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Role of Magnesium Sulphate on Postoperative Delirium in Oncological surgeries- Protocol for a Randomized Controlled trial

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Research Article

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Abstract

• **Background-** Post Operative Delirium(POD) belongs to a wide spectrum of Post-operative Cognitive dysfunction(POCD) occurring after major surgeries. It adds to the morbidity and mortality of the patient as well as increases the financial burden. It has various risks and predisposing factors, which can be an interplay of factors from the pre-operative to post-operative period. The elderly age group is one non-modifiable predisposing factor. Various pharmacological and non-pharmacological methods have been tried to decrease the incidence. Magnesium sulphate is a drug that has multiple uses, but its role in the prevention of delirium is not yet known. We aim to find its role in decreasing postoperative delirium in elderly patients.

• **Methods**: Consenting elderly patients, with no neurocognitive decline of ASA II to III physical status, posted for oncological surgeries under general anesthesia of more than equal to 2 hours duration and planned for extubation at the end of the surgery, will be enrolled for this study. They will be enrolled equally into either of the two groups- Magnesium Sulphate and Placebo. A computer-generated numbers list will randomise patients; allocation concealed with opaque sealed envelopes. The enrolled patients will undergo the Montreal Cognitive Assessment pre- and post-surgery. Patients with a score less than 26 will be excluded. Patients will be assessed for IL-6 and CRP pre- and post-surgery. Other assessments include optic nerve sheath diameter's correlation with POD, length of ICU and hospital stay, analgesic requirement and complications between the groups.

• **Sample size-**Based on previous literature and unpublished data from our institute on delirium, we estimated the baseline incidence of POD as 40% with an expected relative risk reduction post-intervention as 0.5. Considering a 1:1 allocation ratio, power of 80%, type I error (α) of 5% and expecting a minimal attrition rate of 10% the total number of patients needed to be recruited is 180 (i.e., 90 patients per group).

• **Discussion**: This will be the first study in an oncological setup to assess the role of magnesium sulphate in POD. Previous studies on the role of delirium were inconclusive. This study's findings will help in reformations in our practice, if required.

• **Trial registration**: CTRI/2023/10/058995, Clinical Trials Registry India. http://ctri.nic.in/Clinicaltrials/advsearch.php. Registered 20th October, 2023.

Administrative information

Title {1}	**Role of Magnesium Sulphate on Postoperative Delirium in Oncological surgeries- Protocol for a Randomized Controlled trial**
Trial registration {2a and 2b}.	CTRI (CTRI/2023/10/058995) CTRI collects all items from the World Health Organization Trial Registration Data Set.
Protocol version {3}	Protocol version 3.0(02 July 2025)
Funding {4}	Nonfunded
Author details {5a}	Dr. Manisha Sahoo Senior Resident Department of Onco-Anaesthesia and Palliative Medicine Dr. B.R.A IRCH,All India Institute of Medical Sciences, New Delhi Dr. Brajesh Kumar Ratre Associate Professor Department of Onco-Anaesthesia and Palliative Medicine Dr. B.R.A.IRCH, All India Institute of Medical Sciences, New Delhi
Name and contact information for the trial sponsor {5b}	None
Role of sponsor {5c}	None
Committees {5d}	Institute Ethics Committee Chief Anesthesiologist from Investigating Team

Introduction

Background and rationale {6a}

Post-operative cognitive dysfunction (POCD) is the reduction in the dynamic state of mind, involving domains such as memory, language, orientation, perception, and visuospatial ability, occurring mainly after surgery. It is not an uncommon complication after a major surgery involving all age groups, especially in the elderly age group. It can present acutely within hours to days or can present later, ranging from weeks to months. There are various risks and predisposing factors for the same [(3)]. Few risk factors include preoperative undiagnosed cognitive decline, elderly age group, female gender, lower education level, intraoperative hypotension, preoperative or intraoperative or postoperative electrolyte derangements are to name a few. Currently, the incidence of POCD in India, post-oncological surgeries, ranges from 5 to 51% [(4)]. POCD is associated with increased morbidity and mortality. Postoperative

delirium (POD) comes under the spectrum of postoperative cognitive dysfunction disorders, which can present within hours to days [2]. POCD is important currently because it adds to the financial burden in healthcare. It increases the duration of Intensive Care Unit (ICU) and hospital stay. It also increases the morbidity and mortality of the patients. It can affect the quality of life of the patients as well as their caregivers.

