Clinical Trial Details (PDF Generation Date :- Tue, 13 Oct 2020 09:34:29 GMT)

CTRI Number	CTRI/2020/10/028375 [Registered on: 13/10/2020] - **Trial Registered Prospectively**
Last Modified On	12/10/2020
Post Graduate Thesis	No
Type of Trial	Observational
Type of Study	Prospective Observational Study
Study Design	Other
Public Title of Study	A study to evaluate the treatment given in the ICU for pain and occurrence of altered mental status of patients in ICU
Scientific Title of Study	NATIONAL (iNdian AnalgosedaTION And deLirium) : Multi-center Prospective Observational Study of Current Analgo-Sedation Practices and the incidence of delirium in Indian ICUs: INSTINCT II study (INhaled SedaTion INCriTically ill patients –INSTINCT study Group)

Secondary IDs if Any

Secondary ID	Identifier
3559_Protocol Version 2.0 dated 24.08.20	Protocol Number

Details of Principal Investigator or overall Trial Coordinator (multi-center study)

Details of Principal Investigator	
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Details Contact Person (Scientific Query)

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Source of Monetary or Material Support

Source of Monetary or Material Support
> ISCCM Indian Society of Critical Care Medicine 6, Hind Service Ind. Premises, Dadar, Mumbai, Maharashtra 400028

Primary Sponsor

Primary Sponsor Details	
Name	Tata Memorial Hospital
Address	Dept of Anaesthesia, Critical care and Pain, Dr. E Borges Road, Parel,Mumbai
Type of Sponsor	Research institution and hospital

Details of Secondary Sponsor

Name	Address
NIL	NIL

Countries of Recruitment

List of Countries
India

Sites of Study

Name of Principal Investigator	Name of Site	Site Address	Phone/Fax/Email
Dr Atul Kulkarni	Tata Memorial Hospital	Department of Anesthesia Critical care and Pain Second floor, Main Building, Tata Memorial Centre Dr E Borges Road Parel Mumbai Mumbai Mumbai MAHARASHTRA	9869077526 kaivalyaak@yahoo.co.in

Details of Ethics Committee

Name of Committee	Approval Status	Date of Approval	Is Independent Ethics Committee?
Institutional Ethics Committee II	Approved	21/09/2020	No

Regulatory Clearance Status from DCGI

Status	Date
Not Applicable	No Date Specified

Health Condition / Problems Studied

Health Type	Condition
Patients	Symptoms and signs involving the circulatory and respiratory systems

Intervention / Comparator Agent

Type	Name	Details
Intervention	NA	NA
Comparator Agent	NA	NA

Inclusion Criteria

Inclusion Criteria	
Age From	18.00 Year(s)
Age To	90.00 Year(s)
Gender	Both
Details	1. Age > 18 years 2. Anticipated duration of ventilation > 48 hrs 3. Need for sedation for >48 hrs

Exclusion Criteria

Exclusion Criteria

Details	1. Severe Brain Injury GCS 2. Mechanical ventilation needed 3. Mechanical Ventilation initiated > 24 hrs. after ICU admission (NIV counts as Mechanical Ventilation) 4. Not expected to survive for > 24 hrs. 5. Admitted for end of life care

Method of Generating Random Sequence	Not Applicable
Method of Concealment	Not Applicable
Blinding/Masking	Not Applicable

Primary Outcome

Outcome	Timepoints
The incidence of delirium using the CAM-ICU score	From admission till discharge/death in ICU

Secondary Outcome

Outcome	Timepoints
Mean (± SD) pain score each day in the ICU, and proportion of time spent in target sedation range (RASS 0 to -2).	From admission till discharge/death in ICU

