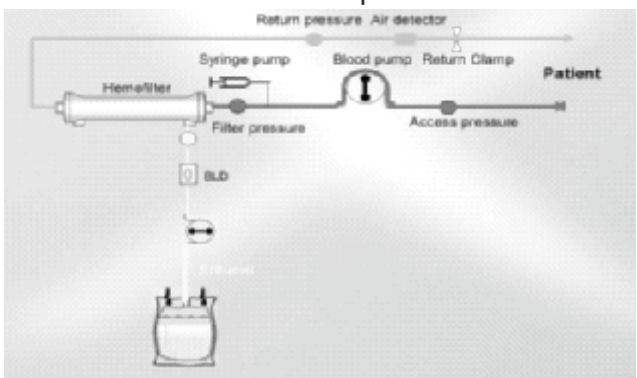

Fig: 1- Slow continuous ultrafiltration technique (SCUF)

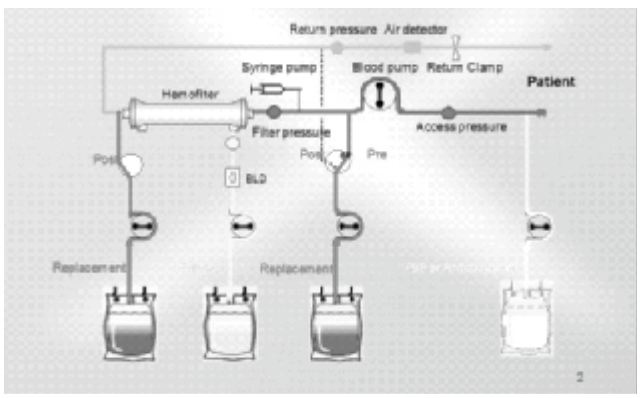

Fig : 2 Continuous veno-venous hemofiltration technique (CVVH)

2 CONTINUOUS VENO-VENOUS HEMOFILTRATION (CVVH)

Primary therapeutic goal: Solute removal and safe management of fluid volume

Primary indications: Uremia, severe acid/base or electrolyte imbalance, when removal of larger molecular weight substances is required

Principle used: convection

Therapy characteristics: Requires replacement solution to drive convection. No dialysate solution

Effective at removing small and middle molecules. Figure[2] shows Continuous veno-venous hemofiltration technique

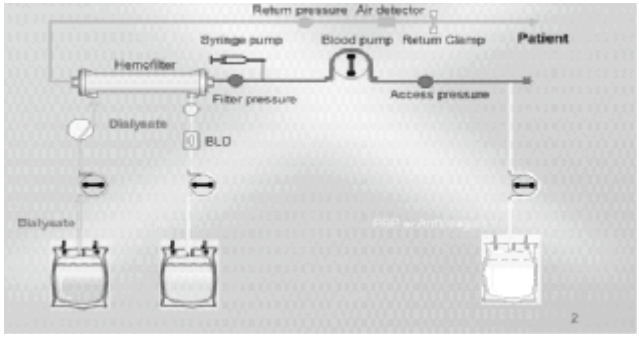

Fig :3 –Continuous veno-venous Hemodialysis (CVVHD) technique

3.CONTINUOUS VENO-VENOUS HEMODIALYSIS (CVVHD)

Primary therapeutic goal: Solute removal and safe management of fluid volume
Primary indications: Uremia, severe acid/base or electrolyte imbalance
Principle used: diffusion
Therapy characteristics: Requires dialysate solution to drive diffusion. No replacement solution
Effective at removing small molecules. Figure 3 demonstrates the technique of continuous veno-venous hemodialysis (CVVHD).

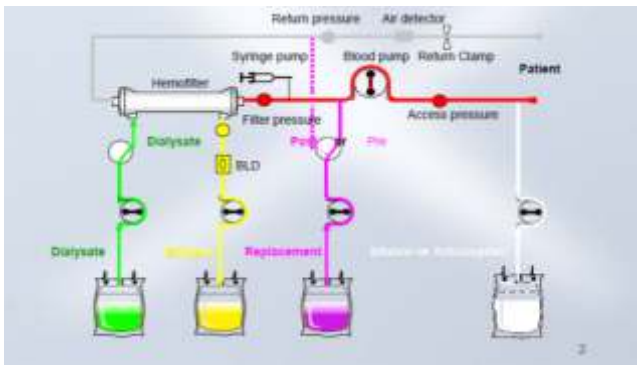

Fig :4- Continuous venovenous haemodiafiltration (CVVHDF) technique

MEMBRANE

The membrane used in CRRT are synthetic membranes which has large pores and huge adsorptive surface allowing a lot of bigger molecules to pass and also helping in adsorption of molecules. The newer membranes are also more biocompatible and chances of complement activation are minimal.

However, in severe metabolic acidosis, especially in patients who are on ACE inhibitors, and if priming is done by banked blood, there is severe hypotension and pulmonary congestion at the start of the therapy, in uncoated AN69 membranes (2). This reaction called bradykinin release syndrome has largely being avoided by using polyethyleneamine coated AN69 membranes (3,4).

The following recommendations are given regarding the membranes

1. It should be synthetic, coated, with large adsorptive surface and pore size.
2. Banked blood should be avoided in priming the circuit.
3. Active vigilance in patients of severe metabolic acidosis and those who are on ACE inhibitors

VASCULAR ACCESS

Vascular access is a basic prerequisite to perform any type of extracorporeal therapy. Access is particularly important in CRRT where catheter performance is tested 24 hours a day. Ultrasound guided vascular catheter placement has to be done. The choice of vein in order is as follows, right internal jugular vein> femoral vein. The subclavian and left internal jugular vein has to be avoided. The right internal jugular gives the best result as there is a pool of blood in the form of right atrium which helps in a less resistant flow in the catheter. If femoral vein is to be selected, the catheter has to be introduced at least > 20 cm in order to avoid recirculation inside the catheter (5). Using a blood pump, the patient's blood is removed via the red coded line (Access) typically connected to the red port of the catheter and delivered through the haemofilter back to the patient via the blue coded line (Return) typically connected to the blue port.

We recommend the following points has to be followed in placing a catheter

1. Should be placed under ultrasound guidance under strict aseptic precautions
2. An intensivist with sufficient experience in placing catheters should be placing the catheter.
3. It should be soft, polyurethane, uncuffed, untunneled.
4. First choice is right internal jugular vein, second choice is right femoral vein.
5. Length of insertion should be 15 cm for right internal jugular vein.
6. Length of insertion should be 20-24 cm for right femoral vein to avoid recirculation.
7. 11F catheter has a flow of 250-300 ml/min.

REPLACEMENT FLUID

As a lot of fluid is removed by convection, it has to be replaced to the patient. Management of replacement fluids helps in precise handling of volume in critically ill patients in contrast to the intermittent therapies. The fluid can be replaced either pre-or post-filter. Whereas pre-filter replacement compromises with convection but prolongs filter life, post filter replacement helps in optimal convection at the cost of circuit life. The composition of fluids also has to be taken care of as the commercially available fluids are deficient of potassium and phosphate. There are also different buffers based fluids like bicarbonate, acetate or lactate, each having its own advantages and disadvantages.

The following recommendations are made regarding replacement fluids-

1. Bicarbonate, rather than lactate or acetate should be used as buffer
2. The fluids should be judiciously distributed between pre-and post-filter.
3. The filtration fraction should be < 25%.
4. Regular measurement of electrolytes should be done – at least 4 hourly
5. Replacement of potassium should be started if serum k+ < 4 mmol/L
6. Replacement can easily be given separately to the patient.

INDICATIONS

CRRT has been extremely useful in hemodynamically unstable patients. It has an added advantage of precise volume control which leads to precision in fluid removal especially in patients of cerebral and pulmonary edema. Patients of sepsis where after initial adequate fluid resuscitation, a late conservative pattern of fluid removal is advocated, where CRRT comes to its rescue. Moreover, patients who are in severe ARDS, where oxygenation is not an issue, ECCO2R via CRRT might help in reducing the tidal volume further preventing lung injury thus avoiding the complicated process of ECMO.

We recommend the following conditions where CRRT can be used

1. AKI in septic shock, KDIGO Stage 2/3
2. Cerebral oedema
3. Pulmonary oedema
4. Acute metabolic acidosis in sepsis
5. Hyperkalemia and hemodynamically unstable patients
6. Refractory fluid overload
7. Permissive hypercapnea.
8. Refractory septic shock
9. Acute liver failure
10. Hyperthermia > 400c without response to medical therapy
11. Permissive hypercapnea

BIOMARKERS IN AKI DIAGNOSIS

Kidneys are not as lucky as heart to have biomarkers which promptly diagnose its dysfunction. By the time serum creatinine is raised, more than half of the kidney dysfunction has occurred.

Biomarkers have been used in diagnosis, progress and prognosis of AKI with limited success. Some of the prominent biomarkers are Serum and urinary NGAL, serum and urinary Cystatin C, KIM-1, L-FABP, IL-18 to name a few.

NGAL (neutrophil gelatinase associated lipocalin) is a 25 kDa protein expressed in neutrophils and

different epithelia including kidney tubules. It is released in both urine and plasma and increases within 2 hours of acute kidney injury. It has been found to be a diagnostic as well as prognostic markers in certain studies (6).

Cystatin C is a non-glycosylated LMW cysteine protease synthesized at relatively constant rate and released in the plasma by all nucleated cells. It is freely filtered by glomerulus and completely reabsorbed by proximal tubule. Systemic cysteine C is a measure of GFR. Urinary cystatin C is indicative of tubular dysfunction (7).

Cell cycle arrest markers IGFBP (insulin like growth factor binding protein) and TIMP 2 (tissue inhibitor metalloproteinases 2 have been the latest one used to diagnose AKI. The product of both (> 0.3) (nephrocheck) have been found to be predicting the development of moderate to severe AKI within 12 hours of testing (8-10).

WHEN TO START CRRT

Consensus regarding as to when to start CRRT is yet to be achieved. Most of the earlier studies in the initial part of the decade were in favour of early start of therapy (11, 12). However, the criteria of early therapy were vague. The RIFLE, AKIN and KDIGO classification has helped in classifying AKI according to the increasing order of severity. The recent trials of AKIKI (13) and ELAIN (14) have contradictory results. The general consensus is to individualize patients and start CRRT accordingly. Figure 4 shows the practical approach in starting RRT.