The brain is the hub of neurocognitive function through various centres and neural mediators. Major neurobehavioral changes are seen mainly in the postoperative period due to alterations in the normal physiology due to anesthesia or other intraoperative factors. This can lead to changes in various inflammatory markers, which might result in cognitive errors. Inflammatory markers like Interleukin-6(IL-6), C-Reactive Protein(CRP), and S-100B can play a role in neurocognitive disorders as well.

Various pharmacological as well as non-pharmacological methods have been tried to decrease the incidence of POCD. Dexmedetomidine, an alpha agonist, has been a well-established agent in reducing POCD [5,6]. But dexmedetomidine has been associated with complications like hypotension and sinus bradycardia. Haloperidol and S-Ketamine have also been tried for decreasing delirium. Non-pharmacological agents like probiotics have been tried as well.

Magnesium sulphate(MgSO4) is an N-methyl-D-aspartate receptor antagonist. It has an action on various systems of our body. But its role in POD has not yet been established, even though it is an excellent analgesic, adjuvant in nerve blocks, anti-arrhythmic, etc. There are a few trials involving the role of $MgSO_4$ on POCD, which have shown mixed results [7,8]. It has been used on children in reducing emergence delirium postoperatively [9].

Through this study, we wish to find out the role of $MgSO_4$ on postoperative cognition errors and its role on neuroinflammatory markers. This will help in finding an alternative to the existing agents that reduces the incidence of POD. We also aim to find the correlation between the changes of Optic Nerve Sheath diameter (ONSD) and POCD. Even though the $MgSO_4$ is known to be an excellent analgesic, we still aim to observe this further in oncological practices to decrease the intraoperative opioid requirement.

- **Objectives {7}**

Aims: To evaluate whether instillation of magnesium sulphate intraoperatively in elderly patients undergoing oncological surgeries will result in decreased incidence of postoperative delirium, inflammatory markers, analgesic requirements, and a better quality of recovery. We also aim to find the effect of the change of intracranial pressure and inflammatory markers on postoperative delirium.

Objectives:

Primary Objective:
To compare the incidence of postoperative delirium with Magnesium sulphate and placebo in elderly patients in oncological surgeries.

Secondary objectives:

1. To compare the difference in IL-6 and CRP levels pre- and post-operatively between the groups
2. To compare the variations in optic nerve sheath diameter and their correlation with post-operative delirium
3. To compare the lengths of ICU stay and hospital stay between the two groups
4. Difference in complications in both groups

Trial design {8}

This will be a single-centre, parallel-group, prospective, randomised controlled trial in a 1:1 allocation ratio.

Methods: Participants, interventions, and outcomes

Study setting {9}:

This study will be conducted at the Department of Onco-Anaesthesia and Palliative Care at All India Institute of Medical Sciences, New Delhi, India, and National Cancer Institute, Jhajjar, AIIMS**.** AIIMS is a centre of national importance with more than 350 beds. It runs underground and offers postgraduate training courses for many medical and surgical specialities. The 2 dedicated cancer centres, as mentioned above, both with a total of 11 functional major operation theatres. The study will be conducted at the operating theatre of both centres.

Eligibility criteria {10}: The participants included in the study will be

1. Patient: Elderly patients (Age >60 years) with ASA I to III functional status undergoing onco-surgical procedures under general anesthesia, expected to last more than 2 hours, can understand and provide valid consent for the procedure. In case a patient has a pre-operative MoCA score of less than 26, other neurocognitive decline, allergic to Magnesium sulphate or being sent intubated to the ICU, then they are excluded from the study.
2. Procedure- Enrolled patients will undergo the Montreal Cognitive Assessment(MoCA) preoperatively. Post induction with fentanyl-2-3 mcg/kg, propofol-1-2 mg/kg and rocuronium-0.6-1 mg/kg, patients will be started on either the study drug or placebo group depending on their allocation. Study drug- Magnesium Sulphate will be given as a loading dose of 30mg/kg over 10 minutes, followed by a maintenance dose of 10mg/kg/hr. The maximum dose allowed is 60mg/kg. Opioids will be avoided intraoperatively. Standard analgesia plan will be followed- epidural, fascial plane blocks or NSAIDs. Along with the standard ASA monitors, Bispectral Index (BIS) and Neuro Muscular Transmission (NMT) will be monitored. Post induction and before extubation, Optic Nerve Sheath Diameter (ONSD) will be measured. Post-operatively, if MoCA shows cognitive decline, then ONSD will be measured. Samples for IL-6 and CRP will be taken pre-induction, on POD1 and POD3/discharge(whichever is earlier).

