

TITLE:

Comparison of postoperative delirium in patients anaesthetised with Isoflurane and Desflurane during spinal surgery

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ABBREVIATIONS

ASA-American Society of Anaesthesiologists

BP-Blood pressure

CAM-Confusion assessment method

CBF- Cerebral blood flow

CDT-Clock drawing test

CMR- Cerebral metabolic rate

CMRO₂.Cerebral metabolic rate of Oxygen consumption

CNS-Central nervpus system

GA-General anaesthesia

GCS- Glasgow Coma Scale

Hb-Hemoglobin

MAC-Mean alveolar concentration

MMSE-Mini mental state examination

NMT-Neuromuscular transmission

NRS-Numerical rating score

POD-Post operative delirium

INTRODUCTION

In simple words delirium is defined as a temporary state of confusion . It is characterized by acute onset, fluctuating course, inattention, disorganized thinking, altered level of consciousness, perceptual disturbances, psychomotor disturbances, altered sleep-wake cycle, and emotional disturbances¹. Postoperative delirium (POD) is disturbance of consciousness seen 24 to 72 hours after surgery. Its incidence varies from 5% to 15% but in high-risk groups such as cardiac and orthopedic patients, the range is 16–62%². Postoperative delirium is not only distressing for patient but also for family members. It is associated with functional decline, need for prolonged nursing care and prevent functional recovery. Hence it leads to prolonged duration of hospital stay and adds to morbidity and mortality in the long term. Exact mechanism responsible for POD is not known but several risk factors are found to be associated with POD. This includes patient related, surgery related and anesthesia related factors.

The incidence of POD in spine surgery in previous studies was found to be between 3.3% to 3.8%^{3,4}. Spine surgeries are associated with significant postoperative pain, blood loss, long duration of surgery and all these factors may be associated with POD after spine surgeries^{2,5,6,7,8}. But for the smooth conduct of spine surgery general anesthesia (GA) is required. During general anesthesia either inhalational volatile agents or intravenous hypnotic agents are used. However effect of the type of anesthetic agents in spine surgeries on postoperative delirium have not been studied previously. Both isoflurane and desflurane are commonly used inhalational agents. Now a days many centers prefer to use desflurane over isoflurane due to its low blood gas solubility which results in faster emergence. Among the inhalational volatile agents, previous studies have

compared the incidence of postoperative delirium with sevoflurane and desflurane especially in children and elderly individuals. But no study has compared the incidence of postoperative delirium with isoflurane and desflurane in middle aged adults undergoing spine surgery .

Desflurane is associated with faster emergence and lesser incidence of postoperative cognitive dysfunction compared to isoflurane^{9,10}. Animal studies have shown that prolonged exposure to isoflurane to be neurotoxic^{11,12,13,14,15}. We hypothesize that the adverse neurological outcomes associated with isoflurane compared to desflurane may be associated with an increased incidence of postoperative delirium. Hence we are conducting this study to compare the occurrence of postoperative delirium with Isoflurane and Desflurane in spine surgery patients.

REVIEW OF LITERATURE

Brain functions are known to be affected during immediate postoperative period after exposure to anesthesia. These effects vary from depressed levels of consciousness with impairment of attention and memory to complete amnesia for several hours. Cognitive disturbances commonly seen in postoperative period are delirium and cognitive disturbances.

Prolonged exposure to anesthetics can lead to neuroapoptosis and neurocognitive problems^{11,12,13,14,15}. However, other studies suggest that even low nonapoptotic concentrations of general anesthetics may inhibit normal synapse formation and damage developing neuronal networks¹⁶. Mechanisms underlying neurodevelopmental toxicity are potentially linked to the same ion channels hypothesized to mediate general anesthesia. General anesthetic actions are attributed in part to both antagonism of *N*-methyl-d-aspartate receptor and potentiation of GABA-A receptor signal transduction, and drugs with either or both of these activities damage developing brains^{17,18,19}.

POST OPERATIVE DELIRIUM-

American Psychiatric Association defines delirium as an acute change in cognition or disturbance of consciousness that cannot be attributed to a pre-existing medical condition, substance intoxication or medication. However various conditions such as age, functional status and substance abuse influence the risk of immediate and post operative delirium. Delirium in the

postoperative period can be divided into emergence delirium and post operative delirium depending on the time of presentation. Emergence delirium or emergence agitation is usually observed immediately after GA and is related to anesthetic drugs. It is common in children with peak age being 2-4 years. It is accompanied by psychomotor agitation which includes a series of unintentional and purposeless motion like pacing around a room, wringing ones hands, pulling off clothing, and self-extubation. It usually occurs within the first 10 minutes of recovery and resolves within minutes to hours without long term neurological effects. It is more commonly associated with less soluble inhalational anaesthetics like sevoflurane and desflurane.