WHAT DOSE

AKI Staging	Urine output	RIFLE	AKIN	KDIGO
1	< 0.5 ml/kg/hr for 6 -12 hours	RISK ser um [illegible]	Rise in serum creatinine 1.5 - 2×baseline or 0.3 mg/dl absolute increase over 48 hours	Rise in serum creatinine 1.5 - 1.9 time the baseline over 7 days or 0.3 mg/dl absolute increase in 48 hours
2	< 0.5 ml/kg/hr > 12 hours	INJURY Serum creatinine>2 times	Serum creatinine 2 -3 times the base line	Serum creatinine 2 -2.9 times the baseline
3	< 0.3 ml/kg/hr > 24 hours OR anuria for 24 hours	FAILURE Serum creatinine >3 times the baseline or serum creatinine increase > 4mg/dl (with	Serum creatinine >3 times the baseline or serum creatinine increase > 4mg/dl (with increase in 0.5	Serum creatinine greater than 3 times the baseline or serum creatinine increase to 4mg/dl or

		increase in 0.5 mg/dl) or initiation of RRT	mg/dl) or initiation of RRT	initiation of RRT
		ESKD : ESKD for refractory fluid overload Refractory septic shock Acute liver > 3 MONTHS		

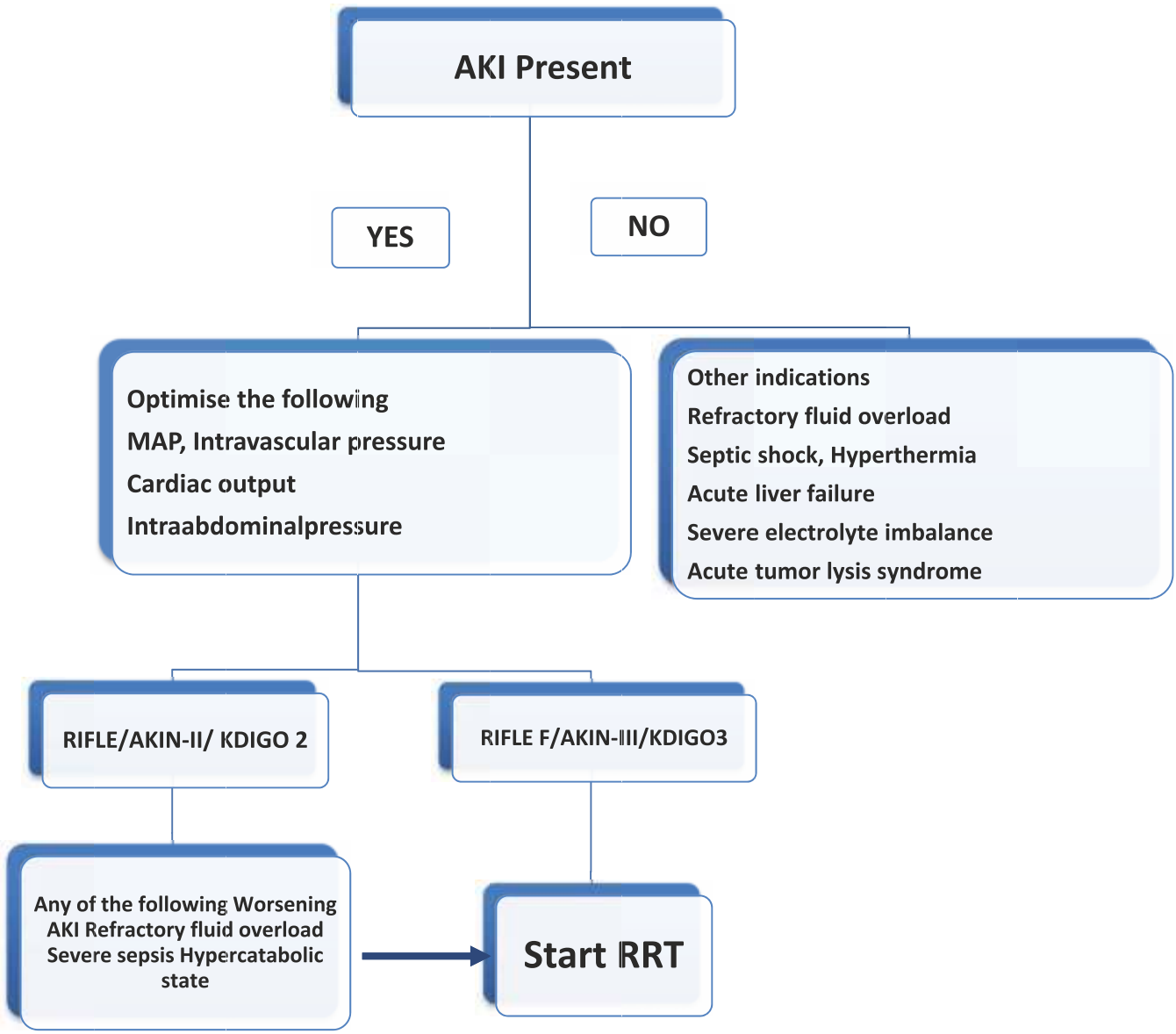

Figure : 5- Practical Approach in starting RRT

It has to be understood that the dosage of CRRT is completely different from that of IHD. Whereas in IHD, KT/V (UREA) is considered to be the dosing option, the same is not true for patients who are critically ill. These patients are having a variable volume of distribution, they are metabolically unstable, frequently on vasopressors, are having some residual kidney function left, making them completely different from relatively stable patients where IHD is an option. In CRRT, dose is calculated on the basis of the rate of effluent volume.

In the earlier part of this century, many users were in an opinion to use a higher dose (40 ml/kg /hr) of effluent volume which was found to have mortality benefit over lower doses (25ml/kg/hr) (15). However, this was challenged by two large trials (16, 17) which showed that higher effluent volume does not have any mortality benefit over lower effluent volumes. Though researchers have found that higher dosage might be useful in reversing the vasopressor use in septic shock, the general consensus is to use a dose of 25ml/kg/hr of effluent volume. However, the prescribed dose should be higher as there might be multiple stoppage times affecting the dosage (18). So, in order to achieve the recommended dose you have to prescribe a higher dose.

The recommendation is

1. Effluent volume of 25ml/kg/hr is the recommended dose
2. Prescribe a higher dose to achieve this dose
3. Dosage must be individualized according to patient needs.

ANTICOAGULATION IN CRRT

In order to keep the filter patent, anticoagulation is necessary. The commonest anticoagulant used is unfractionated heparin in a dose of 5-10 U /kg/hour. The APTT has to be monitored every 6 hourly and should be kept between 45-50 seconds (1.5 times the normal). Heparin may jeopardize the in vivo coagulation process and may be harmful for critically ill patients. Citrate, is used as a regional anticoagulant, and is gradually replacing heparin. Citrate does not alter the coagulation parameters of the patient. It is given in the form of sodium citrate. Post filter ionized calcium level should be 0.3mmol/l. Hypernatremia, metabolic alkalosis and hypocalcaemia are side effects. In liver failure, citrate is not metabolized. This is evident from total ca/ ionised ca > 2.25-2.5 mmol/l. High anion gap metabolic acidosis and increased lactate modification of replacement solution is required to use citrate as anticoagulant.

WHEN TO STOP

- AS PER KDIGO 2012 (19), RRT is discontinued when it is no longer required, either because intrinsic kidney function has recovered to the point that it is adequate to meet patient needs, or because RRT is no longer consistent with the goals of care. However, it should be made sure that the patient is in optimal condition (hemodynamics, volume and electrolyte status, metabolic status) before RRT is terminated. Abrupt stoppage of CRRT is discouraged. It is advisable to shift to conventional intermittent modes till the patient completely regains his/her renal functions.

- Of late, protocolised weaning from CRRT is practiced in many centres. If the patient condition is stable hemodynamically, and his respiratory functions are stable, the probable cause and sequel of AKI has been addressed and the urine output> 30 ml/hour, then measure the 24-hour urinary creatinine in the intradialytic period. If the value of urinary creatinine is > 5.2 mmol/L , cessation of CRRT could be attempted.

NUTRITION IN CRRT

There is massive loss of amino acids, water soluble vitamins, micronutrients , elements like Zinc in CRRT so much so that the phenomenon is called Depletion syndrome. The goal is to achieve

a total energy intake of 20–30 kcal/kg/d in patients with any stage of AKI (20). Energy provision should be composed of 3–5 (maximum 7) g per kilogram body weight carbohydrates and 0.8–1.0 g per kilogram body weight fat. A normal to high protein replacement is indicated in these situations. Administer 0.8–1.0 g/kg/d of protein in non-catabolic AKI patients without need for dialysis. Protein is administered at an amount of 1.0–1.5 g/kg/day in patients with AKI on RRT and up to a maximum of 1.7 g/kg/d in patients on CRRT & in hyper catabolic patients. It is always better to provide nutrition preferentially via the enteral route in patients with AKI.

ANTIBIOTICS IN CRRT

Antibiotic dosing in CRRT is a complex phenomenon. Close monitoring of drugs wherever possible should be done. Loading dose should never be compromised. Maintenance doses should be changed either by increasing the duration especially in concentration dependent antibiotics, or by decreasing the dose but keeping the frequency of doses same in cases of time dependent antibiotic. It is preferable to use single substances over combination therapies. One should be aware of the risk of under-dosing during effective CRRT. Antibiotics getting adsorbed in membrane like fluoroquinolones, need higher dosing. Higher doses should also be considered if convective therapies are used rather than diffusive therapies. Creatinine clearance is a good modality to calculate dose but it ignores tubular drug handling. Therapeutic drug monitoring, if possible, is the best option to decide on doses of drugs in CRRT (21).

CONCLUSION

CRRT is a therapy that is gaining greater acceptance and becoming more widely used for treatment of both renal and non-renal indications. And in the population of critically ill patients CRRT is one of the best RRT options these hemodynamically unstable patients may tolerate. A physician and critical care nurse/ technician plays a very important role through setting up the right prescription, continuous monitoring and identification of any problems and resolving it at the earliest for the success of therapy

Table 1: Antibiotic dosage chart in CRRT

S. No.	Drugs	Route of elimination	Time dependent or concentration dependent	Drug Dose CVVH	Drug Dose CVVHD/CVVHDF	Drug Dose IHD
1.	Acyclovir	Renal	Time dependent	5-7.5 mg/kg q 24h CNS infections 10mg/kg q 12h	5-7.5 mg/kg q 24h CNS infections 10mg/kg q 12h	1.5 mg/kg q 24h CNS infections 5mg/kg q 24 h
2.	Ampicillin	Renal	Time dependent	3g q 12h	3g q 12 h	1-2 g q 12 h
3.	Aztreonam	Renal	Time dependent	1-2 g q 12h	2 g q 12h	1 g q 24h
4.	Cefepime	Renal	Time dependent	1-2 g q 12h	2 g q 12h	2 g q 24h
5.	Cefriaxone	Renal	Time dependent	1-2 g q 12h	2 g q 12h	1-2 g q 12h
6.	Ceftazidime	Renal	Time dependent	1-2 g q 12h	2 g q 12h	1g q 12h f/b 1g post HD

7.	Ciprofloxacin	Renal	Concentration dependent	200mg q 12h	200-400 mg q 12h	400 mg q 24h
8.	Colistin	Renal	Concentration dependent	2.5 mg/kg q 48h	2.5 mg/kg q 48h	1.5 mg/kg q 24h
9.	Polymyxin B	Hepatic	Concentration depenent	15000-25000 U/kg/day q 12h	15000-25000U/kg/day q 12h	No data
10.	Fluconazole	Renal	Time dependent	200-400 mg q 24h	400-800 mg q 24h	400 than 400mg q 24h
11.	Imipenem	Renal	Time dependent	250 mg q 6h or 500 mg q 8h	250 mg q 24h	No data
12.	Levofloxacin	Renal	Concentration dependent	250 mg q 24h	250 mg q 24h	500 mg than 500 mg q 24h
14.	Moxifloxacin	Hepatic	Concentration	400mg q	400 mg q 24h	400 mg q 24h
15.	Piperacillin	Renal	Time dependent	2.25 g q 6h	2.25-3.375g q 6h	2.25 q 24 h
16.	Vancomycin	Renal	Time dependent	1 g q 48 h	1g q 24h	15-20 mg/kg q 24h
17.	Voriconazole	Hepatic	Time dependent	4 mg/kg po q 12h	4 mg/kg po q 12h	4 mg/kg po q 24h

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Dexmedetomidine as an adjuvant to bupivacaine in brachial plexus block: Prospective, randomized, double blind study.

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Abstract

Background: Use of adjuvants to regional blocks has been in vogue in the recent past. Several adjuncts have been studied to potentiate the efficacy of local anaesthetics in brachial plexus block but dexmedetomidine has sparingly been used as an adjuvants.

Aim : To study dexmedetomidine as a sole adjuvant to local anaesthetic bupivacaine in brachial plexus block.