Patients will also be assessed for ICU and hospital post-surgery, analgesic requirement, and complications.

Who will take informed consent? {26a}: The investigators will identify eligible participants based on inclusion and exclusion criteria. A detailed written and oral information on the study will be provided to the patients in an understandable language (English/Hindi), and the investigators will take written informed consent**.** The Montreal Cognitive Assessment will be done either in English or Hindi (validated).

Additional consent provisions for collection and use of participant data and biological specimens {26b}: The written consent will include information regarding the collection of blood samples for IL-6 and CRP.

Interventions

Explanation for the choice of comparators {6b}

Magnesium sulphate has been used as a bronchodilator, analgesic, anti-convulsant, etc, but the use of the same for delirium has limited trials. It has been used effectively for emergence delirium but not on POD, especially in elderly patients undergoing oncological surgeries. It has given mixed results when tried earlier on POCD. So, we wish to find its usefulness in POD.

Intervention description {11a}

Drug- All emergency airway and resuscitation drugs will be available.

Equipment- All ASA monitors, BIS and NMT leads will be available. An infusion pump will be available to inject the drug at the desired rate. USG will be available for ONSD measurement.

Personnel- 1. The consultant or resident anesthesiologist will collect the sample before induction and start the case. He/She will do the ONSD measurements and record the same post-induction, before the start of infusion of study drug and before extubation. In case the patient is found to have POD, then ONSD will be measured again.
The patient will undergo MoCA when fully conscious and oriented in recovery.

2. An operation theatre technician (not a part of the research team) will select a sealed envelope after the patient enters the theatre and the WHO checklist is completed. He will load the drug/placebo.

Medications- All the patients in both groups will undergo a standard anaesthesia technique using Fentanyl 2-3 mcg per kg, 1.5- 2 mg per kg of propofol for induction, and 0.6-1 mg/kg of rocuronium for muscle relaxation. Maintenance of anaesthesia will be with isoflurane or sevoflurane, aiming for an agent appropriate for MAC intubation.

Technique-

Pre-procedure

A day before surgery, the patients will undergo a bedside review and pre-anaesthesia check-up. ASA I – III patients, above 60 years of age, will be informed about the study, whose surgery duration is expected to last more than 2 hours. Consenting individuals will be asked to fill out the Montreal Cognitive Assessment forms. These forms are present in both English and Hindi, along with 28 other languages. Consenting patients will be informed about the assessment test in the language they are comfortable with and will be asked to fill out the form in the same language. These patients will be informed that they will have to fill out the same form after surgery on Days 0, 1 and 3 or discharge, whichever is earlier. Patients having a score less than 26 will be excluded due to pre-operative cognitive decline.

Intra-operative management:

Patients in both groups will be subjected to uniform treatment in all respects.

Pre-operative fasting protocols of 6 hours to light solid food and 2 hours to clear liquids will be followed. Routine use of pre-operative anxiolytics or gastric ulcer prophylaxis is not practised at our institute and will be individualised.

On the day of the operation, the patients will be allocated to their respective treatment group in the pre-operative holding area using the SNOSE method as described above, after confirming consent once more. Once the patient is taken into the operative room, standard ASA monitors (Pulse-oximeter, ECG and non-invasive BP) will be applied, and an IV access will be secured. At the same time, blood samples will be collected for IL-6 and CRP will be collected. Regional Anaesthesia technique, if required, will be done as per the need of the case.

Induction of general anaesthesia, post pre-oxygenation, will be done by injecting Inj. Fentanyl 2 mcg/kg, Inj. Propofol titrated to loss of verbal contact and Inj. Rocuronium 1 mg/kg IV. The patient will be intubated with an appropriately sized endotracheal tube at the end of 3 minutes of bag and mask ventilation.