Target Sample Size	**Total Sample Size=**2000 **Sample Size from India=**2000 **Final Enrollment numbers achieved (Total)=**Applicable only for Completed/Terminated trials **Final Enrollment numbers achieved (India)=**Applicable only for Completed/Terminated trials
Phase of Trial	N/A
Date of First Enrollment (India)	19/10/2020
Date of First Enrollment (Global)	No Date Specified
Estimated Duration of Trial	**Years=**1 **Months=**0 **Days=**0
Recruitment Status of Trial (Global)	Not Applicable
Recruitment Status of Trial (India)	Not Yet Recruiting
Publication Details	None yet
Brief Summary	**Background** The current sedation practices and the incidence of delirium in the Indian ICUs (in 2019) are not known. We also do not know the incidence of delirium in our practice. Delirium has been shown to prolong mechanical ventilation, duration of ICU and hospital length of stay and in some studies even mortality. A questionnaire-based survey carried out by ISCCM in 2013; [1] found the following about analgesia and sedation practices in India. Midazolam was the commonest agent used, while propofol was the second. Few respondents had occasionally used dexmedetomidine. Fentanyl was the most common analgesic agent used, followed by Tramadol and Acetaminophen (Paracetamol). Some respondents used neuromuscular blocking drugs occasionally, while only very few always used it during ventilation. For this, Vecuronium was the most preferred agent, followed by Atracurium. “Analgesia first” approach was used by a few while many used Analgo-sedation approach. Rarely “analgesia only” regimen was used. Most analgesics and sedatives were given as continuous IV infusion by a large number of respondents and as intermittent boluses by a few; and both methods were used by some respondents. About two-thirds of the responders felt that the incidence of delirium in mechanically ventilated patients was less than 10% in their practice. The incidence was reported to be in the range of 10-50% by 31% of the responders, and only 2% of the responders felt that more than half of their

mechanically ventilated patients experienced delirium. Majority reported not assessing delirium in the ICU. Only a fifth of used formal scales to measure delirium, CAM-ICU score being the most preferred one. Haloperidol was the most commonly used drug for the treatment of delirium.

Delirium is a neuropsychiatric syndrome, a disturbance in attention, awareness, and cognition, which develops over a short period of time and fluctuates in severity. [2] High-risk populations include elderly and mechanically ventilated ICU patients. The overall incidence of delirium is 16-89% in hospitalized patients. It is highest in mechanically ventilated patients (81%). Incidence of post-operative delirium varies from 10% to 70%. [3-6]

The PADIS (Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption) guidelines of Society of Critical Care Medicine were first formulated in 2013 and later updated in 2018. [7] These guidelines make a conditional recommendation for intravenous infusion of propofol or dexmedetomidine for sedating patients in the ICU based on low quality evidence. Propofol infusion is an excellent agent for short-term sedation, but has several drawbacks. It can cause hypotension due to vasodilation and myocardial depression, has a potential for respiratory depression and development of hypertriglyceridemia and rarely but disastrously, occurrence of Propofol Infusion Syndrome (severe lactic acidosis and rhabdomyolysis). Dexmedetomidine is better and safer with advantages of quick onset and offset, but is costly. There is an increased incidence of bradycardia and hypotension with bolus dose. It can also cause hypertension due to stimulation of post-junctional alpha-2 receptors located on arterial and venous smooth muscle. Dose adjustment may be required for patients with liver disease. Importantly both agents do not lead to delirium unlike benzodiazepines.

The aim of the study is find out the incidence of delirium and the current sedation practices in Indian ICUs.

Setting: Intensive Care Units in India, willing to share the data for this purpose.

Study design: Multicenter prospective observational study

Study duration: Data will be collected for all consecutive adults patients to the ICU who need sedation and analgesia, for a period of one month after obtaining the IEC approval.

Follow-up period: All patients recruited in the study will be followed up for 30-days. The duration of follow-up for each ICU will last till the 30-day (or discharge from the hospital or death, which ever occurs earlier) follow-up data is collected for the last patient enrolled from that ICU. This will include the data for the secondary outcomes.

Primary outcome: The incidence of delirium using the CAM-ICU score.

Secondary outcomes: Mean (± SD) pain score each day in the ICU, and proportion of time spent in target sedation range (RASS 0 to -2).

The other data that will be collected is as follows:

1. Proportion of time spent in target sedation range (RASS 0 to -2)
2. Mean (± SD) pain score each day in the ICU

3. Overall incidence of delirium i.e. present at any time during ICU stay
4. Delirium present or absent each day in ICU using the CAM-ICU score.
5. Type and duration of delirium
6. Rescue therapies used (haloperidol, dexmedetomidine –dose, route, duration of infusion, antipsychotic medications)
7. Duration of Mechanical ventilation a. invasive b. non-invasive
8. ICU Mortality (if within 30 days)
9. Hospital Mortality (if within 30 days)
10. ICU and Hospital LOS (if < 30 days)
11. Outcome at 30 days (if above not present)

Inclusion Criteria:

1. Age > 18 years
2. Anticipated duration of ventilation > 48 hrs
3. Need for sedation for >48 hrs

Exclusion Criteria:

1. Severe Brain Injury GCS < 9
2. Mechanical ventilation needed < 24 hrs.
3. Mechanical Ventilation initiated > 24 hrs. after ICU admission (NIV counts as Mechanical Ventilation)
4. Not expected to survive for > 24 hrs.
5. Admitted for end of life care