Method: The patients were divided into two groups of 25 patients each. In Group A, 30 ml of 0.5 % bupivacaine with 1 ml normal saline was given for brachial block whereas in Group B, 30 ml of 0.5 % bupivacaine with 1 ml dexmedetomidine (100 µg) was injected. Primary outcome method was onset and duration of sensory and motor block whereas secondary outcome measures were pain scores, requirement of analgesics and haemodynamic changes.

Result: Sensory onset time was 5.76± 2.47 minutes in Group B which was significantly less than group A whereas it was 10.44±3.57minutes. Also onset of motor blockade in Group A was 16.76±4.78 minutes and in Group B was an 11.24±3.81 minute which was statistically significant. The mean duration of analgesia for Group A was 525.4±124.99 minutes and for Group B it was 712.8±103.78 minutes. The mean duration of motor blockade for Group A is 469.8±122.68 minutes and for Group B is 669.4±105.33minuteswhich was also statistically significant.

Conclusion: Dexmedetomidine as an adjuvant to bupivacaine significantly shortens the onset time of sensory and motor block in brachial plexus block. Also total duration of analgesia and motor blockade is prolonged when dexmedetomidine is added to bupivacaine and the requirement for analgesic drugs in the postoperative period is also decreased.

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INTRODUCTION

A peripheral nerve block is the injection of a local anaesthetic around a nerve or group of nerves with blockade of nerve impulse conduction, causing temporary analgesia and loss of sensory and motor function. Peripheral nerve blocks are cost effective anaesthetic techniques used to provide superb anaesthesia and analgesia while avoiding airway instrumentation and the hemodynamic consequences of general and neuraxial anaesthesia.[1]

Satisfactory surgical conditions are obtained with complete sensory and motor blockade. Concurrent sympathetic blockade reduces post-op pain, vasospasm and oedema.2,3The bupivacaine which is an amide local anaesthetic is the most frequently used local anaesthetic.[2,3]

Several adjuncts have been studied to potentiate its efficacy including opioids, midazolam, neostigmine, bicarbonate, hyaluronidase and α-2 agonists.[4-11] The use of α-2 adrenoceptor agonist for enhancement of peripheral nerve blocks has added a new dimension to their clinical application.12 Clonidine, when combined with a local anaesthetic has been found to extend the duration of nerve block.13 Dexmedetomidine is the most recent agent in this group approved by FDA in 1999 for use in humans for analgesia and sedation. Dexmedetomidine, a highly selective potent α-2 agonist, an imidazole compound is pharmacologically active dextroisomer of medetomidine. Dexmedetomidine, when combined with a local anaesthetic, has been found to extend the duration of nerve block.[14-16] It has been postulated that this action could be due to local vasoconstriction, facilitation of C fiber blockade, activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia.[17]

METHODS

After Institutional ethical committee approval and written informed consent, a double blind randomized prospective clinical study was carried out on 50 American society of anaesthesiologists (ASA) grade I & II adult patients of either sex, aged 18-60 years, undergoing upper limb surgery under supraclavicular brachial plexus block. Patients receiving anticoagulants, β- blockers or opioids, patients with history of hypertension, myocardial infarction, alcohol abuse, pregnant patients, psychiatric history, diabetes mellitus, contra lateral phrenic nerve palsy, neurological deficit, peripheral neuropathy or hypersensitivity to local anaesthetic agents, were excluded from the study.

The patients were divided randomly into two groups, using computer generated table.

Group A patients received 30 ml of 0.5 % bupivacaine with 1 ml normal saline whereas 30 ml of 0.5 % bupivacaine with 1 ml dexmedetomidine (100 µg) were given in Group B patients.

Before shifting the patient to the operation theatre, an intravenous access was obtained and routine monitors were attached. Then inj. Ondansetron 4 mg i.v. was given.

All the patients received brachial plexus block through the supraclavicular approach. Neural localization was achieved by using a nerve locator connected to 22 G, 50 mm- long stimulating needle (stimuplex).Persistence of contraction with stimulator voltage decrease to 0.5 Ma was taken as the confirmation of the brachial plexus. The needle was then held immobile and 1ml of the local anaesthetic injected. At this point the twitching should disappear. The mechanism for the immediate disappearance of the twitching is not a result of the local anaesthetic blocking the nerve, but the mechanical displacement of the nerve away from the needle tip(18). So, after

confirming the needle tip is not inside a nerve or a vessel, rest of the drug was injected, after negative aspiration every two to three ml. patients of either group (n =25 each) were given either 1 ml (100µg) of dexmedetomidine (group B) or 1ml of normal saline (group A) along with 30 ml of 0.5 % bupivacaine. The nature of drug or group of the patient was not known to the one performing the block. Inj. Midazolam 0.01- 0.1 mg/kg i.v. was given to the patient once complete block had been confirmed.

We defined the successful block as one that allows the surgery to proceed within a 30 minute time period, without discomfort to the patient or need for any supplemental techniques.

All the patients were observed and values recorded meticulously for the following effects both in intraoperative and in the post-operative period.

Primary outcome method was onset and duration of sensory and motor block whereas secondary outcome measure was pain scores.

Sensory block was assessed by pin prick method. Sensory onset was considered when there was a dull sensation to pin prick. Complete sensory block was considered when there was complete loss of sensation to pin prick. Assessment of sensory block was done at each minute after completion of drug injection till complete sensory blockade.

Assessment of motor block was carried out by the same observer at each minute till complete motor blockade after drug injection. Motor blockade was evaluated by the ability to flex the elbow and hand against gravity as Grade 1(Ability to flex and extend the forearm),Grade 2(Ability to flex or extend only the wrist and finger, Grade 3 (Ability to flex or extend only the fingures) and Grade 4 (Inability to move the forearm, wrist, fingers).The block was considered to be incomplete when any of the segments supplied by median, radial, ulnar and musculocutaneous nerve did not have analgesia even after 30 min. of drug injection. when more than one nerve remained unaffected, the block was judged to have failed. In this case general anaesthesia was given. Patients were monitored for hemodynamic variables such as heart rate, blood pressure and oxygen saturation every 15 min after the block intraoperatively and every 60 min post operatively for 24 hours.

Duration of sensory block was defined as time from injection of drug to appearance of pain, requiring analgesia. Pain was assessed on a rating scale, zero representing no pain and 100 meaning worst possible pain. Injection tramadol 2mg/kg i.v. was given as rescue analgesic when the pain score was more than 40. Pain scores were recorded at thirty minutes, two hours and at eight hours after the surgery.

Duration of motor block: it was defined as time from injection of drug till complete return of motor power.

The collected data were analysed using Windows Microsoft excel 2007 version and Graph pad software prism[6].

Patient's demographic data were analysed using unpaired t -test. Pain Scores was analysed using chi square test. The difference was considered statistically significant at a p value of <0.05 with 95% confidence interval.

RESULTS

Both the groups were comparable in terms of age, gender, weight and type of surgeries. (Table 1). Mean Sensory onset time in Group A was 10.44±3.57minutes (Table 2) and in Group B was 5.76± 2.47 minutes which was statistically significant.

Onset of motor blockade in Group A was 16.76±4.78 minutes and in Group B was an 11.24±3.81 minute which was also statistically significant (p <0.0001).

The mean duration of analgesia for Group A was 525.4±124.99 minutes and for Group B it was 712.8±103.78 minutes.

The mean duration of motor blockade for Group A was 469.8±122.68 minutes and for Group B was 669.4±105.33 minutes (Table 2). The difference in the duration of analgesia and motor blockade was statistically significant with a p value of <0.0001for both.

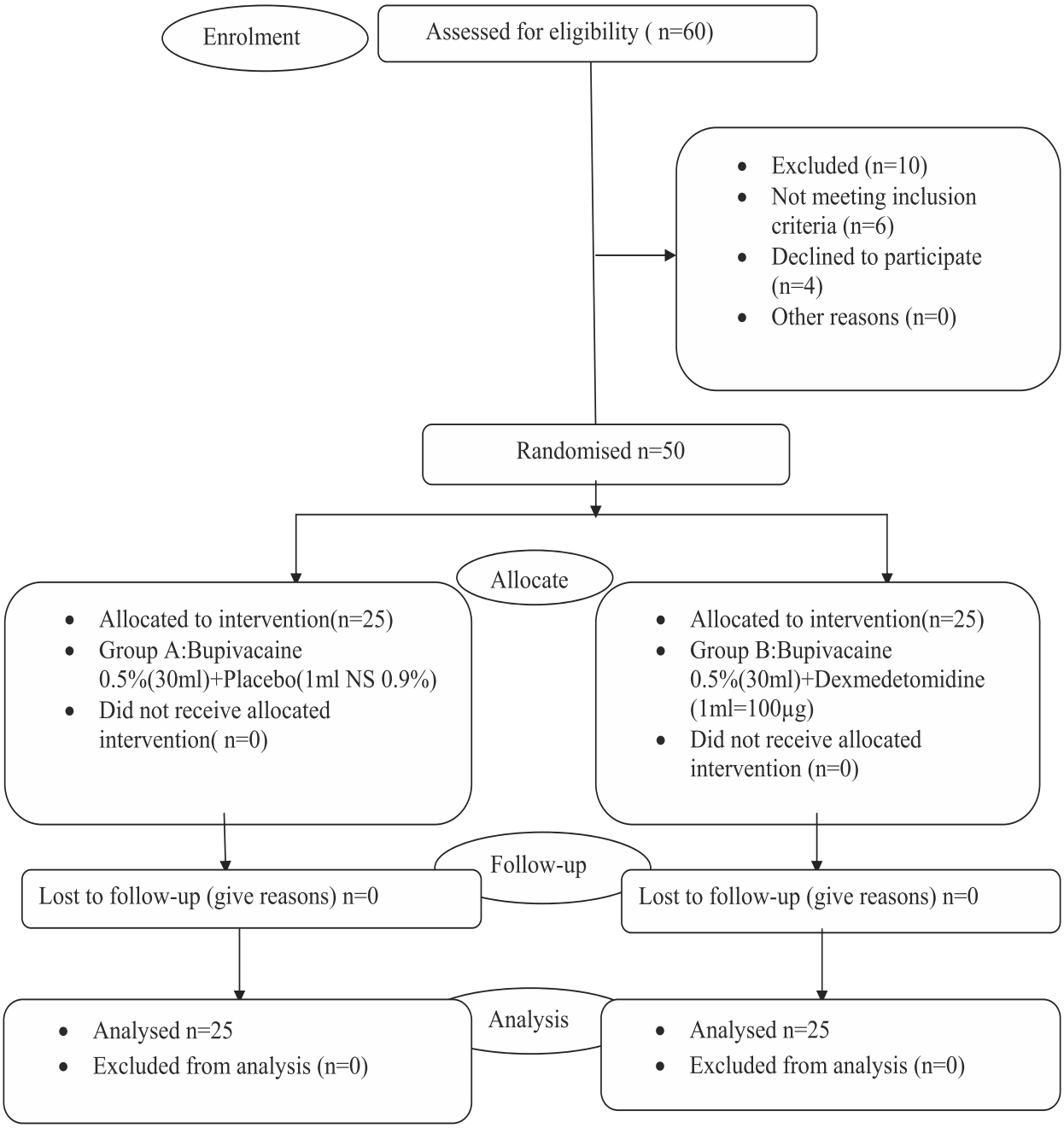

Diagram: Consort flow chart

Table 2: Comparison of sensory and motor onset time and duration in both the groups

	GROUP A Mean+SD	GROUP B Mean+SD	P Value
Sensory onset time (min)	10.4+3.57	5.76+2.47	<0.0001
Motor onset time (min)	17+4.8	11.2+3.81	<0.0001
Sensory duration (min)	525+125	713+104	<0.0001
Motor duration (min)	470+123	669.4+105.3	<0.0001

Table 3: Comparison of Pain scores in both the groups

Time	GROUP A Mean±SD (Pain Score)	GROUP B Mean±SD (Pain Score)	P Value
30 min	0	0	0
2 hr	3.2±5.65	0	0.0067
8 hr	45.6±15.02	5.2±11.59	<0.0001

DISCUSSION

In this randomized double-blinded study, we studied the efficacy of Dexmedetomidine as an adjuvant to bupivacaine in peripheral nerve stimulator PNS guided supraclavicular brachial plexus block. The addition of 100µg dexmedetomidine to (PNS) guided supraclavicular brachial plexus block increased the duration of both sensory and motor blockade and the need for analgesic in postoperative period was also reduced significantly.