Postoperative Delirium(POD) usually presents 24-72 hours following a lucid interval. It usually resolves within hours to days. Post operative delirium can have lasting effects beyond the perioperative period. POD has also been associated with postoperative depression, posttraumatic stress disorder-like syndrome which may impede recovery. As a result, delirium may have long-term mental health complications²⁰.

POD has been previously reported to occur following several kinds of surgery, including general surgery , head and neck cancer surgery, cardiac surgery , vascular surgery , hip fracture and joint replacement surgery^{21,22,23,24,25,26,27}.The incidence of post operative delirium(POD) in various studies ranges from 5% to 15%.Within certain high-risk groups such as hip fracture patients, the range is 16–62% with an average of 35%². The incidence of POD in spine surgery in previous studies was found to be between 3.3% to 3.8%^{3,4}.

RISK FACTORS FOR POSTOPERATIVE DELIRIUM-

The mechanism of postoperative delirium is not clear. However ,studies have shown that major risk factors include age >70 years, pre-existing cognitive impairment, preoperative use of narcotics

or benzodiazepines, previous history of POD, alcohol abuse, breast and abdominal surgeries, long duration of surgery and preoperative cognitive dysfunction^{2,6,7,8}. Precipitating factors include: the use of physical restraints, malnutrition, the use of a urinary bladder catheter and electrolyte and fluid abnormalities. Specific perioperative risk factors include greater intraoperative blood loss, more postoperative transfusions, and postoperative haematocrit of <30%.

Severe acute pain regardless of the method of analgesia (opioid type, method and dose) is associated with POD. Certain types of injury, particularly hip fractures, and serious illness requiring intensive care are also associated with a high incidence of delirium². Several factors with positive correlation with POD may also suggest an association with preoperative anxiety.

Incidence of POD was greater with inhalational anesthetic agents than with propofol². Other risk factors of delirium include vision impairment, severe illness, cognitive impairment, and serum urea nitrogen: creatinine ratio of 18 or greater, vascular risk factors (tobacco use and vascular surgery), decreased cerebral perfusion, low preoperative executive scores and depressive symptoms, pre-existing attentional deficits in non-demented patients². Previous history of illness and long term treatment with antidepressants were associated with a decreased risk for POD^{2,3,4}.

PHARMACOLOGY OF ISOFLURANE-

Isoflurane is a volatile anaesthetic agent. Chemically it is 2-chloro-2-(difluoromethoxy)-1,1,1-trifluoro-ethane. It has a boiling point of 48.5 degree Celsius and a vapour pressure of 238 mm Hg. The blood /gas partition coefficient of isoflurane is 1.4 at 37 degree Celsius and MAC – immobility is 1.28 mm Hg. At concentrations greater than 1 MAC, isoflurane increases CBF and intracranial

pressure. Isoflurane reduces cerebral metabolic oxygen requirements, and at 2 MAC, it produces an electrically silent electroencephalogram(EEG).

Many animal studies have demonstrated the neurotoxic effects of isoflurane-

Studies have demonstrated that there was increased apoptotic cellular degeneration and neurodegeneration following isoflurane exposure in neonatal mice and rhesus monkeys^{11,12,14,15}.Liu J. et al demonstrated that in young adult mice,iisoflurane may cause neurotoxicity by inducing caspase activation and apoptosis with the anesthetic concentration increased and duration prolonged. High concentration of isoflurane exceeding 4 hours may induce a decline of NR2B and ratio of pERK1/2 to ERK1/2 resulting in cognitive impairment¹³.

There are studies which have also demonstrated neuroprotective effects of isoflurane. Liu J. et al demonstrated that in young adult mice ,low concentration of isoflurane in 2 hours can induce a hippocampus-specific elevation of NR2B subunit composition and ratio of p-ERK1/2 to total ERK1/2,thereby producing hippocampal-dependent cognitive improvement¹³.Engelhard K et al demonstrated that desflurane and isoflurane improve neurological outcome after incomplete cerebral ischaemia in rats²⁸.Milner E et al demonstrated improved neurological outcome in subarachnoid haemorrhage in mice with isoflurane²⁹.