Controlled two lung ventilation in the VCV (volume- controlled) mode will be initiated through a closed circuit using the GE Avance CS2 workstation with tidal volumes of 6-8 ml/kg, FiO_2 of 0.5 with air and a PEEP of 5 cm H_2O – the minute ventilation titrated to $EtCO_2$ values between 35-45 mm Hg. Bispectral Index (BIS) monitoring will be initiated, and anaesthetic depth via inhalational Sevoflurane or isoflurane will be titrated between 0.7 – 1 MAC values to achieve BIS values between 40-60.

Analgesia will be maintained as per institutional protocol, with a continuous infusion of 0.25% Inj. Ropivacaine at rates of 4-6 ml/hour, if an epidural is inserted. Or appropriate regional analgesia technique with 0.25% Ropivacaine will be injected either as a single shot or continuously using a catheter under Ultrasound guidance(USG). If additional doses of analgesics are required, then short-acting opioids like fentanyl will be given. Inj. Paracetamol 1g IV and Inj. Diclofenac 75 mg IV will also be

administered unless contraindicated. Muscle relaxation will be maintained with boluses of 10 mg of Rocuronium IV, guided by acceleromyographic neuromuscular monitoring (NMT) and train-of-four (TOF) counts as per standard practice.

Venous access will be taken as per the need of the surgery. The patient will then be positioned in the appropriate position as per the need and handed over to the surgeons. Baseline Optic Nerve Sheath Diameter(ONSD) will be measured. Three readings will be taken for both sides.

The nasopharyngeal temperature was also monitored and maintained at >= 36℃ by the use of warm air blankets.

Intraoperatively, analgesic requirement in terms of extra fentanyl doses will be noted.

The intervention protocol:

In the study group (Group S), post-induction, will receive $MgSO_4$ at the rate of 30mg/kg over 10 mins of loading dose, followed by 10mg/kg/hr infusion dose. The maximum dose allowed is 60mg/kg. The drug will be prepared in a 50-60 ml syringe using 50%w/v $MgSO_4$ ampules and 0.9% Sodium Chloride(NaCl). A total dose of 60 mg/kg will be added and diluted to 60ml volume. 30 ml of the volume will go as a loading dose in 10 minutes, the rest will be infused as a maintenance dose at 10ml/hour. Each ampule contains 1gm of $MgSO_4$.

In the control group (Group C), an equivalent volume of 0.9% of NaCl (60ml will be transfused at a similar rate.

In both groups, the above drugs were continued till the start of closure or a maximum of 3 hours. In case of severe intra-operative hypotension, the infusion will be stopped, and such patients will be excluded from the study if at least 50ml of volume is not transfused to the patient.

Post-operative management:

Just after skin closure, ONSD will be monitored. At the end of the surgery, the patient will be adequately reversed based on NMT monitoring and TOF, and extubated after achieving a TOF ratio > 0.9. In case the patient could not be extubated, then the patient will be excluded from the trial and will be sent to the ICU on elective mechanical ventilation.

Post-extubation ONSD will be measured again. MoCA will be conducted for extubated patients in post post-operative care unit/ICU after the patient is fully conscious, responding well and oriented.

Briefly, all the patients will be observed in the ICU or recovery area, as per indication, post-operatively, prior to shift to the ward. MoCA will be conducted again on POD_1 and POD_3. Blood samples for IL-6 and CRP will be collected too.

Post-operative analgesia will be uniform across both groups to maintain a Numeric Rating Scale (NRS<4).

Intravenous fluids will be continued till the point the patients can accept orally, at a rate determined by the team. The patients will be encouraged to perform incentive spirometry, and chest physiotherapy will be done.

Complications, length of ICU and hospital stay will be noted as well.

Criteria for discontinuing or modifying allocated interventions {11b}

If the patient couldn't be extubated at the end of the surgery for any reason.

Strategies to improve adherence to interventions {11c}

All residents and faculty will be informed about the study protocol for improving adherence. The patient will be informed regarding the procedure and will be given ample time to fill out the MoCA assessment form in the language he is comfortable with.