In 2010 work has been done on similar line by Aliye Esmaoglu et al 16 who added dexmedetomidine to levobupivacaine for axillary brachial plexus block and showed that it shortens the onset time of both sensory and motor block, prolongs the duration of block and the duration of post-operative analgesia. In 2012, Sarita S swami et al. compared clonidine vs. Dexmedetomidine as an adjuvant to 0.25% bupivacaine and reported that the onset of sensory block was faster in dexmedetomidine group.

In 2012, Rachna Gandhi et al 19 reported that onset of motor and sensory blockade was faster in control Group as compared to dexmedetomidine group. But no convincing explanation for their finding could be given. It may be because of the different dose of dexmedetomidine used by them.In our study as well as in various other studies onset of sensory and motor block was

shortened in dexmedetomidine group.
Addition of dexmedetomidine to local anaesthetic in brachial blocks significantly prolonged the duration of sensory (analgesia) and motor blockade in our study as well as the studies done previously by others. The mechanism by which α2adrenergic receptor agonists produce analgesia and sedation is not fully understood, but is likely to be multifactorial. Peripherally, α2 agonists produce analgesia by reducing release of nor epinephrine and causing α2 receptor-independent inhibitory effects on nerve fibre action potentials. Centrally α2 agonists produce analgesia and sedation by inhibition of substance P release in the nociceptive pathway at the level of dorsal root neuron and by activation of α2 adrenoceptors in the locus coeruleus. [20,21]

Moreover, experiments on dexmedetomidine as an adjuvant for nerve blocks have shown that the duration of analgesia is prolonged by block of the hyper polarization-activated cation current (Ih current).22The Ih current is important to bring a peripheral nerve back to the resting potential. The action potential will result in a hyperpolarized state, and the nerve will hardly be able to produce a new action potential.

Therefore, the nerve is refractory to further stimulation. To produce another action potential, the nerve needs to get back to the resting potential. This process occurs in the late phase of the repolarization period. Blocking the Ih current will result in prolonged hyperpolarization of the nerve, which seems to be more distinct in the unmyelinated C fibres (pain) than in motor fibres. Therefore, blocking the Ih current may have a more pronounced effect on pain than on motor response.23However, further studies are warranted to investigate the mechanisms of how an Alpha-2 agonists, and especially dexmedetomidine, prolong the action of local anesthetic in peripheral nerve blocks.

Several studies have found dexmedethomidine to be safe and effective in various neuraxial and regional anesthetics in humans, including intrathecal and IV regional anesthesia.24,25Intrathecal dexmedetomidine in combination with bupivacaine have been studied in human beings without any postoperative neurological deficit.[26]

A dexmedetomidine–lidocaine mixture has been used to provide Bier's block and was shown to improve the quality of anesthesia and tourniquet pain and reduce postoperative analgesic requirement.[24,25]

Another study compared the effect of adding either clonidine or dexmedetomidine to lidocaine during Bier's block and reported that adding dexmedetomidine to lidocaine during Bier's block is superior in quality of anaesthesia, tourniquet tolerance, and intraoperative and early postoperative analgesia than is the addition of clonidine.27Brummet et al.28 reported that large-dose dexmedetomidine enhances the duration of bupivacaine anesthesia and analgesia of the sciatic nerve block in rats. In addition, they histopathologically showed that the nerve axon and myelin were normal in both groups at 24 hours and at 14 days. Same authors in another experimental study reported that clinically relevant doses of dexmedetomidine enhanced blockade when added to ropivacaine.[29]

Kaslo et at.30 reported that dexmedetomidine affinity to "2adrenoceptor agonists is 10 times as compared to clonidine when dexmedetomidine is added to lidocaine for intravenous regional anaesthesia, it has been studied that it improves quality of anaesthesia and intraoperative and postoperative analgesia without causing side effects.[31-33] However, dexmedetomidine also may lead to bradycardia.

The result in this study showed that sensory block tended to last longer as compared to motor block which agrees with the observation by De Jong et al.4 These authors explained that large fibres

require a higher concentration of local anaesthetic than small fibres. The minimal effective concentration of local anaesthetic for large (motor) fibres is greater than for small (sensory) fibres. Thus, motor function return before pain perception and duration of motor block is shorter than the sensory block.[4]

The effect of the procedure on the hemodynamic was also studied in both the groups in this study. Pulse rate and mean arterial blood pressure were recorded and compared at specified intervals i.e. pre-operative, at five minutes, thirty minutes and two hours after the block, then post operatively at thirty minutes, two hours, eight hours and twenty four hours. The mean pulse rate and mean MAP in Group A and B were comparable, preoperatively and at 5 min after block with no statistically significant difference.

The mean pulse rate and mean of MAP were significantly lower in Group B than those in Group A at 30 minutes, 2 hours and in postoperative period. The difference was statistically significant. Mean pulse rates and mean of MAP, before and after the block were also compared separately in both Group A and Group B to know the effect of respective drugs; especially the dexmedetomidine on pulse rate and blood pressure by using the paired t-test.

The comparison was made between preoperative values of mean pulse rate and mean MAP (mm Hg) with mean values at five minutes, thirty minutes and two hours after the block, then post operatively at thirty minutes, two hours, eight hours and after twenty four hours, within Group A and Group B separately.

In Group A, the values for both pulse rate and MAP were found to be statistically significant in two pairs only. At five minutes after the block, the mean pulse rate was 91.00±6.3 per minute, and mean MAP was95.84±3.63 mm of Hg in comparison to pre operative mean pulse rate of 85.84±7.52 per minute and mean MAP of 93.68± 6.10 mm of Hg and at 8 hrs mean pulse rate was 90.36±5.82 per minutes and mean MAP was 96.24±3.19mm of Hg. Both the values were statistically significant with $p < 0.05$ at 95% confidence interval.

The increase in pulse rate and rise in MAP five minutes after the block can be attributed to anxiety and pain related to the procedure, as injection midazolam was given to the patients only after confirmation of sensory and motor blocks. The same reason, i.e. post-operative pain due to regression of sensory block can be held accountable for increase in mean pulse rate and MAP eight hours post-operatively.

In Group B, the values for both mean pulse rate and MAP were found to be statistically significant. Except at 5 minutes, intraoperatively MAP and HR values were significantly lower in Group B ($P<0.05$).

At thirty minutes after the block, mean pulse rate was 75.84± 15.41 per minute, mean MAP was 87.88± 4.41 mm of Hg in comparison to pre-op mean pulse rate of 89.08± 9.4per minute and mean MAP of 93.96 ± 6.16 mm Hg, $p = 0.0008$and $p = 0.0001$respectively. There was significant decrease in pulse rate and MAP in Group B after brachial plexus block with p value < 0.05.

This can be attributed to the effect of dexmedetomidine. Tachycardia and hypertension were not seen in this group eight hours post operatively as patients had prolonged duration of analgesia in this Group And mean pain score was 45.6±15.02 for Group A and 5.2±11.59 for Group B. The difference in pain score between the two is statistically significant with a p value of <0.0001 (<0.05) at 95% confidence interval.

As seen from the data provided above, pain scores were significantly lower in patients who received dexmedetomidine in addition to bupivacaine. Inj.Tramadol 2mg/kg was given to

patients when pain scores were found to be more than 40, on a scale of zero to hundred. The number of patients who required rescue analgesic were 72 % in Group A and 4% in Group B, were significantly lower at eight hours post operatively, in Group B, with a p value of(<0.05) at 95% confidence interval. Also the mean value of boluses of analgesic required up to 24 hr post operatively in Group A was 1.92±0.75as compared to 1.304±0.55in Group B, the difference being statistically significant at a p value of 0.0018 (<0.05) at 95% confidence interval.

Side effects such as nausea and vomiting were not seen in any patients in Groups B; however one patient in Group A experienced nausea about eight hours post-operatively. This was probably a result of repeat antibiotic injection that was administered to the patient, rather than due to the procedure or any of the drugs used for the block.

Dexmedetomidine may lead to side effects such as hypotension and bradycardia with increased dosage along with its effects such as sedation and anxiolysis.34 In this study almost all the patients remain sedated but arousable without any sign of respiratory depression in Group B, however 3 patients in Group B were sedated in the postoperative period but their reflexes were intact. Bradycardia was seen in 8 % of the patients in Group B who responded to inj. atropine. Rest of the patients in either group had an uneventful course without major complications.

CONCLUSION

Dexmedetomidine with bupivacaine significantly shortens the onset time of sensory and motor block in brachial plexus block. Also total duration of analgesia and motor blockade is prolonged when dexmedetomidine is added to bupivacaine and the requirement for analgesic drugs in the postoperative period too is decreased.

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Dexmedetomidine as an Anesthetic adjuvant in patients undergoing craniotomy for space occupying lesion

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Abstract

Background: In neurosurgery anaesthesiologist should provide additional anesthesia care to produce better outcome. Neuroisurgery needs minimum rise in the intracranial pressure and optimize cerebral perfusion pressure and oxygenation and adequate management of fluid volume status to avoid brain edema. We need to investigate new anesthetic drugs or adjuvant to provide adequate analgesia and sedation during the more painful parts of the surgery and provide optimal conditions with a "slack" brain and minimal rise in intracranial pressure (ICP) when recovering from anaesthesia.

Aim and Objective: Evaluation of dexmedetomidine as anaesthetic adjunct in patients undergoing craniotomy for excision of space occupying lesion. We measured BIS guided optimum dose of dexmedetomidine for infusion during intra operative course. Sedative/hypnotic effect of dexmedetomidine was measured as reduced intra operative analgesic effect of dexmedetomidine was measured as reduced requirement of intra operative opioids - fentanyl.

Material and Method: In this double blinded randomized case control study, after taking ethical clearance and informed consent, 75 patents from 18 to 65 years, both sexes with ASA grade 1 and 2 and Glasgow coma Scale (GCS) of 12 or more taken. We used "Bi Spectral Index (BIS) to evaluate Dexmedetomidine as an anaesthetic adjunct in patients undergoing craniotomy for excision for space occupying lesion admitted to the Department of Neurosurgery in King George Medical University, Lucknow, Uttar Pradesh from January 2016 to January 2017. Patients were randomly allocated into three groups (25 patients in each group). On the day of surgery, in operation room all monitors are attached including BIS.

Group A Group B received Dexmedetomidine loading dose at 0.5 microgram/ kg (µg/kg) in 10 minutes before induction of GA. Intraoperatively Dexmedetomdine was given in group A infusion at 0.5 µg/kg/hr and in Group B received 0.3 µg/kg/hr. Group C was the control group received saline infusion only. The infusions were stopped 30 minutes prior to skin closure. We observed the BIS, total fentanyl requirement, Isoflurane consumption during surgery and postoperatively Ramsey sedation score of all patients and other complications.

Results: Intraoperatively in group A requirement of Fentanyl and Isoflurane was less than group B. Further in group A requrment of Isoflurane requrment was almost nil. In group C requirement of fentanyl and Isoflurane to keep heamodynamics stability and BIS index with in

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range was much higher than Group A and Group B.