PHARMACOLOGY OF DESFLURANE-

Desflurane ,a volatile anesthetic agent was introduced into clinical practice in 1992. Chemically it is fluorinated methyl ethyl ether. Two most important physical properties of desflurane are that it has a boiling point of 22.8⁰C and a vapour pressure of 664 mmHg. So it boils at room temperature and hence a special vaporizer is required to deliver desflurane. It has a blood/gas partition coefficient of 0.45 at 37 degree Celsius which is the least among the inhalational agents and a MAC- immobility of 6.0 mmHg. This favors rapid achievement of alveolar concentration

necessary for production of anesthesia followed by rapid recovery on discontinuation. This anesthetic property makes it a favourable anesthetic agent for neurosurgery.

Central nervous system (CNS) actions: Desflurane decreases cerebral metabolic rate (CMR) by 35%. Cerebral blood flow (CBF) may increase or decrease depending on concentration used. At 1 minimum alveolar concentration (MAC), desflurane decreased CMRO₂ by 50%, CBF by 22% and at the same time cerebrovascular reactivity is preserved. Desflurane has been found to be neuroprotective in certain animal studies²⁸. The mechanism of neuroprotection involves reduction of glutamate, potentiation of GABA receptors, regulation of intracellular calcium responses and activation of potassium channels. However it may raise ICP more than isoflurane, hence it should be used cautiously in patients with unstable ICP.

AIMS OF THE STUDY-

- 1)To compare the incidence of postoperative delirium with isoflurane and desflurane on adults undergoing spine surgery .
- 2)To determine the perioperative factors which can influence postoperative delirium.

MATERIALS AND METHODS

The proposed study will be a prospective randomized clinical trial. It will be carried out for a period of 15 months from January 2016 to June 2017 in 60 adult patients scheduled for spine surgery at PGIMER, Chandigarh. Ethical clearance will be sought from the human and ethics committee of the institute. Written informed consent will be taken from all the patients. The patients will be randomly divided into two groups of 30 each - Group I (Isoflurane) and Group D (Desflurane) prior to surgery.

Selection of patients-

Inclusion criteria

- Patients scheduled for spine surgery.
- Age between 18-65 years
- American Society of Anaesthesiologists (ASA) Grade I and II patients
- Patients with Glasgow Coma Scale (GCS) of 15
- Postoperative Aldrette score > 9

Exclusion criteria

- Cardiorespiratory disorders
- Associated cerebral disease
- Psychiatric illness
- Electrolyte and hormonal imbalance
- History of drug abuse

- Postoperative meningitis
- Administration of high dose steroids

Randomization and blinding

Randomization will be done using computer-generated random numbers. The patient will be randomized to receive isoflurane or desflurane anaesthesia prior to surgery. All the patients involved in the study will be blinded to group allocation. The physician administering anaesthesia will be presented with envelopes containing the random numbers with the assigned groups just prior to surgery. The investigator will be blinded to group allocation.

Anaesthesia Protocol

All the preoperative medications will be continued on the day of surgery. Anaesthesia will be induced with propofol 2-2.5 mg/kg and fentanyl 2 ug/kg. Vecuronium 0.1 mg/kg will be to facilitate endotracheal intubation. All the patients will be monitored with 5 lead electrocardiogram, pulse oximeter, non-invasive blood pressure, temperature, airway gas levels, end-tidal carbon-dioxide concentration and urine output. Maintenance of anaesthesia will be carried out with either isoflurane or desflurane as per the randomization. The depth of anaesthesia will be monitored using entropy (to keep state entropy between 40 and 60). Analgesia will be maintained with fentanyl 0.5-2 ug/kg/hour and Vecuronium 0.06 mg/kg will be used intermittently for neuromuscular blockade to maintain less than two twitch response on neuromuscular transmission (NMT) monitoring. Replacement fluid will consist of normal saline. Intraoperative haemodynamics, oxygen saturation, temperature and blood loss will be recorded and compared among the two groups. The patients will be administered an antiemetic intraoperatively. At the end of the procedure neuromuscular blockade will be antagonized with neostigmine (0.05mg/kg)

and glycopyrrolate (0.01mg/kg). The patients who cannot be extubated at the end of the procedure will followed up in the postoperative period. The patients who cannot be extubated within forty-eight hours following surgery will be excluded from the study.

Study protocol

The screening for preoperative cognitive dysfunction will be done using the mini-cog test which includes a three word recall test and clock drawing test. The patients with preoperative cognitive dysfunction will also be included. The primary outcome variable will be assessment of delirium at day one and day three following surgery. Post operative delirium will be diagnosed using the 3D-CAM(Confusion Assessment Method) which tests for four features with a series of questions. The features include 1) acute onset and fluctuating course,2) inattention,3) disorganized thinking and 4) altered level of consciousness. Diagnosis of delirium is made if features 1 and 2 and either 3 or 4 are present. Similarly the severity of POD will be assessed on day one and day three following surgery. Severity of postoperative delirium will be assessed using the CAM-S long form delirium severity score.It assesses ten features including 1) acute onset and fluctuating course,2)inattention,3)disorganized thinking , 4)altered level of consciousness, 5) disorientation, 6)memory impairment ,7)perceptual disturbances ,8)psychomotor agitation, 9)psychomotor retardation and 10) altered sleep-wake cycle. The scores range from 0 to 19.