Relevant concomitant care permitted or prohibited during the trial {11d}

For the study, no standard treatment shall be withheld. No differential treatment or partiality in any form will be extended to a patient who has refused to be a part of the study or who voluntarily withdraws from the study at any point.

Provisions for post-trial care {30}

In the improbable event of any untoward events arising from the intervention, the researchers will treat them within the available institutional facilities.

Outcomes {12}

Primary outcome measures: 1) To compare the incidence of postoperative delirium with Magnesium sulphate and placebo in elderly patients in oncological surgeries.

This will be done using MoCA.

Secondary outcome measures to be assessed will be to compare the difference in IL-6 and CRP levels pre- and post-operatively between the groups, to compare the variations in optic nerve sheath diameter and their correlation with post-operative delirium, to compare the lengths of ICU stay and hospital stay between the two groups, and the difference in complications in both groups

Participant Timeline {13}

TIMELINES	BEFORE SURGERY	BEFORE INDUCTION	POST INTUBATION	START OF CLOSURE	POST EXTUBATION	POD0	POD1	POD3 OR DISCHARGE
ENROLLMENT								
INFORMED CONSENT	**X**							
ELIGIBILITY CRITERIA	X							
ALLOCATION	X							
GROUP1			—	—				
GROUP 2			—	—				
ASSESSMENT	X							
DEMOGRAPHIC	X							
MOCA	X					X	X	X
IL-6, CRP		X					X	X
ONSD			X	X	X			
DOCUMENTATION OF OPOIOD USE			—	—				
USEFLUID / BLOOD PRODUCT USE			—	—	—			
BLOOD LOSS			—	—				
COMPLICATION			—	—	—	—	—	—

Sample size {14}

We have calculated the sample size from the following data published in recent literature and based on unpublished data from our departmental audits:

1. We have calculated the sample size from the following data published in recent literature and based on unpublished data from our departmental audits.
   The incidence of post-operative delirium (POD) following a non-cardiac surgery in elderly age group is 5-51% [4,12,14,43].
2. A systematic review with meta-analysis reveals that the administration of dexmedetomidine reduced from 43% to 77% the likelihood of cognitive and behavioral dysfunction in the postoperative period of adult patients submitted to general anesthesia for non-cardiac surgery [6].
3. Corroborating with the data from our previous departmental audits (unpublished), we estimated the baseline incidence of POD as 40% with an expected relative risk reduction after the intervention as

0.5.

- Hence, for testing the null hypothesis, comparing two proportions using the Chi-squared test in two independent sample groups for two sided equality using a 1:1 allocation ratio, power of 80% (1- β), a type I error (α) of 5% and expecting a minimal attrition rate of 10% and rounded to nearest number, it was calculated that **the total number of patients that need to be recruited is 180 (i.e., 90 patients in each group).**
- The above calculation was done using two online sample size calculators – http://powerandsamplesize.com and https://sample-size.net (from UCSF). The calculated sample size was concordant between the two calculators used.
- **The following data were used for the calculation:**
    - Number of participants in Study Group = n_A
    - Number of participants in Control Group = n_B
    - Incidence of POD in the Study Group = I_A
    - Incidence of POD in the Control Group = I_B
    - Sampling ratio between the two groups, $\kappa = n_A / n_B = 1$ (since 1:1 allocation)
    - Power, (1- β) = 0.8
    - Type I error rate, α = 0.05
    - The null hypothesis, $H_0 : (I_A - I_B) = 0$
    - The alternate hypothesis, $H_1 : (I_A - I_B) \neq 0$
    - Given the expected Relative Risk between the Study and Control- expecting 50% as effect side or decrease in delirium after intervention- I_A / I_B
    - The online software use the following formulae for the sample size calculation

The standard normal deviate for $\alpha = Z_\alpha = 1.9600$
The standard normal deviate for $\beta = Z_\beta = 0.8416$
Pooled proportion = $\bar{P} = (q_1 * P_1) + (q_0 * P_0) = 0.3000$
$A = Z_\alpha \sqrt{\bar{P}(1-\bar{P})(1/q_1 + 1/q_0)} = 1.7963$
$B = Z_\beta \sqrt{P_1(1-P_1)(1/q_1) + P_0(1-P_0)(1/q_0)} = 0.7528$
$C = (P_1 - P_0)^2 = 0.0400$
Total group size = $N = (A+B)^2/C = 162$

Sample size (without continuity correction)

	N	Outcome+	Outcome-
Group 1:	81	16	65
Group 0:	81	32	49
Total:	162	48	114

Note: This calculator uses the normal distribution (with and without the continuity correction) as an approximation to the binomial distribution.