Conclusion: Dexmedetomidine when used as an adjuvant to GA in craniotomy causing decrease dose of fentanyl and Isoflurane intraoperatively. Dexmedetomidine dose of 0.5mc/kg/min. is seems to be an optimum dose for better outcome.
Keywords: Neuro Anesthesiology, Dexmedetomidine, Craniotomy, BIS (Bi Spectral Index),

Introduction

Neurosurgery brings additional responsibility on the anaesthetist to ensure a good outcome. The anaesthetist should providing anaesthesia for brain tumor surgeries with minimal rise in the intracranial pressure and optimize cerebral perfusion pressure and oxygenation and adequate management of fluid volume status to avoid brain edema. Adequate analgesia and sedation should be provide during the more painful parts of the surgery-head pinning, skin incision, craniotomy and provide optimal conditions for the neurosurgeon with a “slack” brain and minimal rise in intracranial pressure (ICP) when recovering from anaesthesia. Inhalational agents and opioids are conventionally used to blunt the haemodynamic responses intra operatively. Opioids are used to blunt airway and haemodynamic responses during recovery and extubation – but these have their own side effects. Since the start of practice of modern anaesthesia, the search for an optimal sedative agent has always insearch. The ideal agent should have a good sedative effect and should not cause any respiratory depression, should provide pain relief if possible with minimal hemodynamic alterations.

Dexmedetomidine, a selective alpha-2 adrenergic agonist has generated much interest in the field of anaesthesia and intensive care unit for sedation. This drug was first approved by the Food and Drug Association (FDA) in 1999 for use short term sedation lasting less than 24 hours1. The ability to cause sedation without clouding of mental status i.e patients are rousable and responsive after minimal stimulus is an excellent characteristic of this drug2. Several studies have been conducted which have tried to evaluate the role of this drug into peri operative application ranging from pre operative sedation, sedation for procedures like fibre optic guided intubation3 intra operative sedation and analgesia, post operative sedation, day care procedures like ERCP4 etc,.

Most of the studies concluded that use of dexmedetomidine was beneficial and improved patient outcomes. Literature from various authors have shown beneficial role of dexmedetomidine’s in achieving good sedation in minor procedures such as ERCP, dental extraction procedures and as anaesthetic adjuncts in surgeries requiring general anaesthesia and as adjuncts in neuraxial blockade. In 2000, Hall JE et al.5 studied the sedative, amnestic, and analgesic properties of small-dose dexmedetomidine infusions on seven healthy young volunteers. Small-dose dexmedetomidine provided sedation, analgesia, and memory and cognitive impairment. In 2015, Wang X et al.6 showed the neuro-protective effect of dexmedetomidine. Dexmedetomidine significantly attenuates isoflurane induced cognitive impairment in ageing rat. In 2017, Endesfelder et al.7 in his study shows that dexmedetomidine may have neuro-protective effects in an acute hyperoxic model of the neonatal rat. Dexmedetomidine shows a high ratio of specificity for the alpha-2 receptor α2 / α1:1600/1 compared with clonidine α2 /α1:200/1.This effect is seen at low to moderate dosage of infusions8. The physiologic effect is mediated via stimulation of post synaptic α2-adrenergic receptors that activate a pertussis toxin sensitive guanine nucleotide regulatory protein (G protein) resulting in inhibitory feedback and decreased activity of adenyl cyclase. This results in decreased cAMP and cAMP dependant protein kinase activity leading to

dephosphorylation of ion channels9 ultimately resulting in decreased neuronal activation and clinical effects of sedation and anxiolysis. The hypnotic and sedative effects of α2-adrenoceptor activation have been attributed to the high concentration of α2 receptors in the locus ceruleus of the brain stem10,11, an area which is recognized to play a role in important brain functions including arousal, sleep, anxiety and drug withdrawal syndromes associated with CNS depressants such as opioids. Unlike traditional sedatives such as benzodiapenes or propofol, dexmedetomidine does not activate the GABA (gamma amino butyric acid) system. Therefore by its action on locus ceruleus it confers a co operative form of sedation in which the patient can easily transition from sleep to wakefulness and task performance when aroused and then go back to sleep when not stimulated12 Locus Ceruleus is also origin for the descending medullospinal noradrenergic pathway an important modulator for nociception pathway. Dexmedetomidine exerts its analgesic effect through this pathway as well as through direct inhibition at spinal cord by inhibiting release of substance P13and is often used as an adjunct in neuraxial blockade to prolong the effects of the Local Anaesthetics14. Dexmedetomidine has moderate analgesic effect although the analgesic effect is not as strong when compared with fentanyl15 or remifentanyl[16].

Dexmedetomidine with its primary action on central alpha-2 receptors reduces the central sympathetic flow much like its predecessor drug clonidine and increases haemodynamic stability. This property can be applied to achieve better haemodynamic outcomes in surgeries where haemodynaic stability is a priority such as neurosurgeries, cardiac surgeries. The drug also provides moderate analgesia owing to its action on the Locus Ceruleus in the brain stem and thus has an opioid sparing effect. The reduced requirement of intra operative opioids can help to limit the side effects associated with these drugs. Dexmedetomidine has also been found to be neuro-protective and prevents neuronal cell injury. The hypnotic and sedative effects of α2-adrenoceptor activation have been attributed to the high concentration of α2- receptors in the locus ceruleus of the brain stem 17,18 , an area which is recognized to play a role in important brain functions including arousal, sleep, anxiety and drug withdrawal syndromes associated with CNS depressants such as opioids. Unlike traditional sedatives such as benzodiapenes or propofol, dexmedetomidine does not activate the GABA (gamma amino butyric acid) system. Bi Spectral Index (BIS) is an intra operative EEG based monitoring technique that helps to predict the possibility of intra operative awareness. It generates a number between 0 to 100. Keeping a BIS score of 40 to 60 during general anaesthesia can reduce the possibility of intra operative awareness and also prevent overdosing or under dosing of inhalational and analgesic drugs in that pursuit.

In our study we tried to evaluate the role of dexmedetomidine as an anaesthetic adjunct in patients undergoing surgery for brain tumor. As we know that Dexmedetomidine is known to have analgesic, sedative and sympatholytic effects. We have given dexmedetomidine as infusion in our patients.

Aim and Objective

Evaluation of dexmedetomidine as anaesthetic adjunct in patients undergoing craniotomy for excision of space occupying lesion. We measured BIS guided optimum dose of dexmedetomidine for infusion during intra operative course. Sedative/hypnotic effect of dexmedetomidine was measured as reduced intra operative requirement of inhalational agent isoflurane and analgesic effect of dexmedetomidine was measured as reduced requirement of intra operative opioids - fentanyl. We also observed the post operative sedation by Ramsay sedation score and any other side effect.

Material and Methods

In this double blinded randomized case control study, after taking ethical clearance from the ethical committee of King George Medical University. After informed consent, we have taken 75 cases from 18 to 65 years, both sexes with ASA grade 1 and 2 and Glasgow coma Scale (GCS) of 12 or more. We used "Bi Spectral Index (BIS) to guide Dexmedetomidine as an anaesthetic adjunct in patients undergoing craniotomy for excision for space occupying lesion admitted to the Department of Neurosurgery in King George Medical University, Lucknow, Uttar Pradesh from January 2016 to January 2017. All the patients were conscious, oriented before induction of anesthesia and posted for elective craniotomy of 4-5 hours for space occupying lesion. Patients not giving informed consent, hypertensive, history of coronary artery decease, angina pectoralis, peripheral vascular disease, cerebrovascular accident (CVA), thrombo embolism or hypersensitivity to dexmedetomidine or Fentanyl were excluded from the study.

Patients were randomly allocated into three groups (25 patients in each group) with the help of computer generated random number by Anaesthetist A- who would not be monitoring the patient intra operatively. On the day of surgery the solution of Dexmedetomidine was prepared by anesthetist A, by diluting 200µg/ml of drug with normal saline to a volume of 50ml to give a solution of 4 µg/ml. The screen of the infusion pump displaying infusion rate would be covered so that it is not visible to the Anaesthetist B – doing intra operative monitoring. After the patient was taken to the OR, all monitors were attached – Pulse-oximetry, ECG, invasive blood preesure, BIS and baseline readings were recorded following which the infusion was started by Anaesthetist A. Three groups were created. Group A received Dexmedetomidine loading dose at 0.5 microgram/ kg (µg/kg) in 10 minutes before induction followed by intra operative infusion at 0.5 µg/kg/hr. Group B received Dexmedetomdine loading dose at 0.5 µg/kg in 10 minutes followed by intra operative infusion at 0.3 µg/kg/hr. Group C was the control group received saline infusion only (for blinding).

After 10 minutes of loading dose, Anaesthetist A will change the rate of infusions and then leave the operating room. Then Anesthetist B will start induction of the patient for general anesthesia with help of fentanyl at 2µg/kg, propofol 2 milligram/kg (mg/kg), Vecuronium at 0.1 mg/kg. Maintanence of anaesthesia by oxygen and nitrous at 1:1 ratio with Isoflurane. We repeated Fentanyl 1µg/kg if heart rate or mean arterial blood pressure goes more than 20% of baseline values or BIS score more than 60 in spite of Isoflurane at 1vol%. We could only decreased the Isoflurane to maintain the BIS value between 40-60. The infusions were stopped 30 minutes prior to skin closure. Post extubation patient's level of sedation will be assessed with the help of Ramsay Sedation Score. We calculated the total consumption of fentanyl and Isoflurane and Ramsey sedation score.

STATISTICAL ANALYSIS - The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD. Chi square test was used to observed frequency and expected frequency. The ANOVA test was used to compare the within group and between groups.

We also used

Mann-Whitney U test. Level of significance "p" value was observed as $p > 0.05$ Not significant, $p < 0.05$- Significant, $p < 0.01$ - Highly significant, $p < 0.001$ - Very highly significant.

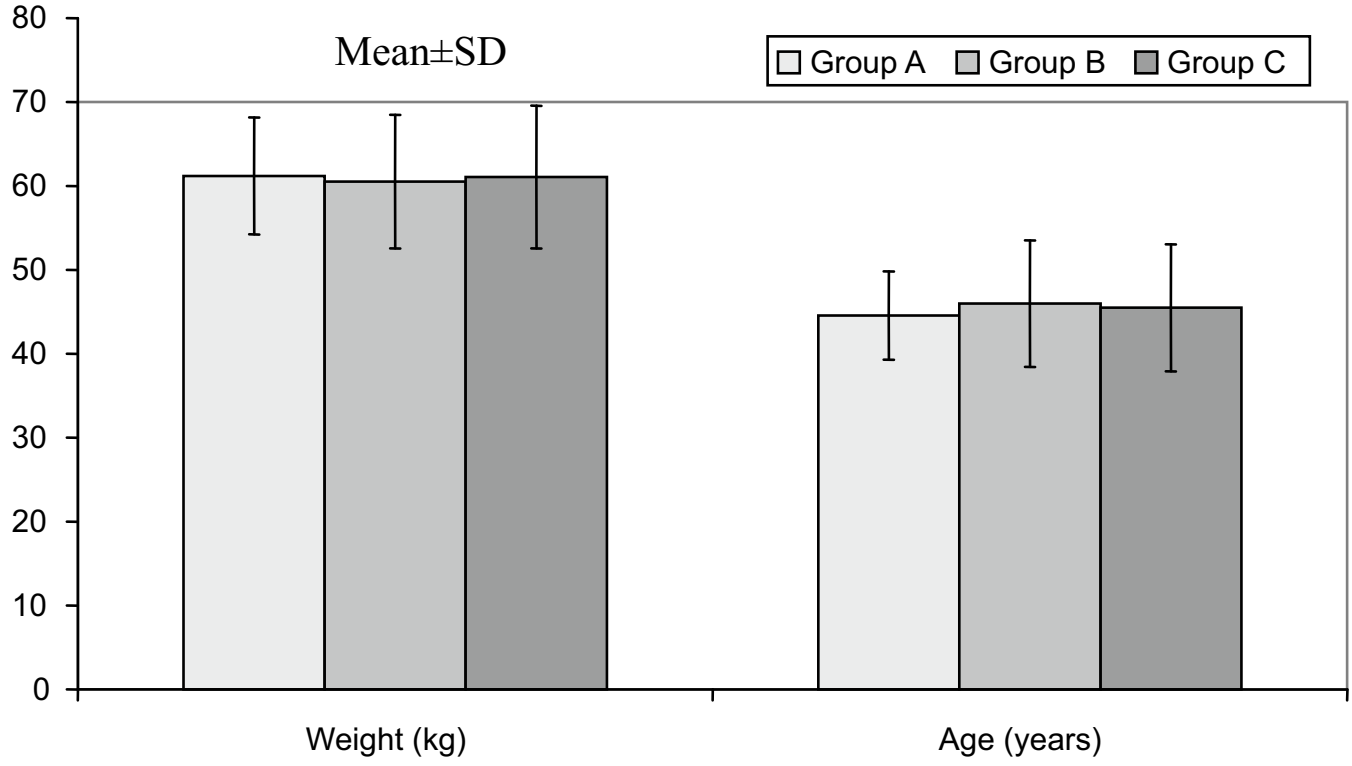
Observation and Results

Only 75 patients fulfilling the inclusion criteria were enrolled in the study and were randomly divided in three groups.