The demographic data of the patients,type and site of surgery will be noted. Preoperative hemoglobin, serum electrolytes, blood urea and serum creatinine will be recorded. The average of 3 blood pressure (BP) readings measured preoperatively will be recorded as baseline. Intraoperative hemodynamics will be monitored using non invasive blood pressure monitoring. Systolic BP <30% of baseline will be recorded as hypotension and systolic BP >30% will be

recorded as hypertension. The management of intraoperative hypotension and hypertension will be at the discretion of the attending anaesthesiologist. The intraoperative factors like duration of surgery and anaesthesia, use of intravenous fluids , blood loss, number blood units transfused and opioid use will be studied at the time of surgery. The time to emergence and extubation following the completion of surgery will be noted. Emergence time will be the time from cessation of anesthetic agent to the time the patient responds to verbal commands. Extubation time will be the time interval between cessation of anesthetic agent and extubation of trachea.

The postoperative factors like postoperative pain, nausea and vomiting, fever, hemoglobin, serum electrolytes, blood urea and serum creatinine will be noted.

Preoperative and postoperative pain will be assessed using the numerical rating score on a scale of one to ten.

The association of various preoperative, intraoperative and postoperative factors with POD will be determined.

STATISTICAL ANALYSIS-

Sample size calculation-

Incidence of POCD was 0% and 27% in a previously conducted study with 15 patients in each group with the use of desflurane and isoflurane respectively and the reported p value was 0.028.⁶

We used these results to calculate sample size in our study to prove superiority of desflurane over

isoflurane with a margin of atleast 5 percent using an alpha error of 0.05 and power of 85%.The estimated sample size was 60 with 30 in each arm.

STATISTICAL ANALYSIS

All analysis will be done using SPSS version 22 (SPSS Inc., Chicago, IL, version 16.0 for Windows). Descriptive statistics will be obtained for demographic patient related and treatment related variables. The variance between both the treatment groups will be analysed using two way ANOVA. The primary end points will be compared between the two groups using chi square statistics. As a secondary outcome measure, univariate and multivariate analysis will be done to identify the factors that may influence post operative delirium.

ORGANIZATION OF WORK ELEMENTS

1. Preoperative Workup

- a) Recruitment of patients as per the inclusion-exclusion criteria
- b) Informed written consent from patient for participation in the study
- c) The patient will be assigned a computer generated random number for allocation to the study group.
- d) Demographic details and relevant details will be recorded.
- e) Pain scores will be assessed using the numerical rating score
- f) Cognitive function will be assessed using the mini-cog test.
- g) Hemoglobin, serum electrolytes, blood urea and serum creatinine will be noted.

2. Intraoperative Period

- a) The attending anaesthesiologist will be briefed about the anaesthesia protocol. The random number sealed envelope containing the randomized study group will be handed over to the anaesthesiologist.
- b) The attending anaesthesiologists will administer the anaesthetic agent as per the randomization.
- c) Factors including duration of surgery and anaesthesia, intravenous fluids used, intra operative blood loss, number of blood units transfused, intra operative hemodynamics, intra operative opioid use ,time to emergence and time to extubation will be noted.

3. Postoperative Period

The patients will be followed up on day one and day three following surgery. The patient will be subjected to psychological tests for evaluating delirium. Pain scores will be assessed using the numerical rating score. Postoperative factors like nausea and vomiting, fever, hemoglobin, serum electrolytes, blood urea and serum creatinine will be noted.

ETHICAL JUSTIFICATION

The anesthetic agents that will be used in our study have been in use for many years and have been largely safe. Use of isoflurane and desflurane in surgery has been practiced extensively and has not been found to be detrimental to the patients.

- (1) The patients involved in the research project will be informed of the methods, anticipated benefits and potential risks of the study and the discomfort it may cause and the remedies thereof.
- (2) Written informed consent will be obtained.
- (3) Every precaution will be taken to respect the privacy of the patient, the confidentiality of the patient.
- (4) The patient has right to abstain from the study or to withdraw consent to participate at any time of the study without reprisal.
- (5) Due care and caution will be taken at all stages to ensure that the patient is put to minimum risk or suffer from irreversible side effects and probably benefit from study.