References:
Hulley SB, Cummings SR, Browner WS, Grady D, Newman TB. Designing clinical research : an epidemiologic approach. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013. Appendix 6B, page 75.

(Continuity Correction) Fleiss JL, Tytun A, Ury HK. A simple approximation for calculating sample sizes for comparing independent proportions. Biometrics 1980;36:343-46.

Considering loss of 10%- Sample size= N/1-10%

= 162/1-0.1

= 162/0.9 = 180

Recruitment {15}

The patients posted for surgery under general anesthesia will be assessed for eligibility criteria from the preoperative period. It is estimated that with the volume of surgeries the institute sees every year, the sample size can be achieved.
The last date of recruitment would be 31st of July 2025

Assignment of interventions: allocation

Sequence generation {16a}

The enrolled participants will be randomized to one of two groups. A web-based random number generator (randomizer.org) will be used for the simple randomization scheme. Participants will be randomized to either of the two groups at a 1:1 allocation ratio.

Concealment mechanism {16b}

Once a patient has been enrolled, the operating room's technical staff will open an opaque sealed envelope containing the group allocation.

Implementation {16c}

Neither front-line care providers, investigators, nor participants will be aware of whether the next eligible participant will be receiving treatment or control intervention. One of the team members will enroll the participants and leave a set of sequentially numbered sealed opaque envelopes with the OT technician (OTT) responsible for anesthesia for the patient. The OTT will not be a part of the research team and will open the sealed envelopes to read the randomization sequence, which will be matched with the random number sequence generated earlier.

Assignment of interventions: Blinding

Who will be blinded {17a}

The patient, the outcome assessor, and the data analyst will be blinded to the study intervention. The intraoperative anesthesiology team will not be blinded to the study.

Procedure for unblinding if needed {17b}

In infrequent circumstances that may hamper the patient's safety, unblinding may be done.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All demographic and clinical data will be entered into paper-based case record forms which will later be tabulated.

The case record forms can be collected by emailing the corresponding author of this manuscript.

Plans to promote participant retention and complete follow-up {18b}

As the patient will be with the same anesthesia team, retention will not be a significant concern once recruited. In case the patient refuses to fill the MoCA assessment postoperatively, we will motivate him/her for the same and ask him/her to fill after sometime whenever comfortable.

Data management {19}

All data (case record forms and videos) will be stored in a password-protected computer in an excel spreadsheet for further analysis. All measures will be taken to provide a backup of stored data in case of data loss.

Confidentiality {27}

The participants' identity and sensitive personal details will remain confidential with the principal investigators and will not be disclosed in any form.

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Blood samples will be collected in this study for IL-6 and C-reactive protein measurement.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The independent categorical variables like sex, ASA physical status, co-morbidities, surgical procedure, etc. will be represented as a percentage of the total population while continuous data like age, BMI, operative duration, etc. will be represented as mean ± standard deviation (SD) or as median with interquartile range depending on whether they satisfy the assumptions of normal distribution.

The outcome measures will be similarly represented.

The tests of normality applied will be the Kolmogorov-Smirnov test or the Shapiro-Wilk test.

For testing the null hypothesis, we will use the Chi-squared test for the primary outcome variable. For the secondary outcome variables, the Chi-squared test/Fisher's exact test (depending on the least count in the contingency table) will be used for comparing categorical variables. For the continuous variables, unpaired Student’s t test or Mann-Whitney U test will be applied depending on whether their data distribution is parametric or not, respectively.

The SPSS software from IBM will be used for the statistical analysis of the data, while pictorial/ graphical representations will be done either by importing from SPSS or using Microsoft Excel.

Interim analyses {21b}

An interim analysis is planned after ninety cases, and approval granted from the ethics committee. The chief guide will have access to the results of the interim analysis.