Table 1: Intergroup Comparison of Anthropometric and Demographic Variables of Study Population

Variables	Group A (n=25)		Group B (n=25)		Group C (n=25)		ANOVA	
	Mn	SD	Mn	SD	Mn	SD	F	P
Weight	61.20	6.97	60.52	7.95	61.08	8.51	0.054	0.948
Age (years)	44.56	5.26	46.00	7.54	45.48	7.58	0.281	0.756
Female vs Male (40:60)	36% vs 64%		44% vs. 56%		40.0% vs. 60%		c^2=0.333 (df=2); p=0.846	

Mean±SD



Difference in mean weight of the patients included in the study as Group A (61.20±6.97 kg), Group B (60.52±7.95 kg) and Group C (61.08±8.51) was not found to be statistically significant (p=0.948). Mean age of patients of Group A (44.56±5.26 years) and Group B (46.00±7.54 years) and Group C (45.48±7.58 years) were not found to be statistically significant. Proportion of males was higher in Group A (64%) as compared to Group B (56.0%) and Group C (60.0%) but this difference was not found to be statistically significant.

Table 2 (a): Intergroup Comparison of Bispectral Index (BIS) at different time intervals

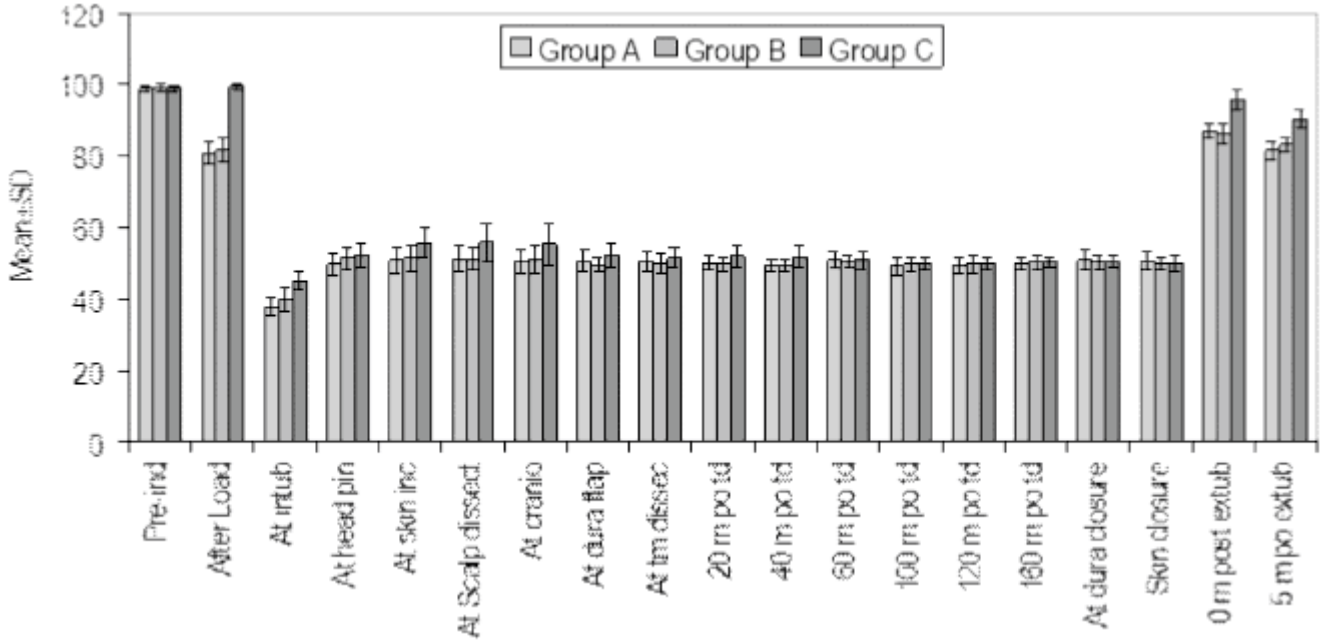
Time period	Group A			Group B			Group C			ANOVA	
	N	Mn	SD	N	Mn	SD	N	Mn	SD	F	P
Pre-ind	25	98.80	0.87	25	98.88	1.05	25	98.92	0.91	0.104	0.901
After Loading	25	80.84	2.85	25	81.64	3.23	25	99.36	0.70	431.817	<0.001
At intub	25	37.80	2.65	25	39.96	3.40	25	45.08	2.36	43.475	<0.001
At head pinning	25	49.68	2.85	25	51.56	3.10	25	52.20	3.27	4.531	0.014
At skin incision	25	50.84	3.78	25	51.48	3.62	25	55.72	4.08	11.982	<0.001
At Scalp dissect	25	51.28	3.52	25	51.24	3.11	25	55.96	5.22	11.190	<0.001
At cranio	25	50.68	3.41	25	50.92	4.02	25	55.36	5.92	8.296	0.001
At duramater flap	25	50.64	3.03	25	49.60	2.08	25	52.08	3.41	4.625	0.013
At tumor dissect	25	50.64	2.75	25	49.88	2.95	25	51.52	2.80	2.095	0.130
20 min post td	25	50.12	1.94	25	49.72	1.77	25	51.88	3.02	6.185	0.003
40 min post td	25	49.24	1.54	25	49.48	1.53	25	51.84	2.93	11.680	<0.001
60 min post td	25	50.88	2.28	25	50.36	1.82	25	50.96	2.57	0.526	0.593
100 min post td	25	49.12	2.28	25	49.80	1.94	25	50.12	1.67	1.669	0.196

120 min post td	25	49.16	2.29	25	49.80	2.40	25	50.00	1.83	1.009	0.370
160 min post td	18	49.89	1.68	14	50.43	1.95	4	50.25	1.26	0.380	0.687
At duramater closure	25	50.92	2.90	25	50.20	1.98	25	50.24	1.69	0.809	0.449
Skin closure	25	50.68	2.30	25	49.84	1.82	25	50.08	2.25	1.025	0.364
0 m post extub	25	87.04	1.86	25	86.36	2.77	25	95.72	2.57	115.145	<0.001
5 m post extub	25	81.56	2.43	25	83.20	2.02	25	90.32	2.63	96.244	<0.001

Table 2(b): Between Group Comparison of Bispectral Index (BIS) at different time intervals -

	Group A Vs. Group B			**Group A Vs. Group C**			**Group B Vs. Group C**		
	Mean diff.	**S.E.**	**'p'**	**Mean diff.**	**S.E.**	**'p'**	**Mean diff.**	**S.E.**	**'p'**
Preind	-0.08	0.27	0.952	-0.12	0.27	0.895	-0.04	0.27	0.988
After Loading	-0.80	0.71	0.503	-18.52	0.71	<0.001	-17.72	0.71	<0.001
At intubation	-2.16	0.80	0.024	-7.28	0.80	<0.001	-5.12	0.80	<0.001
At head pinning	-1.88	0.87	0.085	-2.52	0.87	0.014	-0.64	0.87	0.743
At skin incision	-0.64	1.08	0.826	-4.88	1.08	<0.001	-4.24	1.08	0.001
At Scalp dissect	0.04	1.15	0.999	-4.68	1.15	<0.001	-4.72	1.15	<0.001

At craniotomy	-0.24	1.29	0.981	-4.68	1.29	0.002	-4.44	1.29	0.003
At duramater flap	-1.04	0.82	0.417	-1.44	0.82	0.191	-2.48	0.82	0.009
At tumor dissect	0.76	0.80	0.612	-0.88	0.80	0.519	-1.64	0.80	0.109
20 min post td	0.40	0.65	0.814	-1.76	0.65	0.024	-2.16	0.65	0.004
40 min post td	-0.24	0.59	0.914	-2.60	0.59	<0.001	-2.36	0.59	<0.001
60 min post td	0.52	0.64	0.693	-0.08	0.64	0.991	-0.60	0.64	0.614
100 min post td	-0.68	0.56	0.447	-1.00	0.56	0.181	-0.32	0.56	0.835
120 min post td	-0.64	0.62	0.557	-0.84	0.62	0.367	-0.20	0.62	0.944
160 min post td	-0.54	0.63	0.668	-0.36	0.97	0.927	0.18	1.00	0.982
At duramater closure	0.72	0.64	0.498	0.68	0.64	0.536	-0.04	0.64	0.998
Skin closure	0.84	0.60	0.351	0.60	0.60	0.584	-0.24	0.60	0.917
0 m post extub	0.68	0.69	0.586	-8.68	0.69	<0.001	-9.36	0.69	<0.001
5 m post extub	-1.64	0.67	0.044	-8.76	0.67	<0.001	-7.12	0.67	<0.001



Baseline BIS (pre-induction after loading) of Group C was found to be higher than that of Group A and Group B (98.92±0.91 vs. 98.80±0.87 & 98.88±1.05) but differences were not found to be statistically significant.