INFORMATION TO THE PARTICIPANTS

Investigator's Name: Dr. Steve Joys

Name of Participant: _____

TITLE:

'Comparison of postoperative delirium in patients anaesthetised with Isoflurane and Desflurane during spinal surgery'

You are invited to take part in this research study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have queries or concerned. You are being asked to participate in this study being conducted in PGIMER because you satisfy our eligibility criteria.

Purpose of the research:

To compare the effect of isoflurane and desflurane in patients undergoing spine surgery. After being posted for spine surgery, you will be given either isoflurane or desflurane, which are commonly used for maintenance of anaesthesia in spine surgery. We have obtained permission from the Institutional Ethics Committee for conducting this study.

Study Procedure:

Once you are enrolled in the study you will be assessed for

- (a) Pre-operative Cognitive Dysfunction pain
- (b) Intra-operative hemodynamic parameters
- (c) Post-operative delirium and pain

Possible risks to you:

Some of the side effects of general anesthesia like nausea and vomiting.

Possible benefits to you:

You may not get any benefit from being on this research study, other than treatment benefit and better monitoring but the result of this study may provide benefits to the society in terms of advancement of medical knowledge and /or therapeutic benefit to future patients.

The alternatives you have:

If you do not wish to participate, you have the alternative of getting the standard treatment for your condition.

What should you do in case of injury or a medical problem during this research study?

Your safety is the prime concern of our research. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the consent form. You will be provided the required care/treatment. You will be entitled to your legal rights besides this.

Confidentiality of the information obtained from you:

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, institutional ethics committee and any person or agency required by law like the Drug Controller of India to view your data, if required. The results of clinical assessments and therapy performed as part of this research may be included in your medical record. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you:

Your decision not to participate in this research will not affect your medical care or your relationship with the investigator or the institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, though advisable that you will give investigators the reason for withdrawing, it is not mandatory.

Can the investigator take you off the study?

You may be taken off the study without your consent if you do not follow the instructions of the investigators or the research team or if the investigator thinks that further participation may cause harm.

Right to new information:

If the research team gets any new information during this research study that may affect your decision to continue participating in this study, or may raise some doubts, you will be told about that information.

CONSENT FORM

Name of the participant: _____ Age/ Sex: _____

C.R. No. _____

Name of the Investigator : Dr. Steve Joys

Name of the Institution : Post Graduate Institute of Medical Education and Research

Documentation of the informed consent

I, _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and exercising my free power of choice, hereby give my consent to be included as a participant in the study “Comparison of postoperative delirium in patients anaesthetised with Isoflurane and Desflurane during spinal surgery”.

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. My rights and responsibilities have been explained to me by the investigator.
5. I have been advised about the risks associated with my participation in the study.
6. I have informed the investigator of all the treatments I am taking or have taken in the past _____ months/years including alternate treatment.
7. I agree to co-operate with the investigator.
8. I have not participated in any research study within past _____ months.
9. I am aware of the fact that I can opt out of any time without having to give any reason and this will not affect my future treatment in the hospital.

10. I am also aware that the investigators may terminate my participation in the study at any time, for any reason, without my consent.
11. I hereby give permission to the investigators to release the information obtained from me as a result of participation in this study to the sponsors, regulatory authorities, Government agencies and ethics committee. I understand that they may inspect my original records.
12. My identity will be kept confidential if my data are publicly presented.
13. If despite the following instructions, I am physically harmed because any substance or any procedure as stipulated in any plan (my treatment will be carried out free of cost at the investigational site/the sponsor will bear all the expenses), if they are not covered by my insurance agency or by a government program or any third party.
14. I have had my questions answered to my satisfaction and have decided to be in the research study.

I am aware, that if I have any questions during this study, I should contact at one of the addresses below. By signing this consent form, I attest that the information given in this document has been clearly explained to me and understood by me.

Name and signature / thumb impression of participant / legal representative

_____ (Name) _____ (Signature)

_____ (Date) _____ (Time)

Name and signature of impartial witness (for illiterate patients)

_____ (Name) _____ (Signature)

_____ (Date) _____ (Time)

Address and contact number of the impartial witness: _____

Name and signature of the Investigator or his representative obtaining consent:

_____ (Name) _____ (Signature)

_____ (Date) _____ (Time)

Investigator certificate

I certify that all the elements including the nature, purpose and possible risks of the above study as described in this consent form have been explained to the subject. In my judgement, the participant possesses the legal capacity to give the informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate.

Signature of the investigator : _____

Name of the investigator : _____

Dated : _____

CONTACT PERSONS

For further information / questions, you can contact us at the following address:

Principal investigator:

Dr. Steve Joys

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Others:

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Department of Anaesthesia and Intensive Care,

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