The following data will be collected:

Baseline characteristics:

1. Admission source
2. Demographic characteristics

3. Hospital and ICU admission diagnosis
4. Initial neurological assessment
5. Substance abuse history
6. SAPS III score
7. SOFA score
8. Primary Diagnosis
9. Hemodynamic status
10. Sedation score (RASS)
11. Pain Score (VAS)

The data collection process will be as follows:

1. Patient will be assessed as in baseline characteristics
2. CAM-ICU score before initiation of analgesia and sedation will be recorded
3. Pain score at initiation of analgesia will be recorded
4. Sedation score at initiation of sedation will be recorded
5. Subsequently both scores will be recorded thrice a day
6. Scores will be also recorded at escalation or de-escalation of dosage and the reason for change of dosage (if was there a change) will be recorded

Indications for de-escalation/escalation of dose will be recorded under the following heads

a. No longer needed
b. Neurological assessment
c. Hemodynamic instability
d. Adverse effects
e. Others

Indications for escalation

a. Didn't meet sedation score target
b. Ventilator dyssynchrony
c. Others
d. Others specify

Other data

1. Choice of sedative/s will be recorded
2. Dose and route of administration of sedation will be recorded
3. Choice of analgesic/s will be recorded
4. Dose and route of administration of sedation will be recorded
5. Dose and route of administration of analgesics will be recorded
6. Use of neuraxial analgesia will be recorded
7. Presence of delirium (CAM-ICU score), at each shift change, i.e. 3 times a day, if patient is awake,)
8. Weaning criteria will be recorded as per commonly used scores. (e.g. f/VT)
9. Extubation criteria will be recorded.
10. Duration of mechanical ventilation including post extubation NIV will be recorded.
11. ICU LOS will be recorded.
12. ICU Discharge status will be recorded
13. Hospital discharge status will be recorded

Statistics

Sample size calculation: With a margin of error of 2.5 %, a confidence level of 90%, with large no of ventilated patients (not sure how many across India, therefore chosen 100,000), with a likely sample proportion of 50%, (again this is not known for India), the sample size required is 1663.

For choice of agent tests of frequency will be used. For cumulative dosages Median value and IQR will be used. For comparative parameters like sedation score vs drug dose Chi Square test will be used. Descriptive statistics will be used to calculate the proportion of time spent by each patient in the adequate sedation range (along with Confidence Intervals). P-trend test will be used for to assess a proportional decrease or increase in need for the sedative agent. P value< 0.02 will be assumed to be significant.Uni-variate and multi-variate analysis for causes of delirium, ICU outcomes. Survival analysis will be done by Cox proportional regression analysis

Ethical issues

Each participating ICU will obtain approval to conduct the study with a waiver of informed consent (if possible). If not, then brief consent from LAR with deferred consent from patients will be obtained.

Budget

We have requested ISCCM to endorse the study, create the online entry WebPages and allow us to

use the server for collection and storage the data, which has been agreed to. We will ensure that the finances are not required from the ISCCM research grant.

Process:

1. An e-mail blast will be sent to all ISCCM members, for participating in the study and the participating ICUs will be asked to provide information regarding infrastructure, and ability to contribute data, including their participation in previous ISCCM studies.

The data will be collected on the ISCCM server, using database created by the ISCCM. (Period of 2 months from the end of data collection by the last ICU to start patient recruitment)

2. A training module in the form of a PowerPoint presentation will be sent to all ICUs to train their staff for assessing RASS score, VAS for pain score and the CAM-ICU score.

3. After obtaining IEC approval, all ICUs can start collecting data, with recruitment of first patient from the ICU taken as the first study day for that unit.

4. Thus all participating ICUs will be asked to start recruitment within a 3 month window, to obtain IEC approval and train their staff.

5. All participating ICUs will upload their patient data (which will be anonymised) directly on to the ISCCM server.

6. The members of the steering committee will be in touch with ICU Research coordinator (designated by each ICU), for trouble shooting and ensuring complete follow-up. If necessary, a telephonic reminder will be given.

7. After the end of the data will be analysed using appropriate statistical methods (as described above) and the manuscript submitted to the Indian Journal of Critical Care Medicine, within 3 months of completion of data collection.

8. The first 3 Principal investigators shall be included as authors in the main publication relating to the study.

9. The writing committee will be responsible for supervision of statistical analysis, collation and verification of data, drafting and finalization of the manuscript and submission of the manuscript, and all correspondence related to the manuscript.