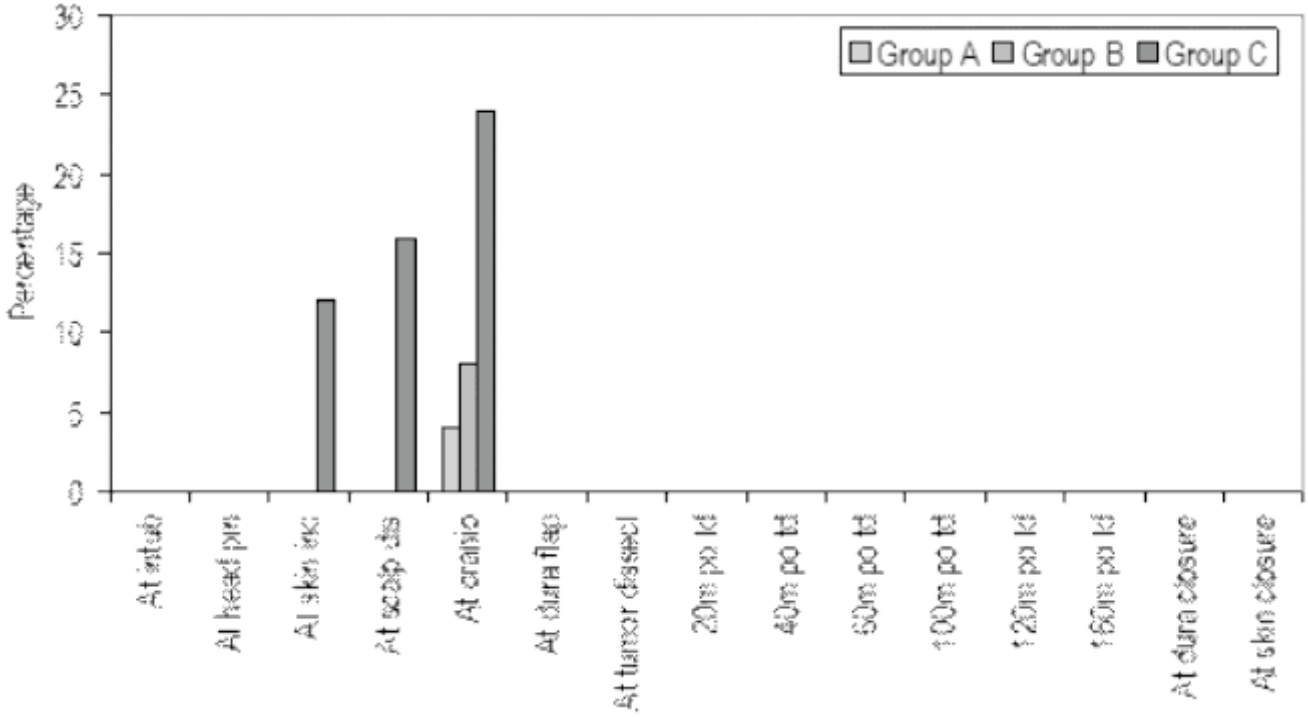
At rest of the periods of observation except at 160 minutes post tumor dissection (td), at duramater and at skin closure mean BIS of patients of Group C were found to be higher than that of Group A and Group B, though these differences were found to be statistically significant only at after loading to at duramater flap, at 20 & 40 minutes post tumor dissection, at extubation (0 min) and 5 minutes post extubation.

In Group A intubation BIS (78.36±3.33) was found to be higher than that of Group B (77.56±2.89) and Group C (76.36±3.08) but difference in BIS among patients of above three groups was not found to be statistically significant. On comparing BIS of patients of Group A & Group B, it was found that mean BIS of Group B patients were found to be higher than that of Group A at all the periods of observation except at scalp dissection, at duramater flap, at tumour dissection, at 20 min. post tumor dissection, at 60 minutes post tumor dissection, at duramater closure, at skin closure and at 0 minutes post-extubation. Difference in mean BIS of patients of Group A and Group B was found to be statistically significant only at 5 minutes post-extubation.

On comparing BIS of patients of Group A & Group C, it was found that mean BIS of patients of Group C was found to be higher than that of Group A at all the periods of observation except at duramater closure and at skin closure. Difference in mean BIS of patients of Group A and Group B was found to be statistically significant at after loading, at intubation, at head pinning, at skin incision, at scalp dissection, at craniotomy, at 20 minutes post tumor dissection, 40 minutes post tumor dissection, at 0 minutes post extubation and at 5 minutes post-extubation.

Table 3: Intergroup Comparison of Requirement of Repeat dose of fentanyl in Study Population at different time periods

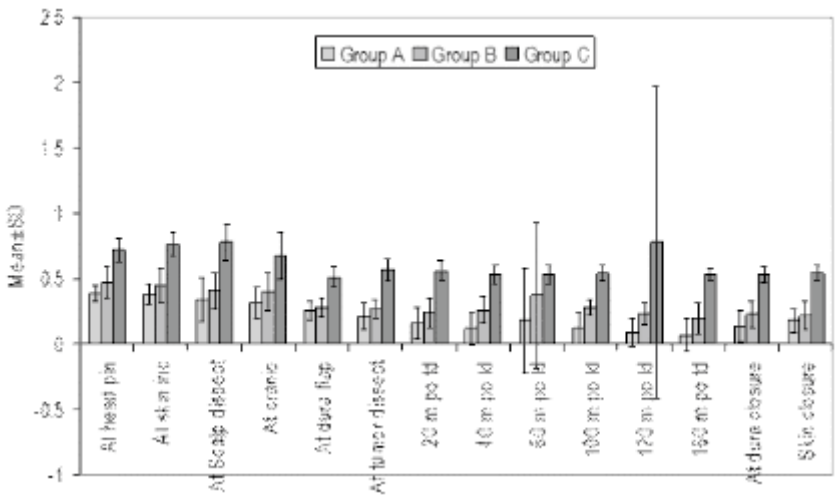
Time	Group A			Group B			Group C			Chi-square test	
	Total	Fent. Reqd	%	Total	Fent. reqd	%	Total	Fent. Reqd	%	c^2	P
At intubation	25	0	0.00	25	0	0.00	25	0	0.00	–	–
At head pinning	25	0	0.00	25	0	0.00	25	0	0.00	–	–
At skin incision	25	0	0.00	25	0	0.00	25	3	12.00	6.250	0.044
At scalp dissect	25	0	0.00	25	0	0.00	25	4	16.00	8.451	0.015
Atcraniotomy	25	1	4.00	25	2	8.00	25	6	24.00	5.303	0.071
At duramater flap	25	0	0.00	25	0	0.00	25	0	0.00	–	–
At tumor dissect	25	0	0.00	25	0	0.00	25	0	0.00	–	–
20 m post td	25	0	0.00	25	0	0.00	25	0	0.00	–	–
40 m post td	25	0	0.00	25	0	0.00	25	0	0.00	–	–
60 m post td	25	0	0.00	25	0	0.00	25	0	0.00	–	–
100 m post td	25	0	0.00	25	0	0.00	25	0	0.00	–	–
120 m post td	25	0	0.00	25	0	0.00	25	0	0.00	–	–
160 m post td	18	0	0.00	14	0	0.00	4	0	0.00	–	–
At duramater closure	25	0	0.00	25	0	0.00	25	0	0.00	–	–
Atskin closure	25	0	0.00	25	0	0.00	25	0	0.00	–	–



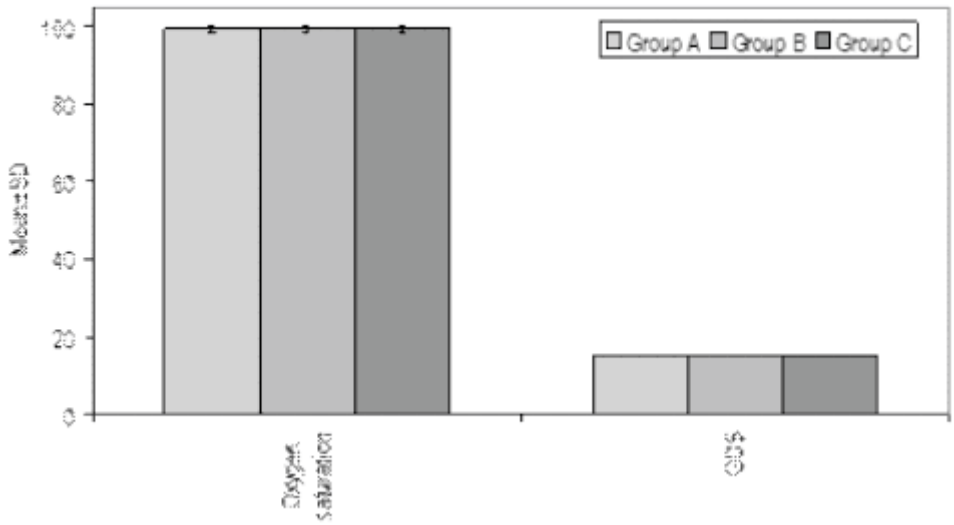
Requirement of repeat dose of fentanyl was observed only at skin incision, at scalp dissection and at craniotomy. Proportion of patients requiring repeat dose of fentanyl was higher in Group C as compared to Group A & Group B at skin incision (12.00% vs. 0.0% & 0.0%), at scalp dissection (16.00% vs. 0.0% & 0.0%) and at craniotomy (24.00% vs. 4.00% & 8.00%). Difference in requirement of repeat dose of fentanyl among patients of above three groups were statistically significant at skin incision and at scalp dissection only.

Requirement of Isoflurane was always higher in Control group C in comparison to Group A and GroupB. In group A an infusion dose of 0.5µg/kg/hr intra operatively decreases requirement of inhalational agent more than an infusion of 0.3 µg/kg/hr in group B. Dexmedetomidine was suffice as the sole anaesthetic agent with an infusion dose of 0.5µg/kg/hr during less painful parts of surgery such as tumor dissection.

Fig 4. Comparison of Isoflurane Volume Percentage at different time intervals -



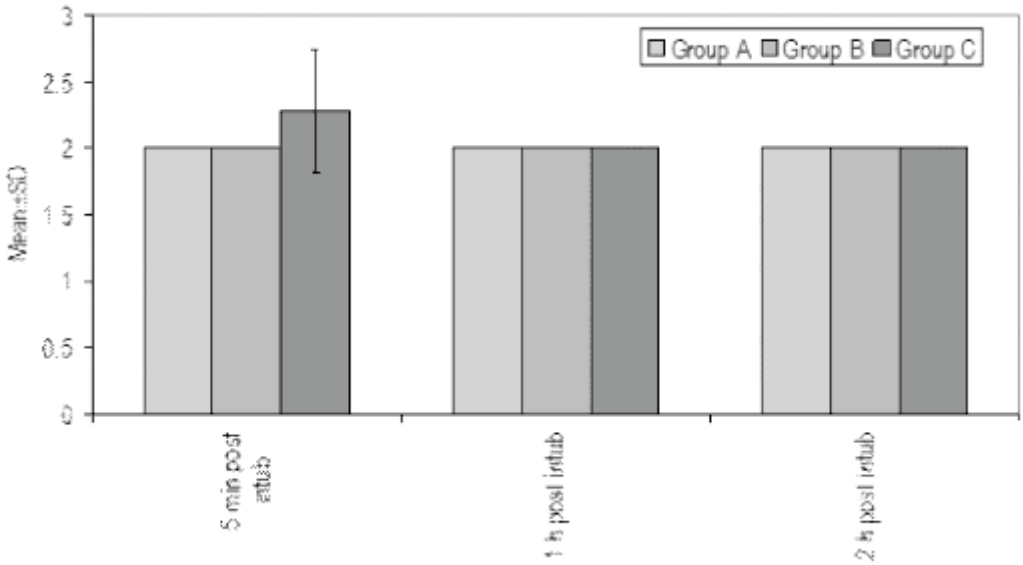
There were no deference in Oxygen saturation and GCS at pre-induction in all study groups.



GCS score of all the patients included in the study was 15.
No intergroup or between group differences in GCS were observed.

Table 5: Between Group Comparison of Ramsey Sedation Score at 5 minutes post-intubation -

Group	Mean diff.	SE	Z	P
Group A Vs. Group B	0.00	0.08	**0.000**	**1.000**
Group A Vs. Group C	0.28	0.08	**2.824**	**0.005**
Group B Vs. Group C	0.28	0.08	**2.824**	**0.005**



Ramsey sedation score(RSS) at 5 min post-intubation of all the patients of Group A and Group B was 2 i.e. range 2-2, median 2 and mean±SD while that of Group C ranged from 2-3, median 2. Mean RSS of Group C (2.28±0.46) was found to be significantly higher than that of Group A (2.00±0.00) and Group B (2.00±0.00). At 1 hr and 2hr post-extubation RSS of all the patients irrespective of any group was 2. (Table 4)

Discussion

Neurosurgery case brings additional responsibility on the anaesthetist to ensure a good outcome. Various parts of the surgery such as intubation, head pinning, scalp dissection and craniotomy predispose the patients to increase in intracranial pressure (ICP). In addition a neurological examination is required immediately after extubation. For this we need a lighter plane of anaesthesia and hence increased risk of bucking/biting of the endotrachial tube by the patient and further increase in intracranial pressure (ICP) and there are risks of bleeding or oedema at operative site. Inhalational agents and opioids are conventionally used to blunt the haemodynamic responses intra operatively, airway and haemodynamic responses during recovery and extubation – but these have their own side effects.