Methods for additional analyses (e.g. subgroup analyses) {20b}

Subgroup analysis is not planned for the study.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

A sensitivity analysis will be done to handle the missing data. Missing data will be handled with multiple imputations. Per protocol and ITT analyses will both be done.

Plans to give access to the full protocol, participant level-data and statistical code {31c}

Reasonable access to the protocol and other documents can be made by requesting the corresponding author.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {5d}

The chief anesthesiologist from the investigating team will review the adherence to trial protocol and overall conduct of the trial every two months throughout the study period.

The institute research committee also oversees the regular progress of academic dissertation-based research.

Composition of the data monitoring committee, its role and reporting structure {21a}

Since the study does not involve any new intervention and endotracheal intubation is a regular procedure done in operating rooms under senior anesthesiologists' guidance, the IEC did not call for a DMC appointment.

Adverse event reporting and harms {22}

Magnesium sulphate is a safe drug, and no new intervention will be investigated. Hence, we do not expect any unexpected adverse events to happen during the study. Rarely, cardiac arrythmias, transient muscle weakness or absent tendon reflexes may occur.

Frequency and plans for auditing trial conduct {23}

We do not have any plans for conducting audits of trial conduct as the study is done as a routine procedure for elective operated patients in healthy cancer patients under senior anesthesiologists' guidance.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

This study was approved by the Institute Ethics Committee for Post Graduate Research, All India Institute of Medical Sciences, New Delhi, on 20th of September 2023 and registered on ctri.nic.in(**CTRI/2023/10/058995**) on 20th of October 2023. Any amendments in protocol will have to be informed to and approved by the Departmental academic lead, head of the department, the institutional research committee, and IEC before being uploaded to the trial's registration body.

Dissemination plans {31a}

The results obtained from this study will be disseminated at anesthesiology conferences (local and international meetings). The key findings will be reported in the trial registry. A complete study report will be submitted for publication in an anesthesia journal, preferably an open-access journal.

Discussion

It is already known that postoperative delirium can increase the morbidity and financial burden of the patient. Various pharmacological and non-pharmacological methods have been tried to prevent the same, some showing promising results. This drug has been successful in preventing emergence delirium, but its role in postoperative delirium is yet to be proved.

This is the first ever study to ascertain the role of magnesium sulphate in preventing postoperative delirium in cancer patients.

Trial status

This study was approved by the Institute Ethics Committee for Post Graduate Research. AIIMS, New Delhi, on 20th of September 2023 and was registered prospectively in CTRI on 20th of October 2023. The first participant was recruited on 23rd of October 2023, and currently, the study is in an ongoing status. The last date of recruitment will be 31st of July 2025, post which analysis will be done.

This is 3rd version of protocol dated 02.07.2025.

Abbreviations

$MgSO_4$
Magnesium Sulphate
MoCA
Montreal Cognitive Assessment
ASA
American Society of Anesthesiologists
OT

operating theatre
SD
standard deviation
IL
6-Interleukin 6
CRP
C-Reactive Protein

Declarations

Acknowledgements

We acknowledge the Department of Onco-Anaesthesia and Palliative Medicine faculty's help, whose ideas strengthened the methodology during the 'Thesis Protocol Presentation' at the institute. We also regard beneficial the help and support from the OT staff.

Authors’ contributions {31b}

MS conceived the study and led the proposal and protocol development. MS and BR contributed to the study design and the development of the proposal. MS and BR were the lead trial methodologists. BR supported by reading the manuscript critically and providing relevant comments. All authors reviewed, read, and approved the final manuscript. All named authors adhere to the authorship guidelines of Trials; the authors have agreed to the publication and have contributed to the manuscript's writing. No professional writer has been involved.

Funding {4}

No extramural funding will be required for the conduct of this study.

Availability of data and materials {29}

The data generated in this study can be shared after a reasonable request to the corresponding author of the manuscript**.**

Ethics approval and consent to participate {24}

The Institute Ethics Committee for Post Graduate Research, AIIMS, New Delhi has approved the study on the 20th of September 2023.

Consent for publication {32}

Not applicable

Competing interests {28}

All the authors declare that they have no competing interests.

Authors' information (optional)

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