This study "Bi Spectral Index (BIS) guided evaluation of dexmedetomidine was undertaken in the intra operative setting to analyse the beneficial properties for improved outcome in brain tumor cases. The available literature about the dexmedetomidine have characterized its "rousable" sedative effect, modest analgesic effect, sympatholytic effect and neuro protective effect. Our study had a sample size of 75 with 25 cases in each group. Difference in mean weight (p=0.948) and age (p=0.756) of the patients included in the study was not found to be statistically significant. Majority of the patients included in the study were males and rest were females. The increased number of the male population in all the groups is possibly supported by the increased incidence of brain tumors in male population.

Zhang et al.19 in 2015 recommended using either 0.4μg/kg or 0.5 μg/kg dose of dexmedetomidine as the initial loading dose. The works of Afsani et al.20 recommended that loading dose of dexmedetomidine of 1.0 μg/kg in time of less than 10 minutes leads to transient hypertension-"biphasic response" by stimulation of peripheral alpha receptors. High dose can lead to bradycardia in young patients with high vagal tone. Considering the results from the above mentioned studies, the loading dose in our study for the dexmedetomidine group was thus kept as 0.5μg/kg given over a period of 10 minutes. There was no significant decrease in heart rate or mean arterial pressure during the infusion time. No cases reported bradycardia during loading dose infusion. An important thumb rule to guide intra operative management of any case for successful outcomes is to give just the appropriate amount of drugs needed to maintain stable hemodynamics while preventing intra operative awareness. It is difficult to establish what is "adequate" if we rely only on the clinical parameters as discussed previously.

Intra operative EEG monitoring such as Bispectral Index (BIS) used in our study comes closest to a parameter that can guide the administration of anaesthetic drugs by titrating the dosages to minimum and at the same time preventing the possibility of intra operative awareness because it monitors the brain activity – the site of most anaesthetic sub-states such as sedation, amnesia, hypnosis, analgesia. In several studies conducted, BIS was found helpful in titrating the anaesthetic drugs and prevented the possibility of under dosing to prevent awareness and overdosing in a pursuit to prevent awareness21 and lead to early patient recovery22. Virtanen et al.23 in 1988 studied characterization of selectivity, specificity and potency of

medetomidine as alpha 2-adrenoceptor agonist. In our study, at the time of extubation patients in the dexmedetomidne group had stable hemodynamicaly. The BIS values after the loading dose dropped to 80.84+/- 2.85 in group A and 81.64+/-3.23 in group B which was not statistically significant but when the BIS score of the two groups were compared with the control group BIS values of 99.36+/- 0.76 there was a significant decrease in the BIS values ($p<0.01$). Study conducted by Brown et al.24 where the administration of dexmedetomidine (at 0.1µg/kg/min.) produced a reduction in BIS values from 95 +/- 4 to 85 +/- 6 at the end of the 10 minutes infusion period. The onset of the sedative effect of dexmedetomidine became evident in significant BIS changes beginning at approximately 7 minutes of the infusion. These results are similar to our study where the BIS scores dropped after the loading doses of dexmedetomidine infusion. In other studies effect of dexmedetomidine infusions on BIS values are mostly available after a loading dose of 1 µg/kg over 10 minutes. Here we used a dose of 0.5µg/kg in 10 minutes therefore our study may add more information to the literature in this regard. With the help of BIS, during tumor dissection we were able to decrease the isoflurane administration to the extent that isoflurane was used at low value of 0.2 to 0.4 volume % (group A and group B) or completely stopped (group A). This was possibly because dexmedetomidine provided adequate sedation as reflected by adequate BIS values.

We would also like to mention an observation that due to the sympatholytic effects of dexmedetomidine heart rate and blood pressure did not increase when patients were experiencing pain during craniotomy, it was high BIS values >60 that were not responding to increase in isoflurane concentration that caught our attention and when repeat dose of fentanyl was administered the BIS scores settled to <60 and isoflurane requirement was also subsequently decreased. Therefore patients may experience pain without evidence of tachycardia or hypertension therefore we recommend EEG monitoring (BIS in our case) for proper intra operative management.

Not a single patient recalled any intra operative events. With the help of BIS, dose titration was a possible for inhalational and opioid in all the groups. In our study Isoflurane requirement as an inhalational agent was statistically significantly higher in Group C as compared to Group A and Group B at all the periods of observation from head pinning to skin closure.

It is well known from the literature present on dexmedetomdine that the drug has opioid sparing effects. In our study Requirement of repeat dose of fentanyl was observed only at skin incision, at scalp dissection and at craniotomy. Proportion of patients requiring repeat dose of fentanyl was higher in Group C as compared to Group A & Group B at skin incision (12.00% vs. 0.0% & 0.0%), at scalp dissection (16.00% vs. 0.0% & 0.0%) and at craniotomy (24.00% vs. 4.00% & 8.00%). In all three group difference in repeated dose requirement of fentanyl were statistically significant at skin incision and at scalp dissection only.

Our study results were also consistent with the study done by Scheinin et al.25, where during surgery, fentanyl was required in a dose of 0.5 µg/kg and 2.8 µg/kg in the dexmedetomidine and control groups, respectively. In the study by Aho et al.26, fewer(4%) patients in the dexmedetomidine group (dexmedetomidine single dose of 0.6µg/kg) required intra operative dose of fentanyl as compared to saline group (29%) and fentanyl group (25%). Similar finding were observed in our study with majority of Group C patients requiring repeat analgesia (52%) as compared to dexmedetomidine groups(group A – 4% , group B – 8 %). Thus, in our study the control group patients required repeat dose earlier at skin incision or scalp dissection and more patients in control group required repeat analgesia.

Ramsay sedation score was taken at 5 minutes post exubation and at 1 and 2 hours post extubation. Ramsay sedation score was 2 in all the patients in both the dexmedetomidine group. In control group it was either 2 or 3. Thus patients in the dexmedetomidine group displayed better sedation score 5 minutes post extubation. There was no difference in the sedation score 1hour or 2 hour post extubation. An important point of observation here is that even though BIS was kept between 40 to 60 intra operatively for all the groups, still patients in group C appeared more drowsy(as reflected by higher Ramsay sedation score) and took longer time to open eyes and get oriented than both the dexmedetomidine group patients. This is probably because of the "rousable" sedative effect of dexmedetomidine.

Postoperative complications such as nausea, vomiting and shivering affect postoperative comfort. Several studies have shown that dexmedetomidine reduces postoperative shivering. Aantaa et al. conducted to investigate nausea-vomiting, the dexmedetomidine group required fewer antiemetics than the control group. In their study, no patient in group Dexmedetomidine exhibited nausea, vomiting or shivering. However, in group Fentanyl, shivering was observed in three patients, and nausea was observed in two patients. In our study we did not have any patient reporting post operative nausea or vomiting, shivering in any of the groups.

There are certain limitations to our study. Our study did not include ASA 3 or 4 patients, hypertensive or ischemic heart disease patients, patients less than 18 years or more than 60 years. Possibly in future studies patients from these profiles will be taken and more information could be obtained regarding the feasibility of dexmedetomidine application to such patients. Aantaa et al. showed that when 1 μg/kg of dexmedetomidine was used as premedication, the thiopental dose necessary for the induction of anesthesia was reduced by 55%. In our study we had used a fixed dose of thiopental, so we were not able to comment on the reduction in the doses of thiopental. In our study we measured consumption of isoflurane as volume %. A better approach would have been to use gas monitoring with the help of gas analysers which could have more accurately reflected isoflurane requirements.

In the end we would conclude with the following - Dexmedetomidine when used as a loading dose of 0.5 μg/kg in 10 minutes does not lead to any adverse haemodynamic or respiratory events and causes sedation as reflected in decreased BIS scores after the loading dose. If used as an intra operative infusion, it blunts the sympathetic response to laryngoscopy and intubation, head pinning, scalp dissection, craniotomy, tumor dissection and extubation. There is significant reduction in the requirement of inhalational agent and opioid analgesia during surgery.

An infusion dose of 0.5μg/kg/hr intra operatively decreases requirement of inhalational more than an infusion of 0.3 μg/kg/hr and may suffice as the sole anaesthetic agent with an infusion dose of 0.5μg/kg/hr during less painful parts of surgery such as tumor dissection. It also provides modest analgesic effect and delay and reduce requirement of repeat analgesia as compared to control groups.

Patients given dexmedetomidine infusions are calm and co-operative during extubation with stable hemodynamics and show less incidence of tube biting/bucking as compared to control group. Post extubation, patient are adequately sedated as reflected by Ramsay sedation score. BIS can serve as an indispensable tool to titrate the reduction in inhalational and analgesic requirement to improve outcome while recovering from anaesthesia without risking the possibility of intra operative awareness. In situations when sympatholytic effects of dexmedetomidine can blunt the haemodynamic response during pain or

other form of intra operative awareness, higher BIS values can help to detect them.

Conclusion

The study conducted that the dexmedetomidine, a centrally acting alpha 2 agonist, which has generated much interest owing to its good sedative and analgesic effect without the risk of respiratory depression and a characteristic rousable sedation - properties not seen in sedative agents of other classes.

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GUIDELINES TO CONTRIBUTORS

Asian Archives of Anaesthesiology and Resuscitation (AAAR) was started in 1971 by initiative of late Prof. W.E. Spoeral of University of Western Ontario, London. He visited JIPMER, Pondicherry in 1970-71 and helped in starting this journal .Since then, AAAR was published under able guidance of (late) Prof. N.P. Singh continuously till date.

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Acknowledgements
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References

1. References correspond to the specifications of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals" promulgated by the International Committee of Medical Journal Editors.
2. References are identified in the text by superscript figures, eg., Miller.
3. Each reference is cited in the text. Those appearing in tables and figures should be cited in the text where the table or figure is mentioned.
4. References are numbered consecutively in the order in which they appear in the text. (Vancouver Style)
5. Unpublished data, personal communications, submitted manuscripts, statistical programs, papers presented at meetings, and non–peer-review publications are not listed in the bibliography.
6. he bibliography is typed double–spaced.
7. Abbreviations of Journal titles conform to those used in Index Medicus, National Library of Medicine.

Tables

1. Each table is typed on a separate sheet of paper with its title.
2. Tables are numbered with Arabic numerals.
3. Each table contains all necessary information in order that it may stand alone, independent of the text.
4. No table contains data that could be included in the text in several sentences.
5. Vertical lines are not used.
6. Irrelevant and extra tables must not be included

Figures

1. Each figure is cited in the text.
2. Two sets are submitted of glossy prints of sonographs, photomicrographs, radiographs, color illustrations, or any other figure that might not reproduce well.
3. Two sets of glossy prints of other figures are submitted.
4. Figures have been prepared with the journal column size in mind.
5. Letters and identifying marks are clear and sharp, and the critical areas of radiographs and photomicrographs are identified.
6. Legends and explanatory material appear in the accompanying caption and not no the figure itself.
7. Legends are typed together on one page. Legends for photomicrographs include information regarding stain and magnification.
8. Nothing is written on the back of the figures. An adhesive label, designating the top, with the first author's name and number of the figure, is attached firmly to the back of the illustration.
9. Figures are placed in a labeled envelop. No glue, paper clips or tape has been used on art.